



HIV Management Guide
for Clinical Care

HIV Management Guide for Clinical Care

Australian National Guide 2024

About the HIV Management Guide for Clinical Care

The HIV Management Guide for Clinical Care is a key resource for health practitioners managing and caring for people living with HIV in Australia. It sets out the basic principles of preventing, diagnosing and managing HIV and HIV associated disease.

First published in 2003, the Guide grew out of an earlier printed monograph that served Australian practitioners for many years, and has evolved across many editions and updates since. It has been reformatted into an online resource and revised to reflect the changing nature of HIV care, with a stronger focus on care delivered in primary and general hospital settings. Some sections were updated before 2024 and may contain language or recommendations that no longer align with current clinical evidence. Readers should refer to other more up to date guidelines for the latest clinical information on HIV in Australia.

The Guide reflects the work of many authors who have generously contributed their time and expertise across successive editions over many years. We gratefully acknowledge their ongoing contribution to this resource.

About ASHM

ASHM is a professional, not-for-profit, member-based organisation. It supports its members, sector partners and collaborators to generate knowledge and action in clinical management and research, education, policy and advocacy in Australasia and internationally.

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The virtual elimination of HIV, viral hepatitis, other BBVs and significant reduction of sexually transmissible infections

Our Mission

To provide leadership in the field of HIV, viral hepatitis, other BBVs and sexually transmissible infections through collaboration, facilitation, direct action, and workforce capacity building

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ASHM develops a comprehensive range of practical resources to support the HIV, viral hepatitis and STI workforce, as well as a series of profession-based booklets for groups most in contact with BBVs and STIs. The resources focus on prevention, diagnosis, management and treatment and are available in printed and/or online formats.

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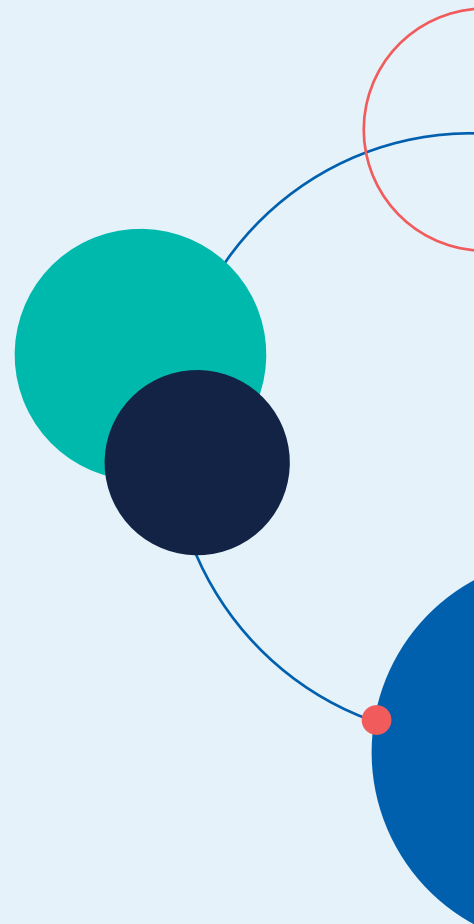
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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Contents

Acknowledgements	12
Glossary of terms.....	13
A word from the editors of the HIV Management Guide for Clinical Care.....	19
1. Epidemiology & Natural History	21
Epidemiology of HIV infection in Australasia.....	22
HIV surveillance in Australia	22
History of HIV infection in Australia	23
HIV infection in Australia in the last 5 years	24
Key populations in the Australian HIV epidemic.....	26
Summary	28
References	29
Natural history of HIV infection.....	32
Sexual transmission of HIV.....	32
Mother-to-child transmission of HIV infection.....	35
HIV transmission by other bodily fluids.....	36
Disease progression.....	36
Host and viral factors affecting disease progression.....	39
HIV superinfection and recombinant HIV viruses	42
References	44
2. Virology & Immunology	49
Basic HIV virology.....	50
Introduction	50
The taxonomy of HIV and primate immunodeficiency viruses	50
HIV structure and organisation.....	51
HIV life cycle	53
HIV transmission and biomedical prevention	57
Challenges in achieving a HIV cure	58
References	62
HIV immunology.....	69
Immunological aspects of HIV pathophysiology	79
Immunological control of HIV infection in specific patient groups	88
Escape of HIV from host immune responses.....	90
Immune activation in the pathogenesis of HIV disease.....	91
Eradication of HIV cellular reservoirs and HIV cure	95
References	98
3. Diagnostic & Monitoring Tests.....	104
Virological tests	105
Virological tests for diagnosing and monitoring HIV infection.....	105
HIV antibody and antigen testing	105
HIV quantification	111
HIV tissue culture.....	114
Antiretroviral drug resistance testing.....	114
Antiretroviral drug resistance genotyping.....	115
Genotypic determination of HIV-1 CCR5/CXCR4 tropism.....	118
HLA-B*57:01 allele genotyping for assessing the risk of abacavir hypersensitivity reaction.	119
References	121
Immunological tests used to monitor HIV infection and disease	123
Introduction.....	123
Routine monitoring of blood lymphocyte subpopulations in people with HIV infection	124
Assessment of HIV-specific T cells.....	125
References	126

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

4. Primary HIV Infection 127

Primary HIV Infection.....	128
Introduction.....	128
Pathogenesis of primary HIV infection.....	128
Clinical manifestations of primary HIV infection.....	130
HIV rapid testing.....	131
Antiretroviral drug resistance testing in primary HIV infection.....	132
Management of primary HIV infection.....	132
Conclusion.....	133
References.....	134

5. HIV-infectious Disease & Cancer 137

Respiratory tract infections in patients with HIV infection.....	138
Introduction.....	138
General approach to the assessment of respiratory tract infections.....	139
Sinusitis.....	144
Bacterial pneumonia.....	145
References.....	157
Mycobacterium tuberculosis infection in people with HIV infection.....	164
Introduction.....	164
HIV/TB co-infection.....	165
Diagnosis.....	166
Management of active tuberculosis.....	169
TB-associated immune reconstitution inflammatory syndrome.....	173
Treatment delivery and monitoring.....	174
Treatment of latent tuberculosis infection (preventive treatment).....	175
References.....	177
Non-tuberculous mycobacterial infections in people with HIV infection.....	180
Introduction.....	180
Other non-tuberculous mycobacteria.....	184
References.....	185
Gastrointestinal disease in people with HIV infection.....	187
General approach to the assessment of gastrointestinal symptoms in HIV patients.....	187
Specific gastrointestinal disorders associated with HIV infection.....	189
References.....	192
Ocular disease in patients with HIV infection.....	193
Introduction.....	193
HIV-associated disease of the anterior segment.....	195
HIV-associated disease of the posterior segment.....	198
Other infections and tumours.....	206
References.....	207
Opportunistic infections acquired in localised geographical regions of the world.....	208
Introduction.....	208
Endemic fungal infections.....	209
Endemic parasitic infections.....	212
Other opportunistic infections.....	214
References.....	216
Human papillomavirus infection and associated malignancies in HIV-infected people.....	219
Introduction.....	219
Cervical cancer.....	219
Anal cancer.....	222
Oropharyngeal cancer.....	224
Vulval cancer.....	225
Vaginal cancer.....	226
Penile cancer.....	226
The role of vaccination in preventing HPV-associated malignancies.....	227
References.....	228
Dermatological Conditions.....	234

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Introduction	234
Clinical History Taking and Physical Examination.....	234
Viral infections.....	235
Herpes simplex virus.....	235
Varicella zoster virus	236
Cytomegalovirus and Epstein-Bar Virus.....	238
Human papilloma virus (warts).....	239
Molluscum contagiosum	240
Mpox.....	241
Fungal infections.....	242
Candida infections.....	242
Malassezia infections	243
Cryptococcosis.....	243
Parasitic infections	244
Non-infectious disease	245
Xerosis	245
Psoriasis	246
Pityriasis rubra pilaris.....	247
Eosinophilic folliculitis, pruritic papular eruption and other inflammatory folliculitides	247
Serious adverse drug eruptions including Stevens - Johnson syndrome and toxic epidermal necrolysis	248
Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).....	249
References	250

HIV-related opportunistic infections (OI) in the central nervous system (CNS)..... 257

Introduction.....	257
Cryptococcal meningitis/ meningoencephalitis.....	257
Progressive multifocal leukoencephalopathy	260
References	262

6. Other HIV-Associated Disease 263

Haematological disorders in people with HIV infection 264

Introduction.....	264
Anaemia.....	264
Thrombocytopenia and immune thrombocytopenic purpura.....	265
Neutropenia, pancytopenia and myelodysplasia.....	265
Paraproteinaemia	266
Thromboembolic disease	266
Investigations	266
References	267

Heart disease in HIV infection 268

Introduction.....	268
Pulmonary hypertension	268
Pericardial effusion and cardiomyopathy.....	269
Cardiac malignancy.....	269
Infective endocarditis.....	269
Cardiac arrhythmias	270
References	271

Rheumatological disease in patients with HIV infection..... 272

Introduction.....	272
Myalgia and arthralgia	273
Arthritis	273
Avascular necrosis of bone.....	275
Diffuse infiltrative lymphocytosis syndrome	275
Vasculitis	275
Systemic lupus erythematosus	276
Bacterial Infections of joints and connective tissue	276
Myopathy.....	277
References	278

Neurological Disease 280

Approach to neurological symptoms.....	280
--	-----

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Neurological disorders in HIV infection.....	282
HIV associated central nervous system diseases	283
HIV-associated CNS opportunistic infections.....	287
Primary CNS Lymphoma (PCNSL)	289
HIV-associated spinal cord diseases.....	289
HIV associated transverse myelitis (TM)	289
Vacuolar myelopathy (VM)	290
HIV-associated diseases of the peripheral nervous system	291
Acute and chronic inflammatory demyelinating polyneuropathy	293
Mononeuritis multiplex	293
References	294

Pulmonary Disease: Including Sarcoidosis and COPD..... 298

Introduction - HIV and Lung	298
HIV and COPD	299
HIV related effects on COPD	302
Sarcoidosis.....	302
Other pulmonary conditions	303
References	305

7. Co-infections..... 307

Sexually transmissible infections among people with HIV infection 308

Introduction.....	308
Neisseria gonorrhoeae and Chlamydia trachomatis infection	308
Lymphogranuloma venereum	309
Mycoplasma genitalium infection.....	311
Trichomonas vaginalis infection.....	311
Syphilis.....	312
Herpes simplex virus infection.....	315
Conclusions	317
References	318

Hepatitis C virus co-infection..... 324

Hepatitis C in the setting of HIV	325
Diagnosis.....	325
Staging of liver disease.....	327
Management.....	328
Summary	332

Hepatitis B virus co-infection..... 335

Introduction.....	335
Epidemiology and pathogenesis.....	335
Diagnosis.....	335
Disease progression.....	336
Management.....	338
Anti-HBV therapy.....	338
Conclusions	340
References	341

Hepatitis E virus infection 344

Introduction.....	344
Virology.....	344
Epidemiology and pathogenesis.....	344
Diagnosis.....	345
Clinical manifestations	346
Chronic HEV infection.....	346
Prevention of HEV infection.....	347
HEV vaccines.....	347
References	348

HTLV/HIV-1 Co-infection..... 350

References	351
------------------	-----

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

8. ARV Drugs & other Therapies..... 355

Antiretroviral drugs	356
Antiretroviral drug classes	356
Recommended regimens for treatment of HIV infection	357
Nucleoside and nucleotide reverse transcriptase inhibitors	357
Non-nucleoside reverse transcriptase inhibitors.....	360
HIV protease inhibitors	362
HIV integrase inhibitors	365
HIV entry inhibitors	367
New antiretroviral agents	368
Contraindicated antiretroviral drug regimens	369
References	370
Initiation of antiretroviral therapy in the treatment-naïve patient.....	372
When to start therapy in the individual with HIV.....	373
Which regimen to use in the individual with HIV infection	376
Antiretroviral treatment strategies.....	380
Antiretroviral treatment in specific clinical scenarios.....	381
References	394
Long-term management of antiretroviral therapy	399
Introduction.....	399
Routine monitoring of PWH receiving ART	400
Virological failure	402
Principles of managing antiretroviral drug resistance.....	403
Immunological failure: persistent CD4+ T cell deficiency.....	404
Principles of managing antiretroviral drug toxicity and drug-drug interactions	405
ART regimen simplification.....	406
Retention in Care.....	408
References	409
Immune reconstitution inflammatory syndrome and other immune reconstitution disorders	410
Introduction.....	410
Terminology and classification	410
IRIS definitions and diagnosis.....	411
Immunopathogenesis of an IRIS	411
Clinical presentation of an IRIS	412
General approach to the management of an IRIS.....	413
Prevention of an IRIS.....	414
Autoimmune disease and immune-mediated inflammatory disease in patients receiving ART	415
References	416
Drug-drug interactions in patients with HIV infection	418
Overview	418
Types of drug-drug interactions.....	418
Important drug-drug interactions to consider.....	420
Adverse reactions to antiretroviral and other drugs in people with HIV infection.....	423
Introduction.....	423
Non-immune mediated adverse drug reactions.....	423
Immune-mediated drug hypersensitivity reactions	424
Pathogenesis of antiretroviral drug hypersensitivity reactions.....	426
Abacavir hypersensitivity syndrome	427
Nevirapine hypersensitivity reactions	428
Raltegravir hypersensitivity reactions.....	428
Approach to assessing antiretroviral drug hypersensitivity	429
Tables and Figures	430
References	433
Vaccines in people with HIV infection.....	437
Introduction.....	437
Diphtheria, tetanus and pertussis vaccine.....	437
Hepatitis B virus vaccine	437
Hepatitis A virus vaccine	438

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Human papilloma virus vaccine.....	438
Influenza virus vaccine	439
Measles, mumps, rubella (MMR) vaccine.....	439
Meningococcal vaccines.....	440
Pneumococcal vaccines	440
Vaccination recommendations for children with HIV infection.....	441
Varicella zoster virus vaccines	442
VACCINE REFERENCES.....	443

9. Co-Morbidities..... 447

Atherosclerotic vascular disease in people with HIV infection 448

Introduction.....	448
Pathogenesis of cardiovascular disease in people with HIV infection.....	448
Inflammation and immune activation as a cause of atherosclerosis in HIV infection	451
Impact of co-infections on cardiovascular disease risk	451
Coronary artery disease outcomes.....	452
References	453

Endocrine disorders in people with HIV infection 456

Introduction.....	456
Diabetes mellitus	456
Thyroid disease	460
Adrenal disease.....	460
Disorders of calcium metabolism and osteoporosis	461
Sex steroids.....	462
Obesity	463
References	464

Bone disease in patients with HIV infection..... 467

Introduction.....	467
Osteoporosis.....	467
Management of osteoporosis.....	471
Osteomalacia.....	472
Osteonecrosis.....	472
Bone Disease in other groups	473
References	475

Renal disorders in people with HIV infection 478

Introduction.....	478
Epidemiology of renal disease in HIV-infected people.....	478
Risk factors for renal disease in HIV-infected people.....	479
Detection of renal disease.....	480
Management of abnormal screening tests	481
HIV-related renal disease	483
Antiretroviral therapy and renal disease.....	484
Treatment of renal disease in people with HIV infection	487
Dialysis and renal transplantation	487
Summary: renal disease in HIV-infected patients	488
References	489

10. Special Patient Populations 491

Ageing with HIV infection..... 492

Introduction.....	492
Optimising ART in the older HIV patient.....	493
Disease and disease-related disability from non-AIDS co-morbidities	495
Renal function and ageing	496
Malignancy in older people with HIV infection.....	498
Liver function and ageing in people with HIV infection	498
Cardiovascular disease and associated risk factors.....	500
Neurocognitive impairment in the older person with HIV infection.....	500
Sexual function and sexuality.....	502
Mental health and psychosocial functioning	504

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

The Geriatric Syndromes: Frailty, Multimorbidity and Polypharmacy	505
End-of-life care	510
References	511
Psychiatric disorders in people with HIV infection	517
Introduction	517
Depression	519
Anxiety	521
Mania	521
Cognitive disorders	522
Substance abuse disorders	524
Psychotic disorders	524
Principles of pharmacotherapy for mental illness in people with HIV infection	525
References	526
HIV infection in adolescents transitioning to adult care	528
Introduction	528
Disclosure of HIV infection	528
Antiretroviral therapy in adolescents	528
Psychosocial support	529
Developing health independence	529
Transition to adult HIV services	530
Adolescents with horizontally-acquired HIV infection	530
References	531
HIV infection in Aboriginal and Torres Strait Islander people	532
Introduction	532
References	534
Pregnancy and reproductive health in women with HIV infection	535
HIV testing in pregnancy – a priority	536
Conception counselling	536
Contraception	537
Prevention of mother-to-child transmission	539
Principles of antiretroviral use in pregnancy	541
Recommendations for the use of antiretroviral drugs in pregnancy	542
Special issues when using antiretroviral therapy in pregnancy	544
Specific drug safety issues in pregnancy	546
Preterm delivery	548
Monitoring of HIV-infected women during pregnancy	548
Diagnostic tests in pregnancy	549
Paediatric referral	549
Reproductive options for HIV seroconcordant and serodiscordant couples	549
Case studies	550
Resources	551
References	552
11. Nurses & Midwives	555
New HIV Diagnosis	556
Introduction	556
Engagement	557
Ensuring engagement and a person-centred approach	558
Contact tracing	561
References	562
Late presentation of new HIV diagnosis	563
Introduction and definitions	563
The importance of early diagnosis and linkage to care	563
Barriers to testing and reasons for late diagnoses	564
Nursing implications of late diagnosis – severe disease, treatment and prevention of opportunistic illnesses	564
Late presenters and the risk of immune reconstitution inflammatory syndrome	566
References	567
Partner notification and contact tracing	568
What is partner notification?	568

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Why is partner notification important?	568
What is the meaning of 'index case'?	569
Methods of partner notification	570
Patient referral: how does this work in the clinical setting?	570
Provider referral: how does this work in the clinical setting?	570
Conditional referral	571
Partner Notification Officers and Contact Tracers: who are they and what qualifications do they have?	571
Conclusion	571
References	572
Key Affected Populations	573
Introduction	573
First Nations people	574
Health Service Considerations	574
Nursing Considerations	575
Asylum seekers and refugees	576
Other migrants and international students	577
Privacy and confidentiality	577
Nursing considerations	577
Men who have sex with men	578
People who inject substances	578
Nursing considerations	579
Women with HIV	579
People experiencing homelessness	579
Violence and key populations	580
Nursing and midwifery strategies for working with key populations: summary	580
Self-care for nurses and midwives caring for key populations	581
Summary	581
References	583
Pregnancy and midwifery considerations in HIV	586
Introduction and global overview	586
Preconception	587
Pre-natal Period	587
Emotional care and support during pregnancy	587
Birth	588
Mode of feeding	588
Care of the infant in the first 18 months of life	589
PEP for the infant	590
Infant testing	590
Multidisciplinary care	590
Education and stigma reduction	591
Useful resources	592
References	593
Considerations In the Nursing care of Children and Young People living with HIV	594
Introduction	594
What's different between children and adults LWHIV?	594
Keeping well: growing children into healthy adults	595
Treatment challenges in children	595
Pill swallowing	595
Psychosocial context and considerations	596
Transition to adult care	596
Sharing of HIV status and health information	596
Useful resources	598
References	599
Client education	600
Educational strategies	600
Client education for HIV prevention	600
Client education at the point of diagnosis	601
Ongoing client education	602
Other useful resources	602

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Sexuality and coming out.....	602
Building up relationships.....	603
Genital anatomy and variances.....	603
References.....	604
Nursing considerations of major clinical issues	605
Accelerated or accentuated ageing	605
Long-term survivors	606
Experiencing multiple losses and grief.....	606
Mental health and resilience.....	606
Multimorbidities	607
Advance care planning	608
Disability, respite, and long-term care.....	609
Resources and links	609
References.....	610
HIV associated neurocognitive disorder	612
Introduction	612
Background	612
Examples of dementia	613
HIV-associated neurocognitive disorder	614
Screening and diagnosis for HAND	614
Predictors of HAND.....	615
General (non-HAND) cognitive impairment risk factors.....	615
Signs and symptoms of HAND	615
Questions to ask PLHIV.....	618
Questions to ask their caregivers:	618
Treatment of HAND.....	618
Significance of early recognition of HAND	619
Impacts of cognitive impairment.....	620
What to do.....	620
Advice for caregivers.....	621
Conclusion	621
References.....	622
Adherence support.....	624
The importance of adherence to antiretroviral therapy	624
Factors affecting adherence and nursing interventions used to promote adherence.....	625
Conclusion and future directions.....	631
Additional resources	632
References.....	633
Health promotion	636
Health promotion in HIV nursing practice in Australia	637
Health promotion into the future in HIV nursing.....	639
Additional resources	639
References.....	640
Clinical supervision for nurses in the HIV sector	641
What is clinical supervision for?	641
Confidentiality.....	642
Why should nurses and midwives working in the HIV sector be provided with routine clinical supervision?.....	642
Remote and Indigenous communities	643
The impact of COVID-19.....	643
Conclusion	643
Resources.....	643
References.....	644
Biomedical HIV prevention.....	645
Introduction.....	645
Non-occupational postexposure prophylaxis (NPEP)	646
Time to first dose.....	649
Incomplete adherence	649
Continued risk.....	649
HIV pre-exposure prophylaxis (PrEP).....	650

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Nurses' roles in PrEP	651
Conclusion	652
References	653
Evolving roles of nurses in HIV care.....	655
National context.....	655
Principles.....	656
International context	657
Summary.....	658
Australasian HIV nursing organisations	658
References	659
Nursing ethics in the care of people with HIV	660
Introduction and background	660
What is the purpose of nursing ethics?.....	661
Stigmatisation and discrimination	662
Impact of HIV-related stigma and discrimination	663
Strategies for nurses to address discrimination	663
Disclosure of HIV status within health care and the 'right to know'	663
Confidentiality.....	664
Informed consent	664
Quality of life, advance care planning and end-of-life decision-making	665
Emerging issues and their ethical implications –Pre Exposure Prophylaxis.....	666
HIV and ethics – Case example.....	667
Conclusion	667
Resources.....	667
References	668
Nursing and HIV during the global COVID-19 pandemic and the emergence of Monkey pox (Mpox) infections.....	670
Introduction	670
Impact on Nursing and HIV Care throughout COVID-19.....	670
Integrating infection prevention and control (IPC) measures.....	671
Psychosocial Support and Patient Education.....	671
Conclusion	671
Resources.....	671
References	672
12. Biomedical prevention	673
Biomedical prevention of HIV infection	674
Background	674
HIV prevention strategies.....	675
Treatment as prevention	676
Post-exposure prophylaxis.....	678
Pre-exposure prophylaxis.....	682
Conclusions	686
References	687
Microbicides for the prevention of HIV infection	689
Burden of HIV infection in women globally and in Australia	690
Microbicides demonstrating efficacy in clinical trials	690
Oral PrEP in MSM.....	690
Oral PrEP in women.....	690
Long-acting injectables and implants.....	691
Multipurpose prevention technologies (MPTs).....	691
Classes of microbicides and mode of action.....	691
Biological factors that attenuate topical microbicide efficacy	695
References	696
PrEP clinical guidelines.....	700

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Acknowledgements

Editors: Martyn French and Elizabeth Crock

The editors would like to acknowledge the invaluable contribution of authors and reviewers to previous editions for sharing their knowledge and expertise.

Contributors to current edition:

Adam Jenney	Deborah Mariott	John McAllister	Phillip Du Cros
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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Glossary of terms

Abbreviation	Denotation
µL	microlitre
3TC	lamivudine
Ab	antibody
ABC	abacavir
ABMT	autologous bone marrow transplantation
ACIP	CDC Advisory Committee on Immunization Practices, USA
ACTH	adrenocorticotrophin hormone
ADCC	antibody-dependent cellular cytotoxicity
AFAO	Australian Federation of AIDS Organisations
Ag	antigen
AIDS	Acquired immune deficiency syndrome
AI	AIDS-defining illness
ALT	alanine aminotransferase or alanine transaminase
Anti-HBc	antibody to hepatitis B core antigen
Anti-HBe	antibody to hepatitis B e antigen
Anti-HBs	antibody to hepatitis B surface antigen
ART	antiretroviral therapy
ARVS	acute retroviral syndrome
ASHM	Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine
AST	aspartate aminotransferase
ATV	atazanavir
AUC	area under the curve
AZT	zidovudine or azidothymidine or ZDV
B cell	a type of immune cell
bd	twice daily (latin: bis die)
bdNA	branched deoxyribonucleic acid
BMD	bone mineral density
CAF	cell-associated factor
cART	combination antiretroviral therapy
CHOP	chemotherapy (cyclophosphanud, doxorubicin, vincristine, prednisolone)
CCR5	chemokine coreceptor on the surface of cells
CD4	cell a helper T-cell which carries the CD4 surface antigen. CD4 cells are the primary target of HIV and CD4 cell numbers decline during HIV disease.
CD8	cell a killer or cytotoxic T-cell which carries the CD8 surface antigen.
CDC	Centers for Disease Control and Prevention, USA
CI	confidence interval
CIN	cervical intraepithelial neoplasia
CMV	cytomegalovirus
CNS	central nervous system
CPE	CNS penetration-effectiveness
CRF	circulating recombinant form
CSF	cerebrospinal fluid

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

CT	computed tomography
CTL	cytotoxic T lymphocyte
CVD	cardiovascular disease
CXCR4	chemokine receptor
d4T	stavudine
DAD	Data Collection on Adverse events of Anti-HIV Drugs
DC	dendritic cell
DC-SIGN	dendritic cell-specific ICAM-3-grabbing non-integrin
ddC	zalcitabine
ddI	didanosine
DEXA	dual-energy X-ray absorptiometry
DHHS	US Department of Health and Human Services
DILS	diff use infiltrative lymphocytosis syndrome
DLV	delavirdine
DM	diabetes mellitus
DN	double negative
DNA	deoxyribonucleic acid
DOT	directly observed therapy
DRV	darunavir
EBV	Epstein Barr virus
EC	elite controllers
EFV	efavirenz
EIA	enzyme immunosorbent assay
ELISA	enzyme-linked immunosorbent assay
ELISPOT	enzyme-linked immunospot assay
ENF	enfuvirtide
ERCP	endoscopic retrograde cholangiography
ETV	etravirine
EVG	elvitegravir
FasL	Fas ligand
FBC	full blood count
FDA	Food and Drug Administration USA
FPV	fosamprenavir
FTA-Abs	fluorescent treponemal antibody absorption test
FTC	emtricitabine
GBV-C	flavivirus GB virus-C
GCSF	granulocyte colony stimulating factor
GH	growth hormone
GHRH	growth hormone-releasing hormone
GI	gastrointestinal
GORD	gastro-oesophageal reflux disease
gp120	glycoprotein on surface of HIV which binds to the CD4 receptor
gp41	glycoprotein on the surface of HIV involved in fusion between HIV and the CD4 cell

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

HAART	highly active antiretroviral therapy (see cART, now preferred terminology)
HAD	HIV-1-associated dementia
HAND	HIV-associated neurocognitive disorders
HAV	hepatitis A virus
HBsAG	hepatitis B surface antigen
HBeAG	hepatitis B envelope antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HD	Hodgkin's disease
HDL	high-density lipoprotein
HEPS	highly exposed but persistently seronegative
HHV8	human herpesvirus type 8
HIV	human immunodeficiency virus
HIV-1	human immunodeficiency virus-1
HIV-2	human immunodeficiency virus-2
HIVAN	HIV- associated nephropathy
HLA	human leukocyte antigens
HPLC	high-performance liquid chromatography
HPV	human papilloma virus
HSV	herpes simplex virus
HZ	herpes zoster
IDSA	Infectious Diseases Society of America
IDU	injecting drug use
IDV	indinavir
IFN	interferon
Ig	immunoglobulin
IL	interleukin
IM	intramuscularly
INR	international normalised ratio (a test of blood clotting)
IRD	immune restoration disease
ISR	injection site reactions
ITP	immune thrombocytopenic purpura
IU	international unit (measurement)
IV	intravenous
JCV	John Cunningham virus
KGF	keratin growth factor
KOH	potassium hydroxide
KS	Kaposi's sarcoma
LDL	low-density lipoprotein
LFT	liver function test
LN	lymph node
LP	lumbar puncture

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

LPS	lipopolysaccharide
LPV	lopinavir
LPV/r	lopinavir/ritonavir
LTNP	long-term non-progressors
LTR	long-terminal repeat
MAC	Mycobacterium avium complex
MACS	Multicenter AIDS Cohort Study
mDC	myeloid dendritic cells
MDMA	Methylenedioxy-methamphetamine (Ecstasy)
MDR	multidrug resistance
MHC	major histocompatibility complex
MIC	minimum inhibitory concentration
MIP	macrophage inflammatory proteins
mL	millilitre
mmol	millimole
MND	mild neurocognitive disorder
MRI	magnetic resonance image
MRS	magnetic resonance spectroscopy
MRSA	methicillin-resistant Staphylococcus aureus
MSM	men who have sex with men
MTCT	mother-to-child transmission
MF	macrophages
NAA	nucleic acid amplification
NAM	nucleoside analogue mutation
NF	nuclear factor
NFV	nelfinavir
NHL	non-Hodgkin's lymphoma
NNRTI	non-nucleoside reverse transcriptase inhibitor
NPEP	non-occupational post-exposure prophylaxis
NRTI	nucleoside reverse transcriptase inhibitors (NRTI)
NSI	non-syncytium inducing
NVP	nevirapine
OC	oesophageal candidiasis
OHL	oral hairy leukoplakia
OI	opportunistic infection
ORF	open reading frame
p24	a core HIV protein, the primary protein detected by the HIV antigen test
PBMC	peripheral blood mononuclear cells
PBS	Pharmaceutical benefits Scheme
PCNSL	primary central nervous system lymphoma
PCR	polymerase chain reaction
PD	programmed death
PEP	post-exposure prophylaxis

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

pg/mL	picogram per millilitre
PI	protease inhibitors
PI/r	protease inhibitors boosted by ritonavir
PJP	Pneumocystis jirovecii pneumonia previously Pneumocystis carinii
PK	pharmacokinetic
PLA	poly-L-lactic acid
PML	progressive multifocal leucoencephalopathy
PNG	Papua New Guinea
PPAR	peroxisome proliferator-activated receptor
PTH	parathyroid hormone
qd	every day (latin: quaque die)
qds	to be taken four times a day (Latin: quater die sumendum)
RAL	raltegravir
RANTES	regulated on activation normal T cell expressed and secreted
RNA	ribonucleic acid
RPR	rapid plasmin reagin
RT	reverse transcriptase
RT-PCR	reverse transcriptase polymerase chain reaction
RTV	ritonavir
SAS	Special Access Scheme
SAT	subcutaneous adipose tissue
SDF	stromal cell-derived factor
s100	a section of the Pharmaceutical Benefits Scheme which provides access to highly specialised drugs
SI	syncytium inducing
SIL	squamous intraepithelial lesions
SIV	Simian Immunodeficiency Virus
SMART	Strategies for Management of Antiretroviral Therapy study
SN	sensory neuropathy
SP	single positive
SQV	saquinavir
SSRI	selective serotonin reuptake inhibitor
STI	sexually transmitted or transmissible infection
SVR	sustained virological response
T-20	enfuvirtide
TAMs	thymidine analogue mutations
TB	tuberculosis
T cell	type of lymphocyte
TcR	T cell receptors
td	three times daily (Latin: ter die)
tds	to be taken three times a day (Latin: ter die sumendum)
TDF	tenofovir disoproxil fumarate or tenofovir
TDM	therapeutic drug monitoring
TEN	toxic epidermal necrolysis

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

TGA	Therapeutic Drugs Administration
Th1	type 1 helper lymphocytes
Th2	type 2 lymphocytes
TLR	toll like receptors
TNF	tumour necrosis factor
TP-PA	Treponema pallidum particle agglutination
TPV	tipranavir
TREC	T-cell receptor excision circles
Treg	specialised regulatory T cells
TRIM5alpha	human tripartite motif 5 alpha
TSG	tumor suppressor gene
TSLP	thymic stromal lymphopoetin
TST	tuberculin skin test
UNAIDS	The Joint United Nations Program on HIV/AIDS
USA	United States of America
UTR	untranslated region
VAT	visceral adipose tissue
VL	viral load
VLDL	very low density lipoprotein
VM	vacuolar myelopathy
VRE	vancomycin-resistant Enterococcus
VZV	varicella zoster virus
ZDV	zidovudine

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

A word from the editors of the HIV Management Guide for Clinical Care

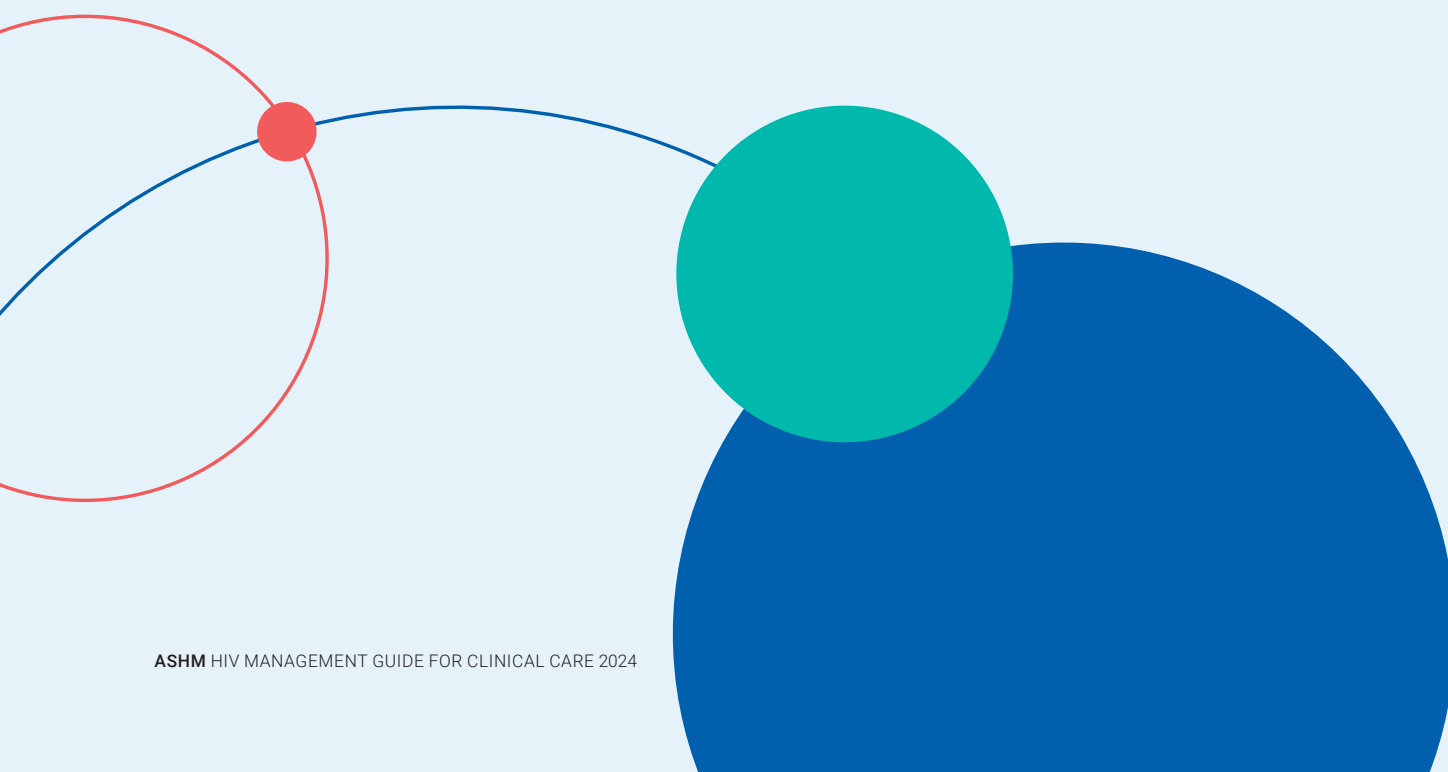
The ASHM HIV Management in Australia website is a reformatting of the 'Green Monograph' and the on-line version of that publication, which have served Australian health practitioners so well over many years. Australia has always had a very dedicated, knowledgeable and productive HIV Medicine workforce and it is important that the knowledge and expertise is made available to those entering the workforce in the future.

The primary aim of the new website is to assist in the education, training and day-to-day practice of health practitioners involved in assessing and managing people with HIV infection in Australia and neighbouring countries. Given the changing face of HIV Medicine over the last decade, the content of the new website has been revised and updated to put more of a focus on primary health care and non-specialist hospital care. It is intended for it to be a 'living resource' with regular updates of content, if needed. Ownership by, and feedback from, Australian healthcare practitioners delivering services to people with HIV infection is expected and encouraged.

I am extremely grateful to the many contributors who have voluntarily given their time to provide content for the website.

Martyn French, honorary editor, 5/11/2019

Emeritus Professor, UWA Medical School and School of Biomedical Sciences



CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

The nursing and midwifery section of ASHM's HIV Management in Australia – a guide for clinical care, was published for the first time in 2016, when Levinia Crooks, ASHM's CEO at the time, recognised the importance and benefits of including the voices and perspectives of nurses and midwives within the guide and invited me to coordinate its development. The section was revised in 2019 and has now been updated in 2024.

In this section, expert HIV, sexual health, and public health nurses from around Australia present a nursing and midwifery perspective on caring for people with human immunodeficiency virus (HIV) infection in the Australian context.

Each section provides a summary of a topic, expands on key principles and provides a guide for practice, drawing from current research evidence. There are cross-references to other nursing and/or medical sections of the guide where relevant. This section is unique in its focus on nursing, and nurses' and midwives' roles in caring for people with HIV from diverse backgrounds from point of diagnosis to end-of-life, and with HIV-related conditions and complications. It addresses nurses' and midwives' roles in HIV education, prevention, and health promotion. Nursing ethics, cultural safety, and the importance of professional supervision for those working in the HIV sector and with members of key affected populations are critically discussed. This edition includes a new section on Mpox and COVID-19. The authors include links to clinical resources and to nursing, midwifery, and peer-based organisations.

We hope that this resource will be a fundamental guide for nurses and midwives working in the HIV, sexual health, and blood-borne virus sector, across all settings. It will also be useful for those working in other areas of nursing and midwifery who may simply wish to access a particular topic, and for nursing, midwifery, and healthcare students. This is a living resource, so we expect and encourage feedback from the sector to enable regular revision.

Where new authors have updated topics, we acknowledge previous authors and contributors. Geraldine Dunne kindly revised and updated the midwifery and paediatric sections, following the death of our colleague, much respected nurse and midwife author Karen Blyth. Daniel Sankar wrote the new section on MPox and COVID-19 in the context of HIV. Cherie Bennett updated the sections on New diagnosis and Biomedical prevention originally written by John McAllister, who retired after a lifelong HIV nursing career. Karyn Gellie updated the section on Health promotion when previous authors were unavailable.

I would like to express my heartfelt thanks to the nurse and midwife authors. I thank those who provided additional peer review – Judy Frecker, Karyn Gellie, and Denise Cummins. All were generous with their time and expertise to contribute to the HIV Management Guide for Clinical Care – Nurses and Midwives 2024 edition.

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1. Epidemiology & Natural History

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Epidemiology of HIV infection in Australasia

HIV surveillance in Australia

Skye McGregor

Kirby Institute

Last reviewed: March 2019

In Australia, the epidemiology of human immunodeficiency virus (HIV) infection is monitored through a range of public health surveillance systems including case reporting, behavioural and biological surveys, and clinical data collection.

Case Reporting

Case reporting involves reporting of newly diagnosed HIV infection by state and territory health authorities to the Kirby Institute.(1), (2) The notification includes a number of demographic and clinical characteristics, including sex, date of birth, date of diagnosis, CD4+ T cell count at diagnosis, source of exposure to HIV, and clinical evidence of newly acquired infection.(3) More recently, information has also been collected on country of birth, year of arrival in Australia, and language spoken at home. Exposure risk is based on self-reported information, and includes sexual exposure, history of injecting drug use, and the receipt of blood products or tissue. The exposure data are used to classify people into the following exposure categories, using a risk hierarchy: men who have sex with men; men who have sex with men and injecting drug use; injecting drug use; heterosexual contact; haemophilia/coagulation disorder; receipt of blood/tissue; mother with/at risk of HIV infection; and health care setting.(4) Case-reporting of HIV infection in Australia also routinely distinguishes recently acquired HIV infections by collecting any available information on prior HIV testing or symptoms

characteristic of primary HIV infection (sometimes referred to as seroconversion illness) in the person diagnosed. Newly acquired HIV infection is defined as a newly diagnosed HIV infection with a negative or indeterminate HIV antibody test result in the last 12 months, or a diagnosis of primary HIV infection within 1 year of HIV diagnosis. Primary HIV infection is the period immediately following infection with HIV, and before an immune response reduces an individual's HIV viral load. Symptoms of HIV infection usually present about 10 days after infection, and include a rash, myalgia, pharyngitis and headaches.(5)

Morbidity associated with HIV infection is also monitored. If HIV infection is untreated, it usually progresses to acquired immune deficiency syndrome (AIDS) 8 to 10 years after initial diagnosis.(6) In Australia, AIDS is defined as a definitive diagnosis of HIV infection and evidence of a defined opportunistic infection or clinical condition as outlined in Clinical Manifestations of HIV Disease.(7) Due to high treatment coverage in Australia, in recent years the focus has shifted from reporting AIDS and AIDS-related deaths, to monitoring late and advanced diagnoses. A late diagnosis is indicated by a CD4+ T cell count < 350/μL and suggests HIV infection was acquired around 4-5 years earlier, with a mean decline in CD4+ T cell count per year of around 50-100/μL.(8) Advanced HIV infection is considered to be present when the CD4+ T cell count falls below 200/μL, and the person is vulnerable to opportunistic infections characteristic of AIDS. Timely diagnosis of HIV infection can reduce an individual's risk of morbidity and mortality, and has public health benefits by providing opportunities to reduce onward transmission, through mitigation of risk-behaviours or commencing treatment to reduce infectivity.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Other surveillance systems

Routine case reporting is supplemented by enhanced surveillance activities in Australia, including a network of sentinel surveillance sites and biological and behavioural surveys. The network of sentinel surveillance sites (called ACCESS) includes sexual health clinics, primary health care clinics, Aboriginal Medical Services and laboratories, and provides information on routine HIV testing and positivity. Repeat surveys provide valuable information on trends over time in risk behaviours and infection. In high-risk populations these surveys include the Gay Community Periodic Survey (9) and the Australian Needle and Syringe Program Survey.(10) Surveys in the general population include the Australian Study of Health and Relationships (11) and the National Survey of Secondary Students and Sexual Health.(12)

History of HIV infection in Australia

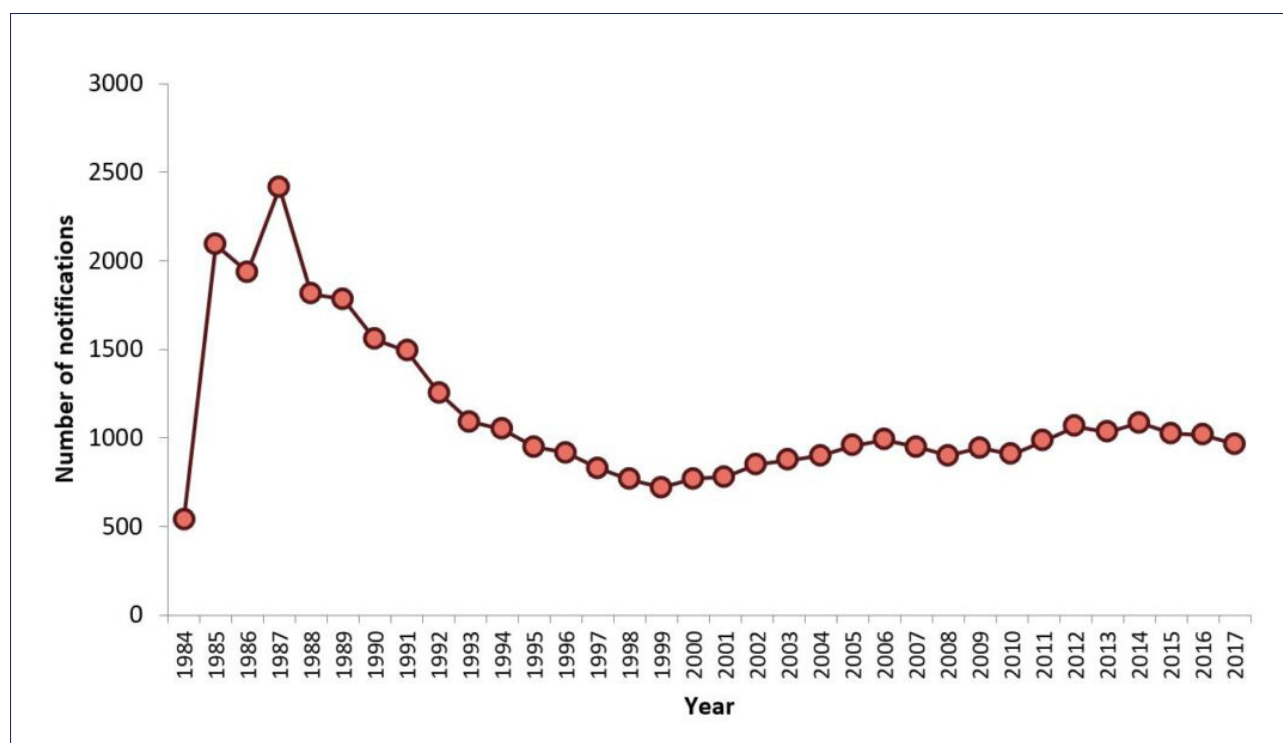
The first AIDS diagnosis in Australia was in 1982,(13) and following the introduction of HIV testing in 1985, cases of newly diagnosed HIV infection peaked at 2,773 in 1987 declining to their lowest level in 1999 (Figure 1).(14) Studies using the back-projection method have estimated that HIV incidence was highest in 1984 (2,890 cases) with a rapid decline in the latter part of the decade.(15) The decline in incidence has been largely attributed to the rapid adoption of HIV prevention practices, including safe sex, and world leading needle and syringe programs.(16);(17)

Early diagnoses in Australia were characterised by low levels of heterosexual transmission and transmission among people who inject drugs, with most cases diagnosed among men with a history of male-to-male sex (86%).(18)(19) Of the 16,765 newly diagnosed cases of HIV infection between 1984 and 1992, the majority were reported in New South Wales (67%). The contribution of diagnoses due to receipt of blood, blood products, tissue or treatment of haemophilia declined rapidly from 14% in 1985-1986 to 1% in 1991-1992. (20) There has been an average of one mother-child HIV transmission per year over the last 10 years. (21) Reflecting the approximately 10-year period from HIV infection to development of AIDS, AIDS diagnoses peaked in Australia at 909 in 1994.(22) The first antiretroviral drugs for HIV infection became available in Australia in 1987 and were initially used as monotherapy then as dual therapy from 1992,(23) leading to a continuing decline in AIDS and AIDS-related deaths. By the end of 2009 there had been 10,446 diagnoses of AIDS and 6,776 deaths following AIDS.(24)

Between 1999 and 2012 HIV diagnoses in Australia increased by 48%, likely attributed to increases in risk behaviour and confidence in HIV therapies.(25)(26) However, in the 5 years from 2013 to 2017, HIV diagnoses in Australia have decreased by 7%.¹ This decrease has been alongside increases in testing, high treatment coverage, and an increased use of pre-exposure prophylaxis (PrEP).¹

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Figure 1. Newly diagnosed HIV infection in Australia by year



HIV infection in Australia in the last 5 years

HIV infection in Australia is characterised by a concentrated epidemic, defined as a prevalence of greater than 5% in subpopulations. The prevalence of HIV infection has remained low in the general population, and was estimated to be 0.1% in 2017.⁽¹⁾ This rate is comparable with New Zealand and the Philippines, but lower than other countries in the region, including Thailand (0.1-10%), Papua New Guinea (0.90%) and Cambodia (0.50%)⁽¹⁾ To the end of 2017, a total of 38,172 cases of HIV infection had been diagnosed in Australia **(Figure 1)**, with an estimated 27,545 (24,141 – 31,126) people living with HIV in 2013.⁽¹⁾

Over the last 5 years, the annual number of cases of newly diagnosed HIV infection has decreased by 7%, dropping below 1000 annual notifications in 2017: (Table 1, Figure 1), with the majority of diagnoses in males (90%).⁽³²⁾ The last 5 years have seen a continued increase in diagnoses from 1,069 in 2009 to 1,236 in 2013.⁽³³⁾ Alongside behaviour changes, the frequency of HIV testing has increased in many settings in the past 5 years, and increased testing can lead to increased diagnoses.⁽³⁴⁾ The median age of diagnosis for males has remained steady at around 37 years. Women have been diagnosed at a slightly younger age, with a median age at diagnosis of 33 years. Over a third (39%) of diagnoses have been classified as late and 19% as advanced. Of all new diagnoses in this period, 15% (840) were previously diagnosed overseas. There have been very few vertical HIV transmissions from mother to child, with five in the last 5 years (1.8% of perinatal exposures).⁽³⁵⁾⁽³⁶⁾

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

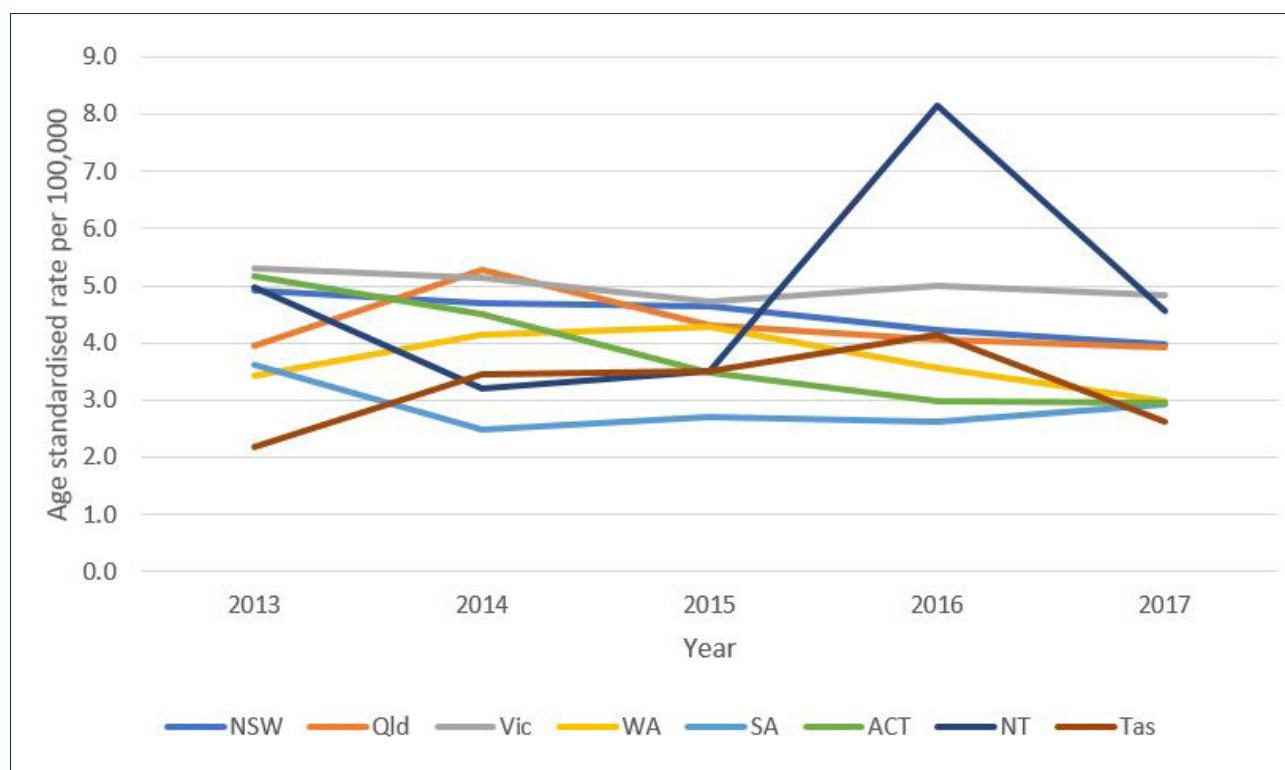
Table 1. Characteristics of cases of newly diagnosed HIV infection in Australia by year, 2013-2017(1)

Characteristic	Year of HIV diagnosis					
	2013	2014	2015	2016	2017	Total ¹
Total cases	1,032	1,084	1,026	1,013	963	5,118
Males (%)	89.5	90.2	89.3	90.1	87.9	89.6
Median age (years)						
Male	37	35	35	34	35	35
Female	34	35	36	34	34	34
Late and advanced HIV infection status at HIV diagnosis						
Late HIV diagnosis (%) ²	31.9	28.5	28.9	32.7	35.9	31.2
Advanced HIV diagnosis (%) ²	18.4	16.7	15.9	19.5	22.5	18.4
Median CD4+ T cell count (cells/ μ L)	420	440	440	420	390	430
State and Territory						
Australian Capital Territory	21	18	14	13	13	79
New South Wales	355	346	348	317	310	1,676
Northern Territory	13	9	9	23	11	65
Queensland	181	246	203	195	185	1,010
South Australia	58	39	44	42	45	228
Tasmania	11	16	16	19	11	73
Victoria	307	302	283	312	310	1,514
Western Australia	86	108	109	92	78	473
HIV exposure category (%)³						
Men who have sex with men	65.9	70.2	68.2	70.3	63.0	67.6
Men who have sex with men and injecting drug use	4.3	4.6	4.8	5.0	5.5	4.8
Injecting drug use ⁴	2.7	2.9	2.9	1.4	3.4	2.7
Heterosexual contact	21.0	18.5	20.0	20.6	24.7	20.9
Receipt of blood/tissue	0.3	0.0	0.8	0.1	0.0	0.2
Mother with/at risk of HIV infection	0.4	0.3	0.4	0.5	0.3	0.4
Other/undetermined	5.4	3.5	2.9	2.1	3.0	3.4

1. Not adjusted for multiple reporting.
2. Late HIV diagnosis was defined as newly diagnosed HIV infection with a CD4+ T cell count of less than 350/ μ L, and advanced HIV infection as newly diagnosed infection with a CD4+ T cell count of less than 200/ μ L.
3. The "Other/undetermined" exposure category was excluded from the calculation of the percentage of cases attributed to each HIV exposure category.
4. Excludes men who have sex with men

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Figure 2. Rates of newly diagnosed HIV infection, 2013-2017, by year and state and territory, Australia



Key populations in the Australian HIV epidemic

Men who have sex with men

Australia's epidemic has been characterised by transmission among men who have sex with men. Sexual transmission between men accounted for 68% of newly diagnosed HIV infection in Australia between 2013 and 2017, increasing to 82% of newly acquired infection.⁽⁶³⁾ The Gay Community Period Surveys found a self-reported HIV prevalence of 8% among men attached to the gay community.⁽⁶³⁾ Data from sentinel surveillance sites reported HIV incidence of 0.85 per 100 person-years in 2016.⁽⁶⁴⁾

The Gay Community Period Surveys shows that each year, about 60% of gay men report that their last HIV test was in the last year,⁽⁶⁵⁾ which is higher than many other countries. Despite this high testing rate, a quarter of HIV diagnoses in men who have sex with men are diagnosed late (25% in 2017)⁽⁶³⁾ and 9% of men who have sex with men were estimated to have undiagnosed HIV infection in 2017.⁽⁶³⁾ Results from the Gay Community Periodic Surveys show that 30% of HIVnegative gay and bisexual men engaged in anal intercourse (insertive or receptive) with casual partners in the past six months, and also reported not consistently using condoms or biomedical preventions with casual partners of unknown HIV or PrEP status.⁽⁶⁵⁾ This proportion has been stable in the last five years. In contrast, the number of men using biomedical prevention strategies, such as PrEP, has increased.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

People who inject drugs

Initial concern that transmissions among people who inject drugs would increase dramatically were unfounded,(47) and less than 3% of HIV diagnoses over the last 5 years have been attributed to injecting drug use. Over the last 20 years, HIV prevalence among people who inject drugs has remained very low, at around 1-2%.(48) Receptive syringe sharing is a major risk factor for HIV acquisition, and the Australian Needle and Syringe Program Survey reported a decline in the proportion of respondents reporting this behaviour in the 20 year period 1994 to 2014.(66) More recent results from the same study indicate that this proportion has remained stable in the last five years and was 24% in 2017.(67) The low rates of HIV transmission and prevalence among people who inject drugs reflect the early and successful implementation of prevention strategies, including needle and syringe programs, which were introduced in Australia in 1987.(51)

Female sex workers

Australia has consistently had extremely low rates of HIV infection in female sex workers.(52) with high condom use,(53) regular testing and other prevention strategies minimising transmission. HIV positivity among women self-identifying as female sex workers and attending sexual health clinics was 0.03% in 2010-2011 and 0% in 2012-2013.(54) A more recent analysis supports this ongoing low rate of HIV infection in this population, with an incidence rate of <0.1 reported for each year of the five year period 2013 to 2017.(63)

Heterosexuals

Notifications of HIV infection attributed to heterosexual contact have increased in recent years with 11% of notifications reporting heterosexual exposure in the period 1982 to 2004, increasing to 25% in the period 2013 to 2017. Of the 1,070 cases of newly diagnosed HIV infection attributed to heterosexual contact between 2013 and 2017, 32% were in people from high prevalence countries (> 1% of population with HIV infection) or with partners from high prevalence countries. The number of new HIV notifications in sub-Saharan African-born populations has been relatively stable in the 10 year period 2008 (15 notifications) to 2017 (11 notifications), compared to a 56% decrease among Asian-born populations.(63) In each of the five years 2013 to 2017, almost half of heterosexual diagnoses were classified as late, with 48% in 2017.(63) In 2013 about 20% (15-25%) of non-men who have sex with men living with HIV infection were estimated to have undiagnosed infection. In the most recent results from The Australian Study of Health and Relationships, inconsistent use of condoms during casual sex in the last 6 months among heterosexuals was reported by 49% of people who had vaginal sex. Over a third (37%) of respondents reported ever having been tested for HIV infection.(58) Surveys among migrants from sub-Saharan Africa and South East Asia report barriers to condom use, including difficulty in bringing up the topic with partners and condoms being unnatural.(59)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Aboriginal and Torres Strait Islander people

Of the 5,118 HIV diagnoses since 2013, 175 were in Aboriginal and Torres Strait Islander people, with the rate of diagnosis of HIV infection in 2017 being higher among Aboriginal and Torres Strait Islander people (4.6 per 100,000) than in Australian born non-Aboriginal and Torres Strait Islander people (2.8 per 100,000).⁽⁶³⁾ In the five year period 2013-2017, the reported exposure in Aboriginal and Torres Strait Islander people differed from that of Australian-born non-Indigenous cases, with a higher proportion attributed to heterosexual contact (21% versus 17%) and injecting drug use (18% versus 3%).⁽⁶¹⁾ Rates of other sexually transmissible infections are much higher in the Aboriginal and Torres Strait Islander population compared to the non-Indigenous population, with Chlamydia infection being three times higher and gonorrhoea seven times higher in 2017.⁽⁶³⁾ Aboriginal and Torres Strait Islander people remain a key population included in the Australian National HIV Strategy.

Summary

While the prevalence of HIV infection in Australia remains very low amongst the general population, and the concentration of the epidemic among men who have sex with men shows promising signs of decreasing, similar trends have not been seen across other vulnerable populations, including Aboriginal and Torres Strait Islander people and heterosexuals from migrant backgrounds.

The prevalence of HIV infection remains low among people who inject drugs and extremely low among sex workers, in contrast to other areas of the world. Risk of transmission through vertical exposure has remained minimal.

The proportion of cases diagnosed late has remained steady in recent years, with the highest proportion among cases of heterosexual transmission.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Natural history of HIV infection

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Last reviewed: November 2019

Introduction

People with HIV infection rarely traverse the full natural history of HIV disease in Australia because the great majority of them are now commenced on antiretroviral therapy (ART) shortly after diagnosis. However, knowledge of the natural history of HIV infection is important for understanding strategies for the prevention of HIV infection and disease.

Transmission of HIV infection

Human immunodeficiency virus (HIV) is transmitted following contact with infected bodily fluids. The typical routes of transmission are unprotected sex, blood-to-blood contact (including sharing injecting equipment and, much less commonly, needle-stick injuries and receipt of contaminated blood products) and vertical transmission (from mother to child before, during and after birth). Less common routes include tattooing, organ and tissue transplantation, artificial insemination and invasive medical procedures. The most common mode of HIV transmission is sexual transmission at the anogenital mucosa, accounting for 75-85% of cases worldwide. The probability of HIV transmission per episode of exposure varies (Figure 1). The risk of transmission per exposure may be influenced by factors such as co-existent genital ulcer disease, type of sexual act, vaginal flora, age, genetic factors and stage of HIV disease of the index case.⁽¹⁾ There is a particularly high risk of transmission from someone with acute HIV infection; it has been estimated that transmission from a person with acute HIV infection accounts for more than 34-50% of cases of newly-acquired HIV infection.⁽²⁾

Sexual transmission of HIV

There are four basic steps in the sexual transmission of HIV from one person to another:

- Contact with mucosal epithelium
- Uptake by dendritic cells (DCs)
- Transport to lymphoid tissues, such as lymph nodes and gut-associated lymphoid tissue
- Infection of CD4+ T cells in lymphoid tissues

Following mucosal contact, HIV breaches the mucosal barrier, most likely following microtrauma, and is captured by DCs in the lamina propria. DCs are antigen-presenting cells that initiate adaptive immune responses by presenting antigens to, and activating, CD4+ T cells. After attachment of HIV, DCs migrate to secondary lymphoid organs where they pass HIV to CD4+ T cells. During this early phase of HIV infection, both CD4 and CCR5 molecules are used as receptors by HIV to enter cells. Other characteristics of HIV that infects cells at mucosal surfaces are different to those of viruses in established infection, such as higher Env content, enhanced cell-free infectivity and interaction with DCs, and relative resistance to IFN-α, suggesting a selective advantage of founder viruses for conditions at the mucosal surface.⁽³⁾

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Attachment of HIV to DCs occurs via binding of HIV envelope proteins to a family of molecules called C-type lectin receptors, which include DC-specific ICAM-3-grabbing non-integrin (DC-SIGN), mannose receptors and langerin. Each of these molecules can bind the HIV envelope glycoprotein gp120, and are expressed on different subtypes of DC.(4-5) DCs not only act as vehicles to transport HIV to lymphoid tissues, where CD4+ T cells becomes infected, they also present HIV antigens to CD4+ T cells leading to CD4+ T cell activation. This potentiates both the infection of, and replication in, CD4+ T cells.(6) While DCs express both CD4 and CCR5 receptors,(7) they do not express CXCR4.(8) This may contribute to the preferential sexual transmission of R5-tropic viral isolates.(9) Early simian immunodeficiency virus (SIV) infection is associated with massive depletion of CCR5-expressing activated CD4+ T cells from lymphoid tissue, particularly gut-associated lymphoid tissue. (10)

Host determinants of HIV transmission

HIV transmission efficiency depends on the size of the virus inoculum from the HIV-infected person and the susceptibility of the exposed person. The most important factor that influences the risk of sexual transmission of HIV-1 is the HIV viral load, as reflected in the number of copies of HIV RNA per millilitre of plasma, with a 2.4 times increased risk of sexual transmission for every 1 log₁₀ increase in plasma HIV RNA level. The sexual activity of people with acute HIV infection, which causes very high plasma HIV viral loads during the first few months of infection, is an important driver of HIV epidemics. A reduction in plasma HIV viral load of 0.7 log₁₀ is estimated to reduce HIV-1 transmission by 50%.(11) People with primary and late-stage HIV infection, both of which are associated with a very high HIV viral load, are more likely to transmit HIV.(12, 13) Plasma HIV viral load usually correlates with HIV viral load in genital secretions.(14) Like plasma HIV viral load, genital fluid HIV viral load is high during primary HIV infection and during the later stages of HIV disease, such as acquired immunodeficiency syndrome (AIDS). Suppression of HIV-1 infection in the anogenital tract resulting from the use of ART, associated with a decline of HIV RNA in secretions, is the most likely mechanism for the prevention of HIV-1 transmission that was observed in HIV-1 sero-discordant couples in the HPTN 052 clinical trial.(15) Other host factors that influence HIV transmission are listed in Table 1.

Table 1. Biological factors affecting sexual transmission of HIV

Factors increasing transmission risk	Index	Recipient
Plasma HIV viral load	✓	N/A
Other sexually transmissible infections	✓	✓
Foreskin	✓	Increased risk for recipient
Menstruation	✓	✓
Bleeding during intercourse	✓	✓
Genital tract trauma	✓	✓
Intrauterine device	–	✓
Medroxyprogesterone	–	✓
Bacterial vaginosis	–	✓
Factors decreasing transmission risk		
CCR5 Δ32 homozygosity	–	✓
Barrier contraception	✓	✓
N/A = not applicable		

Adapted from: Royce RA, Sena A, Cates W, Cohen MS. Sexual transmission of HIV. New Engl J Med 1997; 336:1072-8.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Studies of HIV DNA sequences during acute and early infection suggest that there is a bottleneck in the virus population during transmission, regardless of route of transmission. In contrast to the extensive sequence diversity present during chronic infection, the sequence diversity in acute infection is much more limited; typically only one or a few genetic variants of HIV can be detected.(16)

Role of sexually transmissible infections in transmission of HIV

Transmission and acquisition of HIV may be increased in people with concurrent sexually transmissible infections (STIs).(17), (18) Concurrent STIs also have a strong epidemiological link with increased risk of HIV acquisition. Two of the best described STIs that increase HIV risk are herpes simplex virus type 2 (HSV-2) and human papilloma virus (HPV) infections; each has been associated with a 2–3 fold increased rate of HIV acquisition in large meta-analyses.(19)

Ulcerative STIs are particularly associated with increased transmission of HIV.(12) Both symptomatic and asymptomatic STIs increase anogenital tract HIV viral load and the numbers of cells expressing CCR5.(20) Mathematical models suggest that intercurrent STIs may increase the likelihood of HIV transmission ten-fold.(21) Treatment of STIs has been associated with a decline in genital secretion HIV viral load, which may explain the dramatic reductions in HIV transmission observed following treatment of STIs.(22)

There is epidemiological evidence and biological plausibility to support an association between prevalent HSV-2 infection and HIV acquisition in both men and women.(23) HSV-2 infection was found to have the strongest association with HIV acquisition in women in Tanzania compared with other STIs.(24) The relative risk of HIV acquisition was higher for incident than for prevalent HSV-2 infection in this study. Valacyclovir has been demonstrated to decrease plasma, vaginal and rectal HIV viral load in individuals with both HIV and HSV-2 infection.(25), (26) However, two large randomised trials failed to show a reduction in HIV acquisition in people who received acyclovir to prevent recurrences of HSV-2 disease.(27) Randomised trials of treatment for bacterial STIs also did not show a reduction in HIV transmission.(28) There is no convincing evidence to date that treatment of STIs results in prevention of HIV infection at the population level.(29) Further studies are awaited to determine if the treatment of STIs will have any real impact on HIV transmission.

The role of circumcision

Male circumcision has a profound effect on the risk of acquiring HIV infection in heterosexual couples. Several large randomised prospective studies performed in Africa have shown a 70% reduction in the risk of HIV acquisition following circumcision. (30) (31) However, the role of male circumcision in prevention of HIV infection in men who have sex with men (MSM) remains to be determined. Although male circumcision clearly reduces STIs among heterosexual men, its effects among MSM are unclear. Observational studies of MSM have reported conflicting levels of association with HIV acquisition. A meta-analysis incorporating more than 50,000 MSM did not find an association between HIV status and being circumcised (OR 0.95, 95% CI 0.81-1.11) (32)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Mother-to-child transmission of HIV infection

Mother-to-child transmission of HIV can occur antepartum, intrapartum or postpartum via breastfeeding. Most cases of mother-to-child transmission occur during labour. As with sexual transmission, R5-tropic viruses are more likely to be transmitted from mother to child.(47) The mechanisms underlying these observations are not completely defined. The overall risk of vertical transmission of HIV is 25-30%. As for sexual transmission, maternal plasma HIV viral load is the predominant risk factor for vertical transmission.(48) (49) However, HIV transmission can occur despite a low maternal HIV viral load; mothers with plasma HIV RNA < 1000 copies/mL have transmitted HIV to their infants.(50) The prime determinant of transmission, in this context, is absence of maternal ART. Transmission of HIV from mother to baby occurs in 10% of mothers with a low HIV viral load not receiving ART compared with < 1% of mothers on ART, including in Australia.(51) There is an increased risk of transmission, either perinatally or postnatally, when women contract HIV during pregnancy.

Other factors associated with an increased risk of perinatal HIV transmission include low maternal CD4+ T cell count, prolonged rupture of membranes, pre-term labour, chorioamnionitis, cigarette smoking or illicit drug use during pregnancy, and obstetric procedures such as amniocentesis and amnioscopy. Caesarean section before the onset of labour significantly reduces the risk of HIV transmission,(52) although ART is the mainstay of HIV prevention and there is no additional benefit of caesarean sections in women receiving effective ART with an undetectable plasma HIV viral load at the time of delivery (see section on Pregnancy in women with HIV infection).

Breastfeeding approximately doubles the risk of mother-to-child transmission of HIV and accounts for approximately one third of cases of mother-to-child transmission.(53), (54) High levels of HIV in breast milk cells correlate with increased risk of transmission. Avoidance of breastfeeding has been suggested to reduce the risk of HIV transmission.(55) However, in resource-poor settings, breast milk substitutes may be difficult to obtain and benefits may be off-set by increased respiratory and gastrointestinal infections in non-breastfed infants. Exclusive breastfeeding carries a lower risk of HIV transmission than mixed feeding in South Africa.(56) Other factors which increase the risk of postnatal HIV transmission include maternal nipple lesions, mastitis, low maternal CD4+ T cell count, infant oral thrush and breastfeeding for longer than 15 months.(57)

Variation in the genes encoding some chemokines may influence the rate of mother-to-child transmission of HIV. For example maternal heterozygosity for the SDF-1-3'A variant of the gene encoding SDF-1a (CXCL12) is associated with almost double the risk of transmission of HIV, independent of maternal plasma HIV viral load.(58) Infant chemokine gene variation has not been demonstrated to influence HIV acquisition rates.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

HIV transmission by other bodily fluids

The risk of HIV transmission by oral sex and kissing is very low. While infectious HIV may be detected in the saliva, it is present in substantially reduced quantities compared with blood or genital secretions. Furthermore, the saliva contains endogenous antiviral factors, including HIV-specific antibodies, and a number of soluble factors, such as secretory leukocyte protease inhibitor. (59) Saliva may alter HIV-1 gp120 structure and lyse HIV-infected cells secondary to the inherent hypotonicity of the saliva. While oral sex has been identified as the only reported risk factor for HIV transmission in some men who have sex with men, (60) the findings of large cohort studies in which no cases of HIV transmission were identified have not confirmed this. (61) However, oral transmission of SIV has been reported in a macaque model. (62) There is no evidence that HIV transmission can occur as a result of exposure to tears, sweat, faeces or urine.

Disease progression

HIV disease progression

Phases of HIV disease

HIV disease is characterised by three phases: acute or primary infection (often referred to as seroconversion illness or primary HIV infection syndrome), asymptomatic chronic infection and symptomatic chronic infection. The rate of progression from one phase to another is highly variable.

Following transmission, HIV initially replicates in regional lymph nodes. This results in a rapid rise in plasma HIV RNA to levels in excess of one million copies/mL. This phase is accompanied by dissemination of HIV to cells in other lymphoid tissues, (63) including those of the gut and genital tract. Following the peak in viraemia, plasma HIV viral load decreases co-incident with the development of host cellular immune responses. (64) The peak in plasma HIV viral load and development of HIV-specific immune responses, including antibody responses, is associated with a primary HIV infection syndrome (seroconversion illness) in 60-90% of patients. (65), (66) The following features of primary HIV infection are associated with a poorer prognosis: (67-69)

- Symptomatic primary HIV infection syndrome
- Longer duration of primary HIV infection syndrome
- Neurological symptoms
- Presence of oral candidiasis
- Greater number of signs and symptoms
- Greater severity of symptoms.

The following laboratory test markers during primary HIV infection have been associated with a poorer prognosis: (70) (71)

- Low CD4+ T cell count
- High cellular HIV DNA level
- Slow decay of plasma HIV viral load

While the peak HIV viral load during primary HIV infection is not predictive of HIV disease progression, it is associated with severity of symptoms, which has been linked to a poorer prognosis. (72) A primary HIV infection syndrome generally resolves spontaneously within 14 days. (73) On resolution of a primary HIV infection syndrome, the HIV-infected person enters a prolonged, clinically asymptomatic period. Nevertheless, virological and immunological progression occurs during this period, driven by immune activation and dysfunction.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Progressive, HIV-induced immunopathology results in the development of symptomatic HIV disease, which is divided into two phases that are not necessarily contiguous: symptomatic HIV infection (non-AIDS) and acquired immune deficiency syndrome (AIDS). Patients may present with an AIDS-defining illness without preceding HIV-related symptoms.

Rates of HIV disease progression

The rate of HIV disease progression is highly variable among individuals, ranging from 6 months to more than 20 years. In the absence of ART, the median time to develop AIDS is 10-11 years.(74) The median survival following AIDS in the absence of ART is dependent on the CD4+ T cell count at AIDS diagnosis: 3.7 years if the CD4+ T cell count is < 200/μL and 1.3 years if the CD4+ T cell count is < 70/μL.(75) However, rates of disease progression to AIDS vary from rapid progression within 6 months of seroconversion, (76) to no significant progression.

Individuals with no disease progression were previously referred to as long-term non-progressors (LTNP). By definition, these people had CD4+ T cell counts > 500/μL and were asymptomatic despite more than 10 years of infection without ART. Between 1-5% of people with HIV infection fall into this category.(77) (78) These estimates are complicated by the fact that there is no standardised definition of a LTNP, and thus definitions used (and the way in which they are applied, particularly in the presence of varying follow-up and irregularly measured CD4+ T cell counts) are not consistent. However, with longer follow-up and the use of improved prognostic models, these people do eventually experience HIV disease progression suggesting that rather than representing a distinct group of HIV-infected individuals, LTNP are more likely to represent individuals at one end of a normal distribution curve. (78)

The term HIV controller refers to people with HIV-1 infection who maintain undetectable HIV viral loads in the absence of ART. Approximately 0.6% of people with HIV infection are considered elite controllers (HIV RNA < 50 copies/mL)(79), while people who naturally control HIV infection with plasma HIV RNA levels between 50 and 2000 copies/mL have been referred to viraemic controllers. (78). Elite controllers exhibit stronger HIV specific immune responses compared with people who do not control viral replication and are also more likely to possess alleles of human leucocyte antigen (HLA)-B genes that are associated with slow progression of HIV disease, such as HLA-B*5701; however these factors do not explain the elite controller phenotype in the majority of people.(80) Notably, in one study, 10% of such people had CD4+ T cell counts < 350/mL and 3% had AIDS, which were associated with greater immune activation, when compared with HIV-negative controls, and appeared to be related to increased plasma levels of lipopolysaccharide.(81) Therefore, CD4+ T cell depletion may occur despite optimal control of HIV replication. Although there is clearly an overlap between the LTNP and elite controller groups, not all LTNP have a low HIV viral load, and not all elite controllers have high CD4+ T cell counts.

Laboratory test markers of HIV disease progression

Laboratory test findings, such as rising plasma HIV viral load, falling CD4+ T cell counts and increasing CD38 expression on CD8+ T cells, are non-clinical markers of disease progression. These markers of disease progression correspond to fundamental aspects of HIV disease pathogenesis, namely viral replication, immunodeficiency and increased immune activation, respectively.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

CD4+ T cell count

The CD4+ T cell count was the earliest laboratory test marker used in HIV management. (82) (83) Absolute CD4+ T cell count, CD4+ T cell percentage and CD4+ T cell rate of decline have all been demonstrated to predict progression to AIDS. (84) (85) Furthermore, the risk of development of certain opportunistic infections can be stratified according to CD4+ T cell count. For instance, the relative risk of developing *Pneumocystis jiroveci* pneumonia in patients with CD4+ T cell counts of < 200/μL or CD4+ T cell proportions < 14% is 4.9. (86)

The CD4+ T cell count declines during HIV disease progression with the rate of decline accelerating over time, averaging 80-110 cells/μL per year. (87) Interestingly, host immune function, including thymic function, prior to HIV infection predicts subsequent CD4+ T cell decline. (88) The CD4+ T cell count is predictive of progression to AIDS across all HIV viral load strata, although its predictive value increases with duration of HIV infection. (75) (89) The CD4+ T cell count in blood, however, does not reflect total body numbers of CD4+ T cells, which predominantly reside in lymphoid tissue. The gut-associated lymphoid tissue is affected early in HIV infection, which leads to a dramatic loss of the total body CD4+ T cell pool, and remains depleted throughout the natural history of untreated HIV infection. (90)

Plasma HIV viral load

Plasma HIV viral load is predictive of disease progression at all stages of HIV infection and across all CD4+ T cell strata. Early studies suggested that, following an initial peak during acute HIV infection, plasma HIV viral load declined to a setpoint and remained stable during the asymptomatic phases of HIV infection, and then increased again a few years before the development of AIDS. (91) (92)

Transmission studies assessing the factors associated with HIV viral load setpoint have observed that the HIV viral load of the donor was closely associated with the HIV viral load at presentation in the seroconverting partner. (93) Overall, the HIV viral load setpoint was a function of the source partner HIV viral load, the sex of the seroconverter, the HLA class I alleles of the seroconverter, and the sharing of HLA-class I alleles between partners in a transmission pair. (94) HIV viraemia dynamics and the evaluation of a setpoint therefore require consideration of host and viral genetics. Despite its use in research studies, there is still no standard method for determining HIV-1 viral load setpoint, with multiple methods and definitions having been used. Determination of HIV viral load set point therefore has little value in clinical practice. Proviral DNA levels in peripheral blood mononuclear cells also predict progression to AIDS independently of both plasma HIV RNA level and CD4+ T cell count. (95)

There has been interest in determining whether HIV isolates have become more virulent in recent years. However, large cohort analyses have provided inconclusive evidence based on analyses of the rate of CD4+ T cell decline from HIV viral setpoint. (96)

CD38 expression on CD8+ T cells

CD38 is a cell-surface glycoprotein that is detected on lymphocytes, including CD8+ T cells. Its expression is increased on activated lymphocytes. Upregulation of CD38 expression on CD8+ T cells during primary HIV infection (97) and other stages of HIV disease (98) is predictive of a subsequent decline in CD4+ T cell count. Furthermore, elevated expression of CD38 by CD8+ T cells late in HIV disease is a strong predictor of disease progression. (99) These observations underscore the importance of immune activation in the pathogenesis of HIV disease.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Host and viral factors affecting disease progression

Host factors

Severity of HIV disease after infection is variable. The majority of knowledge on the impact of host genetic variation on outcome of HIV-1 infection has been gained through studies of historical cohorts collected before the implementation of ART. An impact of host genetic variation on susceptibility to HIV-1 infection was identified early in the pandemic, with a major role attributed to the genes encoding HLA-B molecules and the chemokine receptor CCR5. Variants of genes encoding other chemokine receptors, as well as chemokines and cytokines, have been reported to influence HIV disease progression or transmission or HIV (Table 2). However, only variation within or near the HLA genes and, to a lesser extent, the CCR5 locus have been replicated in large genome-wide association studies.⁽¹⁰⁰⁾

Table 2. Variants of genes encoding chemokines, chemokine receptors and cytokines associated with rate of HIV transmission or disease progression

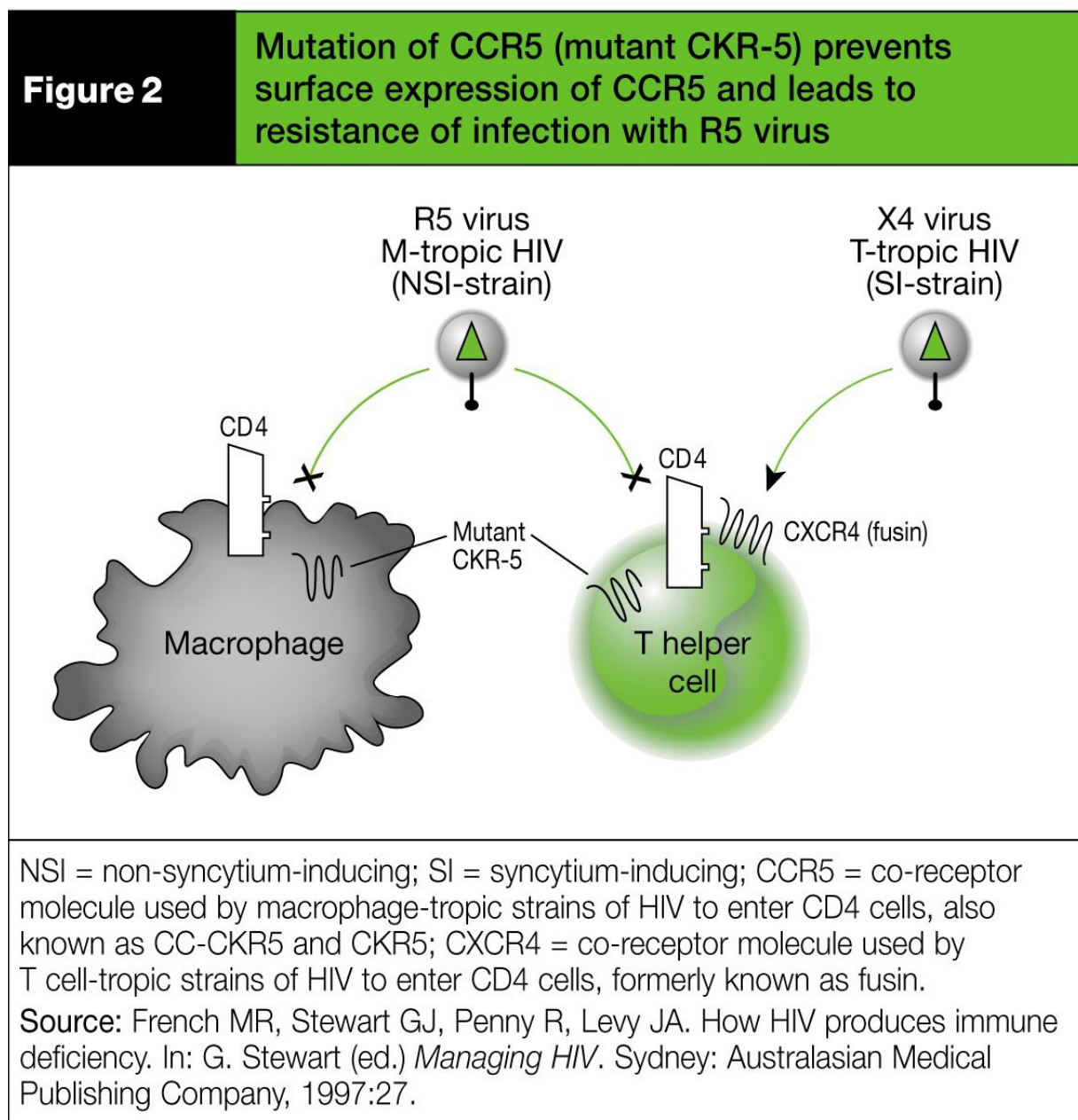
	Gene variant		Influence on natural history		Putative effect
	Site	Codon	Transmission	Disease progression	
Chemokines					
SDF1 (CXCL12)	3'UTR	SDF1-3A'	Decrease MTCT	Decrease	? block CXCR4
RANTES (CCL5)	Promoter	G4	Increase	Decrease	? increase RANTES
Chemokine receptor					
CCR5	Promoter	59029 G		Decrease	Decreased promoter activity
		CCR5P1		Increase	
	ORF	59356 T CCR5Δ32	Increase MTCT	Decrease	
CCR2	ORF	CCR2-64I		Decrease Delayed progression to AIDS then accelerated progression	Linked with CCR5 promoter polymorphism, however mechanism undefined. Once X4 virus is selected disease progression is accelerated.
Cytokines					
IL-4	Promoter	IL-4 589 T		Decrease, increased acquisition of X4 phenotype, associated with delayed progression to AIDS and then accelerated progression	? increased IL-4 production with resultant decrease CCR5 and AIDS then increase CXCR4 expression
IL-10	Promoter	IL-10 5'A	Increase	Increase	Decreased IL-10 inhibition of HIV

IL: interleukin; MTCT: mother-to-child transmission; ORF: open reading frame; RANTES: regulated on activation, normal T cell expressed and secreted; SDF: stromal-derived factor; UTR: untranslated region.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Chemokine receptors and chemokines associated with HIV-1 disease progression

The first reported variant of the CCR5 gene was a 32-base-pair deletion (CCR5 Δ 32). This gene variant encodes for a CCR5 molecule that is not expressed on the cell surface. The absence of CCR5 is the basis for the resistance of some individuals to infection with HIV-1 that uses CCR5 alone as a coreceptor (so called R5 viruses) (Figure 2).⁽¹⁰¹⁾ However, homozygotes for CCR5 Δ 32 can occasionally be infected with HIV isolates which use other coreceptors.⁽¹⁰²⁾ Cell-surface expression of CCR5 is reduced in heterozygotes (CCR5 Δ 32/WT) and this is thought to be the basis of delayed progression to AIDS in these subjects. Variants may also occur in the promoter region of the CCR5 gene. Variants of the gene encoding the chemokine receptor CCR2 are also associated with delayed disease progression.⁽¹⁰³⁾ A chemokine that binds to CCR5, CCL3, also affects HIV acquisition and HIV disease progression. A lower CCL3L1 gene copy number is associated with higher susceptibility to HIV infection and disease progression.⁽¹⁰⁴⁾



CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

HLA-B alleles associated with HIV-1 disease progression

Several alleles of genes encoding HLA-B molecules have been shown to impact on the natural history of HIV-1 infection, particularly HLA-B*5701 and HLA-B*2705, which are associated with decreased rates of disease progression in caucasian people (105). People with HLA-B*5701 are less likely to present with symptomatic acute HIV infection and are more likely to have broader and stronger T cell responses against HIV-1 peptides (106). The association of HLA-B*5701 and other HLA-B alleles with rates of HIV disease progression reflects differences in the capacity of the encoded molecules to present HIV peptides to CD8+ T cells. (105)

Gender differences

Some studies have demonstrated that women develop AIDS at higher CD4+ T cell counts than men.(107) However, this difference may be explained by decreased access to care rather than biological effects. Conversely, other studies have demonstrated that, for a given CD4+ T cell count, women have up to a 0.3 log10 lower plasma HIV viral load than men.(108) This difference is most apparent in the 4 years following seroconversion.(109) After that time, women experience greater rises in plasma HIV viral load. This late rise in HIV viral load in women may account for the lack of gender differences in disease progression observed in other cross-sectional studies.(110) The underlying mechanisms for these observed differences remain undefined. No gender differences have been demonstrated in clinical progression following seroconversion.(111)

Viral factors

Variation in HIV influencing HIV disease progression

Multiple factors affecting the structure and function of HIV have been associated with the rate of HIV disease progression, including deletions in certain viral genes; coreceptor usage; viral subtype and replicative capacity. Slower disease progression rates were observed in people infected with HIV carrying deletions in the Nef gene (Nef-deleted viruses).(112) People infected with dual tropic (ie. mixed R5 and X4 tropic) viral populations progressed to AIDS 3.8 times more rapidly, independent of CD4+ T cell count and HIV viral load, than those with only R5-tropic viruses at baseline.(113) This is because viruses that use the CXCR4 coreceptor are more pathogenic than other strains: they form syncytia (giant, multinucleated cells) in vitro and, therefore, were previously described as syncytium-inducing variants. In contrast, R5 viruses are less pathogenic than X4 viruses: they do not form syncytia in vitro and, therefore, were previously referred to as non-syncytium-inducing strains. Transmission of X4 strains, which occurs rarely, is associated with accelerated disease progression. The viral coreceptor usage changes from R5 to X4 in up to 40% of patients during the course HIV disease and is associated with acceleration in CD4+ T cell loss and disease progression.(114) Subjects with syncytium-inducing (X4) variants are seven-times more likely to progress to AIDS over a 30-month period.

Some studies report that HIV-1 subtype is an independent predictor of HIV disease progression. Women with the Brazilian variant of subtype B HIV infection had a faster progression of HIV disease than women with other subtype B variants.(115) People with subtype A HIV infection were reported to have slower rates of disease progression relative to subtype D and other subtypes.(116) (117) (118) Viral subtypes may also differ in their capacity to be transmitted; for example, HIV-1 subtype C is associated with increased vaginal shedding.(119)

There is also some evidence that HIV replication capacity is associated with CD4+ T cell decline, though not with HIV viral load. People infected with HIV that had a high replicative capacity were more likely to have fast rates of CD4+ T cell decline, independent of plasma viral load.(120)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

GB virus-C co-infection

The flavivirus GB virus-C (GBV-C), previously designated hepatitis G, may have a protective effect on HIV disease progression. No human disease has been associated with GBV-C infection. Epidemiological studies have described an association between GBV-C co-infection and decreased morbidity and mortality in individuals with HIV infection. (121) (122) (123) HIV-infected people with GBV-C co-infection have reduced mortality, increased survival post-AIDS and lower plasma HIV viral loads compared with HIV-infected people without GBV-C infection. Higher CD4+ T cell counts have been demonstrated in some (124) but not all (121) studies of people with HIV/GBV-C co-infection. As GBV-C and HIV share transmission routes, co-infection is common and has been demonstrated in between 16- 40% of people with HIV infection in the USA. This compares with a prevalence of GBV-C infection in 2% of volunteer blood donors and 20% of intravenous drug users in the USA.(125) (126)

Several mechanisms of interaction between GBV-C and HIV have been proposed, including altered cytokine profiles, HIV coreceptor expression, T-cell activation, Fas-mediated apoptosis and direct inhibition of HIV replication.(127) In vitro studies have demonstrated that GBV-C inhibits HIV replication by inducing the production of chemokines, which may inhibit HIV replication and reduce the expression of coreceptors on the surface of T-cell.(128) This is in keeping with the observation that persistent GBV-C virus infection is required for delayed progression, as people who clear GBV-C infection have higher mortality rates than those with persistent infection.(129) At present a causal relationship has not been proven.

HIV superinfection and recombinant HIV viruses

HIV superinfection occurs when a person with HIV infection becomes infected with another strain of HIV. (33,34) In contrast, HIV co-infection refers to the situation where two HIV strains are present at the time of initial infection. Dual HIV infection collectively refers to either HIV superinfection or co-infection. Dual infection is a prerequisite for genetic recombination events to occur between different HIV subtypes resulting in circulating recombinant forms (CRFs) of HIV (see section on Basic HIV Virology).

Cases of HIV superinfection have been reported in a variety of situations, including intersubtype; intrasubtype; wild-type with drug resistant; drug-resistant with wild-type; and R5-tropic only with dual tropic. Recombination of superinfecting viruses has been documented in people with chronic HIV infection. This has involved intersubtype recombination(35) and intrasubtype recombination involving multiclass drug resistant viruses. (36) Cohort based studies have reported that superinfection occurs in 0-5% of patients with HIV infection. (37) (38) (39) (40)

The implications of HIV superinfection for HIV vaccine development, as well as the consequences for the infected individual, are currently unclear. The implications for vaccine development are that if the natural immune response generated by HIV infection is not sufficient to protect against infection with another strain of HIV, it might be difficult to do this with a vaccine.(41) With regards to the HIV-infected individual, case reports have associated superinfection with accelerated clinical and surrogate marker progression.(42) Superinfection with a drug-resistant strain of HIV-1 has been associated with impaired virological responses to ART.(43) However, not all cases of HIV superinfection have been associated with poorer outcomes as this process has been documented in two patients with long-term non-progressive HIV disease.(44) While studies have sometimes been unable to distinguish between HIV co-infection and superinfection, they have consistently associated dual infection with higher HIV viral load set points.(45) On balance, evidence suggests that superinfection may have deleterious effects on HIV disease progression. It is not clear if

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

superinfection itself leads to accelerated disease progression, or if unidentified host factors contribute to the accelerated disease progression independent of superinfection.

It is unknown if all HIV patients are at risk of HIV superinfection or when this is most likely to occur. However, superinfection has been documented to occur up to 12 years after initial infection. (46) To date, superinfection has not been reported in people receiving ART. (37) However, methods used in these studies may underestimate the true prevalence of superinfection. Case reports of superinfection with multiclass antiretroviral drug-resistant HIV potentially suggest that even patients on ART may be at risk of superinfection.(36)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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2. Virology & Immunology

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Basic HIV virology

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Last reviewed: December 2018

Introduction

The acquired immune deficiency syndrome (AIDS) is caused by the human immunodeficiency virus (HIV). HIV-1 was initially identified by Luc Montanier at the Institute Pasteur, Paris, in 1983 (1) and was then more fully characterized in 1984 by Robert Gallo in Washington (2) and Jay Levy in San Francisco. (3, 4) A second virus, HIV-2, was isolated from West African patients in 1986. (5) Viruses similar to HIV-1 and HIV-2 have been isolated from chimpanzees and wild African monkeys. (6) It is most likely that HIV-1 and HIV-2 crossed species from primates to humans in Africa several times over the last hundred years with the earliest known samples of HIV-1 isolated from preserved tissues samples from 1959 and 1960. (6-8) The genetic diversity of these two HIV-1 isolates at that time estimates the most recent common ancestor for HIV-1 to be around 1908. (6-8)

The taxonomy of HIV and primate immunodeficiency viruses

HIV is subdivided into two very broad types: HIV-1 and HIV-2. HIV-1 is by far the most common and broadly distributed HIV type, accounting for most HIV infections worldwide. HIV-2 is genetically closer to simian immunodeficiency virus (SIV) than HIV-1 and as a consequence, HIV-2 can be refractory towards certain HIV-1 reverse transcriptase and HIV protease inhibitor drugs. The pathogenicity of HIV-2 *in vivo* is far less than HIV-1. (9) This also is reflected in the limited global prevalence of HIV-2 (estimated between 1 to 2 million cases worldwide) with restriction primarily to areas within West Africa.

The differences between HIV-1 and HIV-2 reflect their distinct zoonotic origin. (10) HIV-1 is most similar to SIV strains isolated from chimpanzees and HIV-2 to those from the sooty mangabey. HIV-2 results in a less virulent infection than HIV-1, with generally lower viral loads, lower rates of vertical transmission and slower disease progression. (10-13)

HIV-1 lineages-groups

HIV-1 is divided into three quite distinct lineages: groups M, N and O. Again, the worldwide distribution of these groups is not equal: group M (for Main) strains are substantially more common in the global epidemic than the group O (Outlier) strains, which are largely confined to Africa, with sporadic cases reported elsewhere. The group N (non-M, non-O) strains have only been isolated in Cameroon. (14)

HIV-1 subtypes and circulating recombinant forms

There are currently nine subtypes of HIV-1 that are consistently identified as different subtypes regardless of the genomic region analysed (Figure 1.4). Additionally, several recombinant forms of the virus, the genomes of which are made up of different regions from distinct subtypes, have been separately classified as circulating recombinant forms (CRFs).

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

The subtypes and CRFs show strong patterns of distribution in the global pandemic. Western countries, including Australia, continue to have an epidemic that is almost exclusively subtype B in all risk groups. Thailand originally showed a sharp segregation of subtypes between risk groups, with heterosexual transmission largely due to CRF01-AE, and injecting drug use (IDU) transmission due to subtype B; since then CRF01-AE has come to predominate in all risk groups. (15-17) India and South Africa are experiencing explosive epidemics of subtype C. (18, 19) All HIV subtypes described to date have also been detected in sub-Saharan Africa.

HIV subtype A/E was first described in Thailand as a new subtype E. Subsequent analysis of the entire genome of this form showed it to be a recombinant between subtypes A (that is most prevalent in Africa) and subtype E (that is unique). Isolates of this strain were then termed subtype A/E. As this strain is so prevalent in Asia, it was among the first to be renamed under the new nomenclature of CRFs. It is now referred to as HIV CRF01-AE.

Sub-subtype classification

A further refinement in the subtype classification has been made recently to distinguish strains that form distinct groups within subtypes but are not sufficiently different to warrant classification as a novel subtype. A detailed description of the most recent HIV taxonomy has been published by the Los Alamos National Laboratory (USA) HIV Sequence Database and is continuously updated on the Laboratory's database website.

HIV structure and organisation

HIV is classified into the family *Retroviridae*, subfamily *Lentiviridae*, and genus *Lentivirus*. (20, 21) The structure of HIV follows the typical pattern of a complex retrovirus family, comprising a single-stranded, positive-sense ribonucleic acid (RNA) genome of about 9.2 kilobases that encodes structural, enzymatic and accessory proteins. A HIV virion is largely spherical in shape, with a diameter of 100 to 120 nm, and encloses its genome within a fullerene (cone-shaped) capsid core. The virus is enveloped with a lipid bilayer derived from the host cell, thus incorporating proteins found in the host membrane, such as the major histocompatibility (MHC) molecules, (22, 23) CD44 and lymphocyte function-associated antigen 1 (LFA-1). (24) Embedded within this membrane are the viral glycoproteins; the gp120 surface glycoprotein and the gp41 transmembrane glycoprotein. Each envelope subunit displays on the virion surface as a trimer of the outer envelope glycoprotein gp120, non-covalently linked to a trimer of gp41, the transmembrane protein that anchors this glycoprotein complex to the surface of the virion. The envelope protein is the most variable component of HIV, although gp120 itself is structurally divided into highly variable (V) and more constant (C) regions. The constant regions of the gp120 envelope are often associated with the "non-neutralising face", as they are buried within the trimer. (25, 26) In contrast, the variable domains are associated with the "neutralizing face" of the envelope glycoprotein that is exposed to antibodies. Variability of this regions underlies immune escape. The variable domains also give the capacity of the virus to change receptor usage. In particular, the V3 loop of HIV gp120 can change the ability of the virus to use the HIV co-receptors CXCR4 and CCR5 (receptors for HIV will be covered later in this chapter). Finally, the envelope glycoprotein gp120 has over half of its molecular weight attributed to carbohydrate structures, in the form of complex and high mannose N-linked glycans. These glycans decorate the majority of the exposed outer gp120 surface, which is known as the "silent face" given its ability to protect the envelope from antibody responses. (25, 26)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

The viral structural proteins are derived from the Gag polyprotein, which is present in approximately 2,400 copies in an immature virion according to current estimates. (27) Viral maturation leads to the cleavage of the Gag polyprotein, giving rise to Matrix (MA; p17) and Capsid (CA; p24) proteins, as well as the smaller peptides Nucleocapsid (NC; p7), p6, p2 and p1. (28) Matrix associates with the inner membrane of the mature virion, whilst Capsid forms the viral core, enclosing two single strands of viral RNA. The core structure is a cone shape comprised of approximately 1,500 Capsid proteins assembled into hexameric and pentameric rings. (29, 30) Viral proteins found within the capsid core include the NC, which is found associated with the viral RNA, as well as Protease (PR), Integrase (IN) and Reverse Transcriptase (RT) proteins. (31)

The genomic organisation of HIV is extremely efficient. Use of all three reading frames (the triplet codes) of the genetic sequence permits overlapping of gene-coding regions. There are nine genes of HIV. These encode proteins that may be broadly classified into structural, catalytic, regulatory, and accessory classes (Table 1).

In addition to the functions performed by these proteins in the viral lifecycle, the nucleic acid sequence of the virus possesses intrinsic functions. For example, the Rev responsive element, within the coding region for gp41, interacts with the Rev protein to assist export of spliced RNA transcripts from the nucleus of the cell. (32) The long-terminal repeat (LTR) region has a transcription-promoter function in the integrated deoxyribonucleic acid (DNA) provirus (33) and contains regions essential for reverse transcription, integration into the host-cell genome and genomic RNA dimerization. (34)

Table 1. Summary of HIV-1 gene products and their functions

Viral Gene	Viral Protein	Designation and size (kDa)	Function	References
Structural Proteins				
gag	Matrix	MA, p17	Targets virion assembly through binding to PI (4,5) P2 domains at the plasma membrane; binds gp41 to incorporate Env in nascent virions	(35-38)
	Capsid	CA, p24	Forms the capsid-rich core via hexameric and pentameric CA structures; mediates Gag oligomerisation and assembly	(29, 30, 39)
	Nucleocapsid	NC, p7	Binds viral RNA and packages the genome in the core; mediates Gag oligomerisation and assembly	(40-42)
	p6	p6	Promotes membrane fission of nascent virions via PTAP-Tsg101 recruitment of the ESCRT complex; binds Vpr protein and packages it in the core	(43-45)
env	Surface envelope glycoprotein	SU, gp120	Envelope surface protein; binds to CD4 receptor and chemokine receptors on target cell	(46-49)
	Transmembrane envelope glycoprotein	TM, gp41	Envelope transmembrane protein; mediates fusion via 'fusion peptide'	(50, 51)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

pol	Reverse Transcriptase	RT, p66, p51	RNA-dependent-DNA-polymerase; converts viral ssRNA to linear DNA	(52, 53)
	Integrase	IN, p32	Facilitates integration of HIV DNA into host genome; involved in dynein-mediated transport of the RTC.	(54-57)
	Protease	PR, p10	Cleavage of polyprotein components of Gag-Pol	(58, 59)
Regulatory Proteins				
tat	Trans-Activator of Transcription	Tat, p14	Activator of transcription of HIV ssRNA; essential for virus replication	(60-63)
rev	Regulator of Virion protein expression	Rev, p19	Post-transcriptional regulation of viral genes, including export of viral RNA from the nucleus	(32, 64)
Accessory Proteins				
nef	Negative Regulatory Factor	Nef, p27	Infectivity enhancement; CD4 and MHC class I down-regulation; cellular activation and signaling; Counters the restriction factor SERINC to increase virion infectivity	(65-71) (72)
vpr	Viral Protein R	Vpr, p15	Helps in nuclear transport of HIV post entry; induces G2 cell cycle arrest in infected cells	(73-78)
vpu	Viral Protein U	Vpu, p16	Enhances the release of virus particles by counter-acting the interferon induced restriction factor Tetherin; promotes CD4 degradation	(79-81)
vif	Virion Infectivity Factor	Vif, p23	Counteracts the anti-viral activity of APOBEC3 protein group. The latter protein group are HIV restriction factors that hypermutate HIV genomes and render them non-functional.	(82-84)

HIV life cycle

The life cycle of a retrovirus is that of an obligatory intracellular parasite, and thus HIV cannot replicate outside of human cells.

HIV binding and entry

Infection of the host cell commences when HIV binds to specific receptors on the cell membrane. In general, the interaction requires the recognition of two host-cell surface-receptor proteins by the viral gp120 envelope protein. The presence or absence of these cellular proteins restricts the range of host-cell types that are susceptible to infection by a strain of HIV.

The first HIV receptor described was the CD4 protein (46) which is present predominantly on cells of the T lymphocyte and myeloid lineages. The distribution of CD4 receptors has been thought to restrict HIV susceptibility to cells of the lymphocyte, monocyte/macrophage and other CD4-expressing lineages, although there is precedent for HIV-1, HIV-2 and the related virus SIV to be able to fuse with cells not expressing CD4. (34, 85, 86)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Subsequently, the requirement of a second coreceptor for viral entry was recognized. (87-92) This function may be performed by a range of proteins within the class of seven-transmembrane receptors, although the most important are CCR5 (CC chemokine receptor 5) and CXCR4 (CXC chemokine receptor 4). The seven-transmembrane class of receptors is very large, containing over 100 related proteins. Several of these proteins have been shown to facilitate the binding of HIV *in vitro* (Reviewed in (93)). The *in vivo* significance of entry via these minor co-receptors, however, remains unclear.

After HIV gp120 binds to CD4 receptor and the co-receptor, a conformational change in gp41 causes insertion of the N-terminal hydrophobic fusion-peptide region into the target-cell membrane. (94) This insertion results in membrane fusion and the entry of the viral particle contents into the cytoplasm, a process critically dependent upon interactions between the N-and C-terminal regions of the gp41 ectodomain. This intra-protein interaction led to the discovery of a novel class of antivirals called fusion inhibitors, e.g. T-20 (enfuvirtide) which is a short peptide that mimics the structure of the conserved C-terminal region of gp41. (95) Unlike other viruses, HIV does not require to be endocytosed and in CD4+ T cells, primarily fuses at the plasma membrane. (96)

Although all HIV strains will recognize and bind to CD4, affinity for either CCR5 or CXCR4 varies. These differences account for the observed distinct tropisms between HIV strains. Binding ability and tropism of the virus is dependent on the protein structure of gp120. Particular patterns of sequence of the V3 and V4 variable regions, and other regions of gp120, relate to CD4 binding and differential coreceptor affinity. (93, 97, 98)

In general, viral strains that bind to CCR5 (R5 strains) infect macrophages, activated CD4+ T cells and subsets of resting CD4+ T cells where CCR5 is expressed. The majority of strains present *in vivo* are R5 strains and variants of R5 strains known as founder viral strains (see below) are selected during the process of sexual HIV transmission. Other HIV strains that recognise CXCR4 (X4 strains) can exist, but by contrast, infect only T cells and T cell lines and are only present in approximately 40 to 50% of patients during the latter stages of HIV disease. (93) The reason for the lack of CXCR4 variants in early stages of HIV disease, is presently hypothesized to be related to their susceptibility to the adaptive immune response in addition to other factors that limit their growth. (99) The adaptive immune hypothesis does fit well with the time that these isolates emerge, as it is typically at the latter stages of HIV disease when the immune system is being steadily degraded. In theory, CXCR4 isolates can emerge via two mechanisms. Firstly, by CXCR4 viruses being transmitted alongside CCR5 using strains or secondly by progressive genetic evolution of a CCR5 using strain to a CXCR4 using strain. To date the majority of scientific observations support the latter hypothesis. (100) Indeed, investigators would argue that all HIV positive patients would acquire a X4 utilising HIV strain, given enough time (ie. patients often succumb to the effects of R5 HIV prior to the emergence of X4 strains). The emergence of X4 strains is often associated with subsequent accelerated loss of CD4+ T cells and as a consequence accelerated disease progression. This latter phenomenon is a consequence of increased targeting of cells by X4 HIV strains. For instance, whilst CCR5 expression is restricted to a small memory/activated CD4+ T cell subset, CXCR4 is present on upwards of 90% of all CD4 T cells. (101-103) Historically, the growth of X4 strains *in vitro* has been characterised by the presence of syncytial cells, which are formed by the fusion of multiple infected cells and can be observed by light microscopy. Syncytia formation, however, is largely based on the relative expression of CXCR4 on T cell lines used in these assays. The expression of CCR5 expression to similar levels as CXCR4, can readily result in the formation of syncytia when using R5 strains that replicate at similar levels. Indeed, the mechanistic basis of syncytia formation is the level of HIV envelope expressed on the infected donor cells and the HIV receptor expression (CD4 and CCR5 or CXCR4) on the neighbouring recipient cell. This scenario is largely based on the replication of the virus within the donor cell and indicative of overall viral production. Indeed investigators have demonstrated the spontaneous formation of syncytia in cell lines that are exposed to high titer virus. (104).

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Importantly, knowledge of the role of CD4 and associated chemokine receptors in HIV binding to cells led to a new area in HIV therapeutics. A number of small molecules that block binding of HIV to either CCR5 or CXCR4 have been described. Early clinical trials of the CCR5 inhibitor Maraviroc, given in conjunction with an optimised background of other antiretroviral drugs, demonstrated greater virologic and immunologic efficacy profiles compared to placebo in participants having only detectable R5 HIV. (105, 106) X4 specific chemokine receptor inhibitors also exist; the first generation AMD3100 and the second generation AMD11070. Curiously, AMD3100 was discovered in anti-HIV drug screens prior to the knowledge that chemokine receptors work in concert with CD4 to allow HIV entry. (107, 108) Concept trials in humans using the bioavailable AMD11070 CXCR4 inhibitor observed positive outcomes, but further development of this drug class has been delayed due to observations of liver damage in animal models. (109)

The pre-integration complex

The genetic information of HIV is contained within an RNA genome. Following infection of a new host cell, the RNA genome is first reverse transcribed into single-stranded DNA that is then further transcribed to double-stranded DNA. These two polymerase steps are performed by viral reverse transcriptase, which is co-packaged in the viral particle. Self-priming of the single-stranded RNA and DNA and removal of the transcribed RNA strand occur by a complex series of steps dependent upon interactions between the viral LTR and host-cell enzymes. The double-stranded DNA genome forms a complex with host-cell and viral proteins (including matrix, integrase and Vpr) that is actively transported to the nucleus. (110, 111)

During the early steps of the HIV-1 replication cycle, the virus counteracts specific host proteins that have evolved to limit retroviral replication. Two key host cell factors that influence early viral events are i) a protein called human tripartite motif 5 alpha (TRIM5alpha), and ii) sterile alpha motif (SAM) domain and Histidine-Aspartic (HD) domain-containing protein 1 (SAMHD1). TRIM5alpha acts in the early steps of the HIV-1 replication cycle, soon after the entry process and before reverse transcription. (112) TRIM5alpha restricts retroviral infection by specifically recognising HIV-1 capsid and promoting its rapid, premature disassembly. (113, 114) TRIM5alpha from rhesus macaques and African green monkeys inhibit HIV-1 replication, whereas the human homologue is inactive against SIV and HIV-1, leading to the susceptibility of human cells to both viruses. The primary mode of action SAMHD1 was initially hypothesised to be by cleaving nucleotides needed for efficient HIV reverse transcription and subsequent integration. This is particularly apparent in resting cells like macrophages, dendritic cells and resting CD4+ T cells, where there is already a limited nucleotide pool. However recent studies have observed SAMHD1 to also act on HIV RNA and restrict HIV infection through RNase activity (115) and it is presently unclear whether it is the RNase activity combined with dNTPase activity that combines to restrict HIV infection.

Integration and transcription

The double-stranded HIV genome is then either integrated into the host-cell genome by means of DNA splicing, performed by the viral Integrase or forms DNA circles. (116) In the context of chromosomal integration, this process is not random, as recent studies have observed preferential HIV DNA integration in active transcriptional sites within infected cells (reviewed by (117)). The integrated form of HIV is known as the provirus, with identical LTR copies flanking the coding regions. Proviral DNA is replicated as part of the normal cell genome and may persist in this form for long periods and through many rounds of mitotic cell division. Furthermore, integration into long-lived resting CD4+ T cells provides challenges towards attempts at HIV cure as the virus in these cell types is typically dormant/latent.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Transcription of the proviral HIV genome

Transcription is mediated by the promoter in the 5' LTR. Transcription generates a 9.2-kb primary HIV RNA genome that can be directly packaged in the virion through HIV Gag binding to the 5' LTR and psi packaging elements. In addition this transcript can also be subject to splicing and as a consequence, can form up to 30 mRNA transcripts.

Regulation of HIV RNA transcripts

The primary HIV-1 RNA genome contains several splice donors and splice acceptors to generate the pool of 30 HIV spliced RNA transcripts that are designated as incompletely spliced or fully spliced RNA. Incompletely spliced RNA uses the splice donor site located nearest the 5' end of the HIV RNA genome in addition to one of many splice acceptor sites located in the central genomic region of the virus. Incompletely spliced RNA is approximately 4 to 5 kilobases in length, can express Env, Vif, Vpu, Vpr, and Tat and require the expression of HIV Rev for RNA export from the nucleus (ie. like the full unspliced genome of HIV, are HIV Rev dependent).

Fully spliced HIV RNA has spliced out both introns of HIV and can express Rev, Nef, and Tat. These heterogeneous mRNAs do not require the expression of the Rev protein. As they do not require the expression of HIV Rev for RNA nuclear export, they are often referred to as early viral genes.

HIV assembly and release

For full HIV assembly, transcription and subsequent translation must reach a critical threshold for viral assembly to occur. (118) One common misconception with respect to HIV latency is that lack of HIV transcription and translation exists in all latently infected cells. In fact, latency in resting CD4+ T cells may exist where low levels of detectable viral RNA and proteins are present but at a level that does not lead to assembly and production of fully assembled and infectious virions. Once a threshold of viral protein production is reached, proteins that are destined for virions are recruited and assembled at the plasma membrane. (118) Not all virally produced proteins are incorporated with assembling virions, with the dominant virion associated proteins expressed as either a fusion protein with the structural protein HIV Gag (ie. Gag-Pol) or are able to non-covalently associate with HIV Gag (eg. Vpr).

For post translational events, Gag exists as a monomer and oligomerisation of Gag triggers the exposure of a myristoylation motif that binds to the membrane enriched lipid called phosphatidylinositol 4,5-bisphosphate. Whilst gag oligomerisation can proceed when expressed in isolation, it can also be triggered upon viral RNA binding largely through the nucleocapsid domain of Gag, (119) thus ensuring viral inocula have a greater propensity to bud from the cell membrane with its genetic cargo.

Oligomerisation of Gag at the plasma membrane leads to the formation of what is known as the immature viral shell, primarily consisting of repeating Gag polyprotein hexamers. (120) A partially intact spherical shell is hypothesised to leave the membrane, with the aid of scission from the membrane through the Gag-specific recruitment of cellular proteins involved in the ESCRT complex (Endosomal Sorting Complexes Required for Transport machinery), that effectively act as molecular scissors to liberate virions from the membrane.

Shortly after leaving the membrane, the HIV protease is activated and culminates in the sequential cleavage of Gag and Gag-pol proteins. This process, commonly referred to as viral maturation, is marked by condensation of a large pool of HIV capsid, that leads to encapsulation of many viral proteins including HIV RNA-bound nucleocapsid within the conical shaped viral core.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Whilst the above outlines the specific role of the major structural HIV protein Gag, other viral proteins perform a variety of roles to subvert normal cellular function and facilitate viral replication (summarised in detail above in Table 1). Much about these processes remains poorly understood. Vpr acts to alter host-cell transcription and arrest infected cells at the G2/M phase of cell division. (121) Nef induces downregulation of the CD4 receptor and MHC class I molecules. (66, 68, 122) Vpu promotes degradation of CD4 in the endoplasmic reticulum and counteracts an interferon-induced restriction factor known as Tetherin, which acts by tethering and preventing the release of newly formed HIV particles from the plasma membrane. (80) Vif is necessary for subsequent efficient infectivity of the newly produced viral particles (82, 123) and counteracts cytidine deaminases (enzymes present especially in macrophages and T cells) that are naturally occurring host defence mechanisms against retroviruses. These proteins include APOBEC3G and APOBEC3F and are degraded by HIV. (123)

HIV transmission and biomedical prevention

Recent failures and successes of biomedical prevention in conjunction with studies of HIV discordant couples (ie. where one partner is HIV positive and the other HIV negative and thus at risk of acquisition of HIV infection), has led to seminal contributions which give us a greater understanding of how HIV is spread from person to person.

Biomedical prevention in the form of topical microbicides (essentially lubricants that can kill or inhibit HIV) over the past decade has evolved from using formulations that essentially consisted of spermicidal detergents through to gel formulations that contain the same or similar ingredients to current antiretroviral drugs (reviewed in (124)). Whilst the first clinical trials using the spermicidal detergent Noxanol-9 (N-9) actually increased the incidence of HIV transmission (125) and following trials using polyanion based gels either enhanced or had limited effect, (79, 126) they did provide important evidence with regards to how the virus was spread. For instance, the use of N-9 and its deleterious effects on the genital mucosa, illustrated how primary mucosal barriers were essential for blocking the incoming virions. The combined knowledge of the early microbicide trials (including polyanions) further demonstrated that the maintenance of good reproductive health further strengthened these primary barriers and thus limited the numbers of people contracting HIV infection through sex. The more recent studies initially using microbicides with antiretrovirals, (127) combined with studies on pre-exposure antiretroviral treatment for recipients and treatment as prevention in HIV positive donors (128) also emphasized that there is a clear window during HIV transmission that can be targeted at the recipient and donor level. (128) One of the most successful trials in this latter context was HPTN 052. In this trial of HIV serodiscordant couples, treatment of the infected partner led to a reduction in HIV transmission events of 96%. (128) Thus, successful control of HIV viral load in the donor, as is the case with limiting mother-to-child HIV transmission, (129) is paramount in limiting the spread between people.

Whilst the prevention strategies discussed above gave broad insights into HIV transmission and how to prevent it, the studies of early HIV acquisition in HIV discordant couples gave at high resolution, the viral genetic footprint that is needed for a virus to cross hosts. The study of the genetic make-up of HIV strains that are the first detected during infection pointed to an extreme bottleneck where only the fittest virus is transmitted. (130) Curiously, the genetic diversity of transmitting strains is reflected in the ease with which the virus can infect. For instance, there is greater genetic diversity in HIV founder strains that are transmitted from male to female compared to female to male transmitting viruses. In addition those recipients with additional risk factors, such as sexually transmissible infections (STIs), further relaxes the genetic bottleneck of the virus and allows a more diverse viral population to pass rather than a stringently defined transmitting

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

strain. (130, 131) Whilst the genetic make-up of the incoming virions in the early stages of HIV transmission is now mapped in large cohorts at fine detail with near whole HIV genomes, understanding the actual biological phenotype of the transmitting strain is still under consideration. (130, 132-139) Recent studies by Carlson and colleagues point to the transmitting strain being the “fittest” virus. (130) That is, the virus that makes it across the mucosa and has the ability to sustain early and robust viral replication prior to the mounting of an immune response. Whilst most researchers point to changes in HIV envelope, it is rather the overall genetic makeup of the virus that dictates the fitness of virus in vivo. As to whether the HIV envelope in a transmitting strain has a preference for HIV targets, in in vitro assays there is support for founder viruses to rely on high levels of CD4 and thus having a preference for CD4+ T cells. (132, 137, 140) That said, the appearance of HIV within the brain is largely mediated through macrophage infections and thus the clear-cut distinction that transmitting strains preferentially infect CD4+ T cells rather than other known HIV targets like dendritic cells and macrophages, is still a topic of debate. Even if founder strains did preferentially target CD4+ T cells, we must note that other HIV reservoirs, like those in macrophages, do exist in vivo and must be taken into context for the overall pathogenesis in vivo (whether that be during the acute or chronic stages of disease).

Challenges in achieving a HIV cure

Understanding the molecular virology of HIV infection has not only been essential for the development of antiretroviral drugs that block HIV replication but will also be crucial in the development of strategies for curing HIV infection.

Present limitations on therapeutic driven cures

The persistence of HIV infection in the face of antiretroviral therapy (ART) reflects the complex nature of the target cell population – our immune system. The immune system relies on the persistence of long-lived memory CD4+ T cells that can be activated upon future exposure to pathogens. HIV can establish a reservoir of latent infection within this memory CD4+ T cell pool and thus persist for long periods of time (estimated to be several decades with current half-life estimates of 44 months. (141, 142) Treatment with ART is successful in reducing HIV viral loads, reducing onward transmission and limiting viral evolution to a point where it can no longer be detected. (143, 144) However, given the long half-life of the latent reservoir and that it may be clonally expanding over time, (145-148) ART needs to be life-long. Indeed, once on ART, it is recommended that patients do not stop therapy, as clinical trials of treatment interruptions have observed recrudescence of HIV replication after ceasing ART. (149)

Documented precedents for a HIV cure

The latent HIV reservoir provides the primary challenge towards a HIV cure. In hepatitis C virus (HCV) infection, latent reservoirs are not formed and therapeutic cures can be achieved within only 12 weeks of antiviral therapy. (150) Thus, targeting the latent HIV reservoir has received significant attention in efforts towards a HIV cure. In discussing requirements for a HIV cure, two levels of cure have been considered. Firstly, a sterilising cure, which refers to the eradication of HIV from all cells and body tissues, analogous to HCV cures achieved by antiviral therapy. Determination if a sterilizing cure has actually been achieved will, however, be a challenge. The second type of HIV cure is referred to as a functional cure, where HIV replication is controlled at levels below detection in the absence of ART. In this context, a small subset of individuals referred to as elite controllers (EC) fit the definition of functional cure, as they exhibit persistent plasma HIV RNA levels of <50 copies/mL without ART. (151) Augmentation of immune responses against HIV by vaccination to produce this outcome would be the obvious path to replicate this setting. The genotypes of individuals who are classified as

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

EC are enriched for various traits, compared to the general population, which provides clues as to what type of immune responses should be augmented. For example, HLA-B*5701 is carried by about 65% of ECs compared to 10% of the US caucasian population, highlighting the importance of CD8+ T cell driven viral control in this unique population. (152)

Only one case of a HIV cure has been documented ('The Berlin Patient'). Recently, another potential cure case ('The London Patient') has been reported but is cautiously referred to as a patient in long term remission. (153) Whilst these two cases are of particular importance, it is important to note there have been several so-called 'HIV near cures', including the Boston patients and the Mississippi baby. Documentation of failed but 'near cure' attempts are invaluable in vivo observations that help on the path towards a HIV cure. The first documented 'near cures' were observed in what are referred to as the Boston patients. (154) Both patients received an allogeneic hematopoietic stem cell transplantation (HSCT) for treatment of hematologic malignancies and remained on ART. The processes of conditioning for, and engraftment of, the HSCT was associated with a 3 log drop in HIV viral load. However, ART interruption (often referred to as analytical treatment interruptions in HIV cure research) to determine if a HIV reservoir persisted, led to a rebound of HIV replication after 12 weeks in one patient and 36 weeks in the second patient. Additional HSCT cases to the Boston patients have also documented similar findings and in one patient rebound of HIV replication was delayed to 41 weeks. (155) Therefore, whilst HSCT did not result in successful HIV cures, it did highlight that the process of undergoing a HSCT could significantly impact on the HIV reservoir size, as indicated by the lag in rebound of HIV replication once ART was stopped. However, the potential morbidity and mortality associated with HSCT must be considered and compared to that of successful ART. Therefore, HSCT is currently not an acceptable HIV cure strategy at in HIV patients who do not have hematologic malignancies.

In the case of the 'Mississippi baby', the child started ART at 30 hours post-birth (156) with therapy ceased 18 months later. Resumption of HIV replication was not detected until around 27 months post-ART cessation. (157) In this context, while early ART led to long-term suppression of HIV replication, it clearly did not prevent the establishment of a HIV reservoir. This case informed the field that even very small viral reservoirs can persist in the face of ART and, importantly, that the reservoir could recover and expand when ART is ceased.

To date, the only known examples of individuals who are considered to be cured of HIV infection are the 'Berlin patient' (158, 159) and the 'London patient'. (153) The 'Berlin patient' was infected with HIV for over 10 years and underwent treatment for acute myeloid leukemia. Treatment consisted of chemotherapy, anti-thymocyte globulin, total body irradiation and finally a HSCT from a donor who was homozygous for the delta 32 mutation in the gene for CCR5, which leads to lack of CCR5 expression on cells and protection from HIV infection. For close to 10 years off ART, the patient had undetectable HIV using current detection methodology. However, around the 10 year mark, the patient commenced PrEP to prevent future HIV infection (disclosed by the patient at the HIV Gene Therapy conference in Seattle, 2017). The London patient represents a similar clinical case with important modifications to clinical conditioning prior to a HSCT with stem cells from a donor homozygous for the delta 32 CCR5 mutation. (153) In brief, the clinical conditioning for the London patient had greater specificity for targeting the lymphoma and could be used at a reduced intensity. In contrast, conditioning for the Berlin patient was of greater intensity and consisted of combined radiation and chemotherapy treatment. Whilst these cases provide hope for development of a HIV cure strategy, the time between identification of the Berlin patient and the London patient (over 10 years) highlights the rarity of 'HIV cures' and the challenges likely to be encountered in implementing this specific approach. That said, as additional cases beyond that of the Berlin and London patient are observed, the clinical protocols for co-treating lymphoma and HIV may lead to greater numbers of patients in co-remission for HIV and lymphoma.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

As mentioned above, the process of HSCT in the 'Boston patients' reduced the size of the HIV reservoir but failed to eradicate it. (160) Of note, both patients had a HSCT from donors who were genetically permissive to HIV infection (ie. did not carry the CCR5 delta 32 homozygote genotype). (154) Thus, HSCT may require a donor with a homozygous delta 32 mutation to create not only a reduction in the HIV reservoir size but also engraftment of bone marrow with a population of stem cells from which immune cells develop that are resistant HIV infection. However, the low frequency of donors who are homozygous for the delta 32 mutation in the CCR5 gene (161) compromises the feasibility of the Berlin and London patient approaches. In addition, whilst we always note the successful cases, it is also important to consider the repeat attempts at mimicking a cure in this way that have failed. For example, a HSCT carried out on a patient with leukaemia using stem cells from a donor who was homozygous for the CCR5 gene delta 32 mutation was followed by a rebound infection with CXCR4-tropic HIV post-transplant in addition to relapse of the leukemia, (162) both contributing to the patient's death.

Gene therapy

There are many approaches to using gene therapy in HIV cure research at various stages of development. Given the outcome of the Berlin patient, gene therapy to render cells resistant to HIV infection ex vivo is being considered to not only mimic the stem cells of the donor used for the HSCT in the Berlin patient but also to avoid graft versus host disease (as the genetically manipulated cells are derived from the same patient). Advancements in gene therapy techniques that can render cells resistant to HIV include lowering CCR5 expression levels, (163-168) expression of peptides that inhibit the HIV fusion reaction (163, 168, 169) and post-entry manipulation that can transcriptionally silence the virus and thus keep it permanently in a dormant state. (170-172) Treatment may also consist of combination approaches, for example current clinical trials are underway that utilize both reduction of CCR5 expression and use of HIV fusion inhibiting peptides. Whilst the latter gene therapies have great potential, delivery of the genetic information to the right cells still provides issues in terms of feasibility. For example, it is notoriously difficult for peripheral blood CD4+ T cells to acquire genetic information using existing transduction techniques. (173, 174)

Whilst generation of HIV resistance and silencing of the existing HIV reservoir are two means by which gene therapy may contribute towards a HIV cure, others are now using gene therapy to attack the latent reservoir using genetically modified T cells. Chimeric antigen receptor T cells (CAR T cells) are genetically modified CD4+ and CD8+ T cells in which the T cell receptor has been modified to target various antigens, often by using a single chain antibody fragment from an antibody specific to that antigen. This approach has revolutionized cancer therapy. In particular, previously untreatable B cell malignancies can now be treated with this type of gene therapy (reviewed in depth by June and colleagues. (175) Interestingly, preclinical studies in animal models using this approach to target HIV infection have observed promising results. (176) Furthermore, this approach has increased biomedical knowledge at several levels. Firstly, that effective CD8+ T cell responses can lead to control of HIV replication. Secondly, that unique broadly neutralising antibodies to HIV can be isolated and used to generate panels of chimeric antigen receptors to induce CD8+ T cells to attack any cell type expressing HIV envelope glycoproteins (reviewed in (177)). Finally, that CD8+ T cells can be modified to target specific cells in which HIV may persist; for example, follicular helper CD4+ T cells, which contain a significant reservoir of HIV infection in lymphoid tissues (reviewed by (178)). Thus, investigators are now encoding CXCR5 (the chemokine receptor that controls trafficking of T cells to germinal centres in lymphoid tissue) alongside a chimeric antigen receptor that recognises and targets HIV-infected cells. (179)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Whilst gene therapy has the potential to contribute to a HIV cure, accessibility to this treatment will be the biggest challenge moving forward as the cost to treat each person will be in excess of \$500,000. Given the current success of gene therapy for many cancers, increased optimisation of gene therapy protocols and more streamlined clinical efforts will hopefully lead to increased accessibility over time.

Reversal of HIV latency in combination with ART

If ART and immune-based therapies are to exert an effect on the latent HIV reservoir, viral latency should be reversed. Several avenues for waking the latent reservoir have been explored and primarily use what is called latency reversing agents (LRAs). The latent reservoir is well known to 'wake' as a result of T cell activation and, therefore, early studies attempted to activate CD4+ T cells. However, along with the activation came various toxicities with limited reservoir reduction. (180, 181) Subsequent attempts to refine latency reversal led to the use of candidate LRAs such as HDAC inhibitors (182-186) and methylation inhibitors. (187) Clinical trials using potent HDAC inhibitors have demonstrated transient increases in cell-associated and plasma HIV-1 RNA consistent with waking of the latent reservoir. However, to date limited reservoir reduction has been reported. (182, 183, 185, 186, 188) Yet it is presently unclear if the lack of reduction in the reservoir size is due to lack of latency reversal or the failure to subsequently deplete infected cells. Key to the latter, is the ability of immune responses, driven primarily by CD8+ T cells or neutralizing antibodies, to target infected cells. Thus, augmentation of T cell and antibody responses by therapeutic vaccines, passive immunization with potent neutralising antibodies, or even delivery of genetically modified CD8+ T cells (CAR T cells) may be key to the elimination of HIV reservoirs after latency reversal.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

HIV immunology

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Last reviewed: November 2019

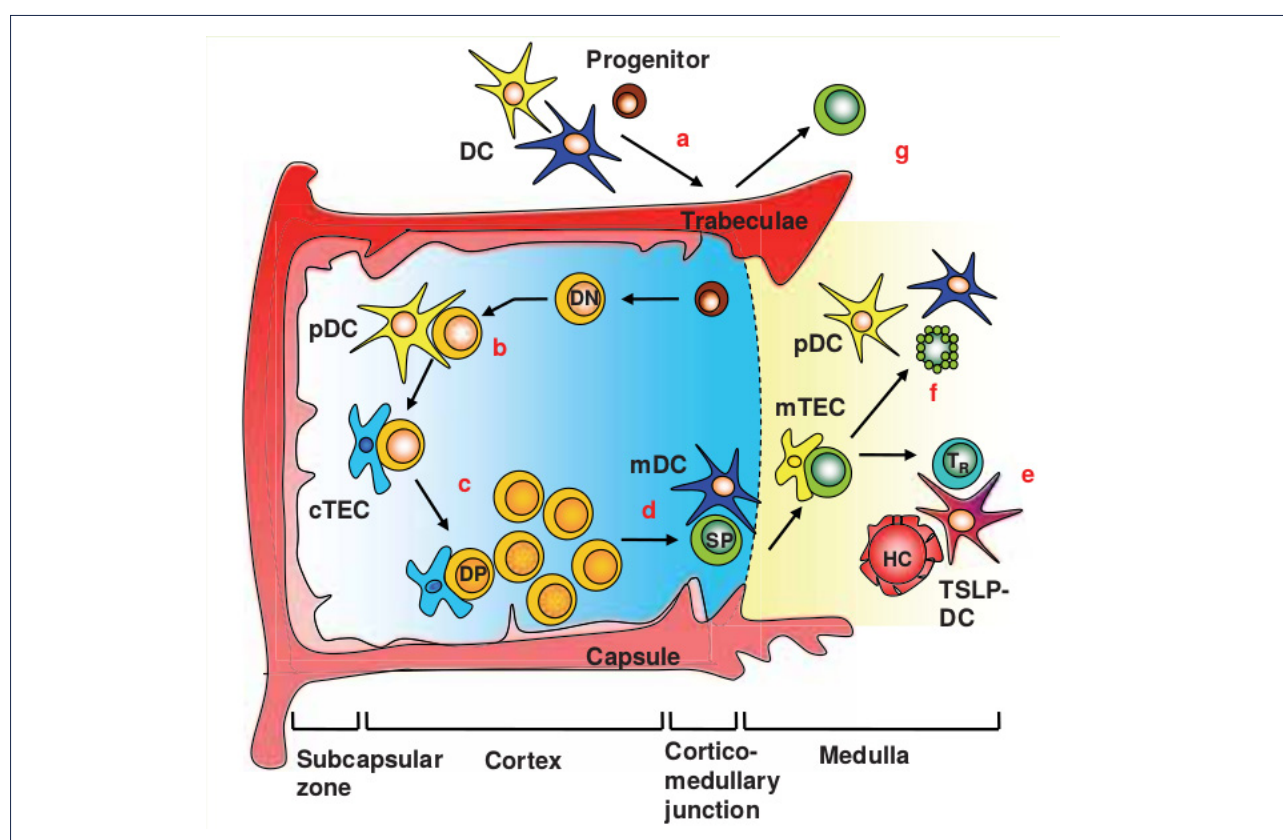
The cellular immune system

The cellular immune system is the main component of adaptive immune responses that target virally infected cells and is preferentially destroyed in HIV disease. This section will highlight aspects of adaptive and innate immunity including T-cell development, antigen presentation and recognition, T-cell memory, chemokine biology, lymph node architecture and B cell development, relevant to HIV disease pathogenesis.

T-cell development

Stem cells continuously migrate from the bone marrow to the thymus. Although the thymus partially involutes with age, T cells continue to develop in the thymus throughout life. (129,151) T-cell development in the thymus involves processes for both positive and negative selection that result in the production of T cells with the capacity to recognise foreign or non-self antigens (Ag) (147) (Figure 1).

Figure 1. Generation of T cells in the thymus



Note: The thymus is divided into lobules separated by trabeculae. Each lobule has a cortex and medulla. T-cell precursors enter the thymus and conditioned naïve T cells exit at the corticomedullary junction (a).

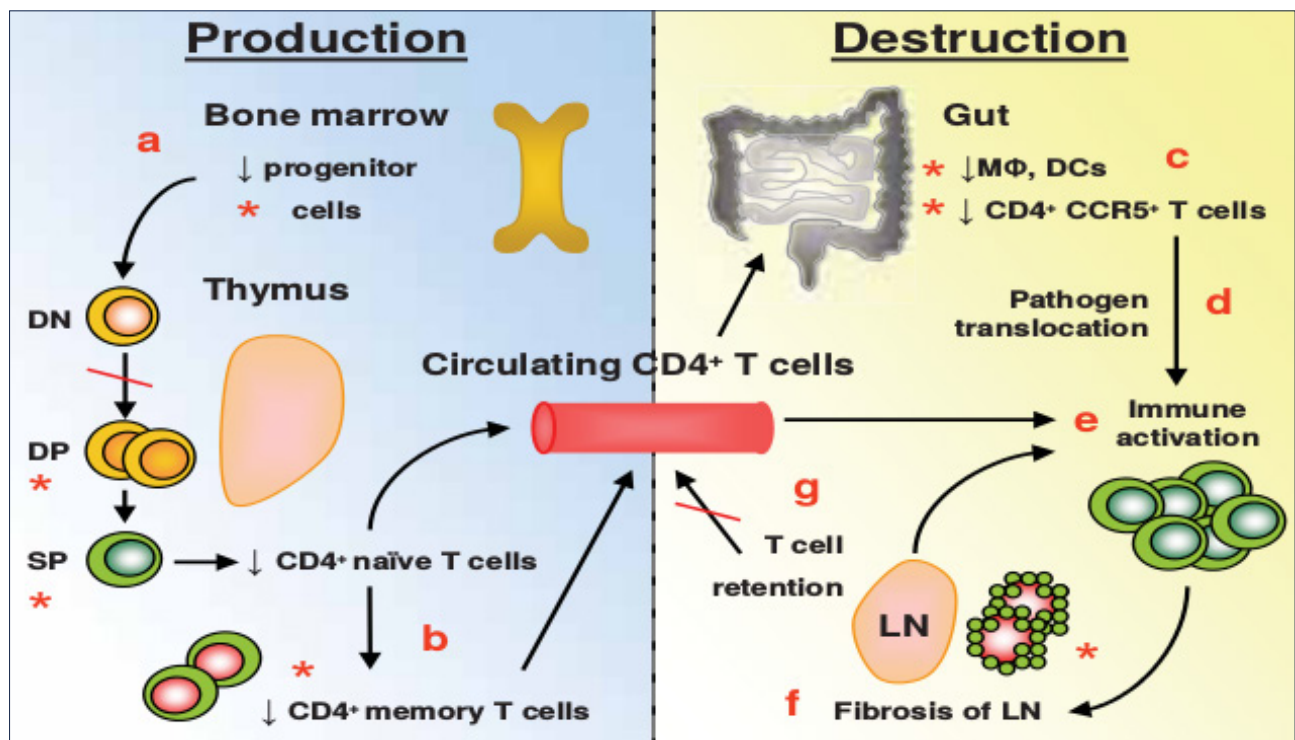
CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

The immature double negative (DN; CD3-CD4-CD8-) thymocytes develop and migrate to the cortex where they interact with plasmacytoid dendritic cells (pDC) and cortical thymic epithelial cells (cTEC) (b). Positive selection for low affinity T-cell receptors (TcRs) interacting with self major histocompatibility complex (MHC) molecules and expansion of double positive (DP; CD3+CD4+CD8+) cortical thymocytes occurs in the cortex (c). The positively selected single positive (SP; CD3+CD4+CD8- and CD3+CD4-CD8+) thymocytes migrate to the corticomedullary junction where further interactions with myeloid dendritic cells (mDC) and pDC and medullary thymic epithelial cells (mTEC) lead to negative selection and elimination of high affinity self-reactive T cells (d). Expansion of thymocytes with intermediate affinity for self, into T-regulatory cells (Treg) occurs during interaction of SP thymocytes with DC modified by the cytokine thymic stromal lymphopoietin (TSLP) generated by the Hassall's corpuscles (HCs) (e). Thymocytes are destroyed during negative selection with DC (f) or survive the conditioning to emerge as recent thymic emigrants (RTE) (g).

Source: Evans VA, Cameron PU, Lewin SR. Human thymic dendritic cells: Regulators of T cell development in health and HIV-1 infection. Clin Immunol 2008; 1126:1-12. Used with permission

In humanised mouse models of HIV infection, reconstitution of the human immune response depends on thymic reconstitution or transplantation. (113) The relationship between thymic production and subsequent destruction of T cells in HIV infection is summarised in Figure 2.

Figure 2. Pathways for CD4+ T cell depletion in HIV infection



Note: Depletion of CD4+ T cells in HIV infection may occur as a result of direct infection (*) and death of CD4+ T cells or by indirect mechanisms. HIV-1 infection has been associated with impaired production of CD34 progenitor cells in the bone marrow (a), reduced proliferation of thymocytes (70) and direct infection of CD4+ thymocytes leading to reduced numbers of recent thymic emigrants and naïve CD4+ T cells. (20) In addition, HIV-1 directly infects circulating CD4+ memory T cells although at low frequency (b). At the same time, there is significant depletion of mucosal CD4+ T cells (by direct infection of both CCR5+ and CCR5- CD4+ T cells), DCs

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

and macrophages (MΦ) (c). (25) This may potentially compromise the integrity of the mucosal barrier leading to increased translocation of bacteria from the intestinal lumen (d). (24) High levels of immune activation (e) increase the proliferation and death of both CD4+ and CD8+ T cells, which are associated with lymph node (LN) fibrosis (f) and retention of T cells in the LN (g) immune activation (e) increase the proliferation and death of both CD4+ and CD8+ T cells, which are associated with lymph node (LN) fibrosis (f) and retention of T cells in the LN (g). (26) DN=double negative; DP=double positive; SP=single positive thymocytes.

Source: Evans VA, Cameron PU, Lewin SR. Human thymic dendritic cells: Regulators of T cell development in health and HIV-1 infection. Clin Immunol 2008; 1126:1-12. Used with permission.

Antigen presentation and recognition

Antigen-presenting cells (see below) process foreign proteins into smaller peptides and express these antigens on their cell surface in association with MHC molecules, also referred to as human leukocyte antigens (HLA). T cells usually express either CD4 or CD8 molecules on their surface. These molecules are crucial in antigen recognition and in the function of the TcR. The primary function of MHC molecules is the presentation of antigen in the form of short peptides to T cells.

These molecules are essential for T cell recognition of antigens. MHC class I molecules (MHC-I) (HLA-A, B and C) are found on the surface of all nucleated cells and present antigens to CD8+ T cells. MHC-II molecules (HLA-DR, DP, DQ) are expressed only on professional antigen presenting cells such as dendritic cells (DC), B lymphocytes and macrophages. They present antigen to CD4+ T cells. Both MHC-I and MHC-II genes are highly polymorphic.

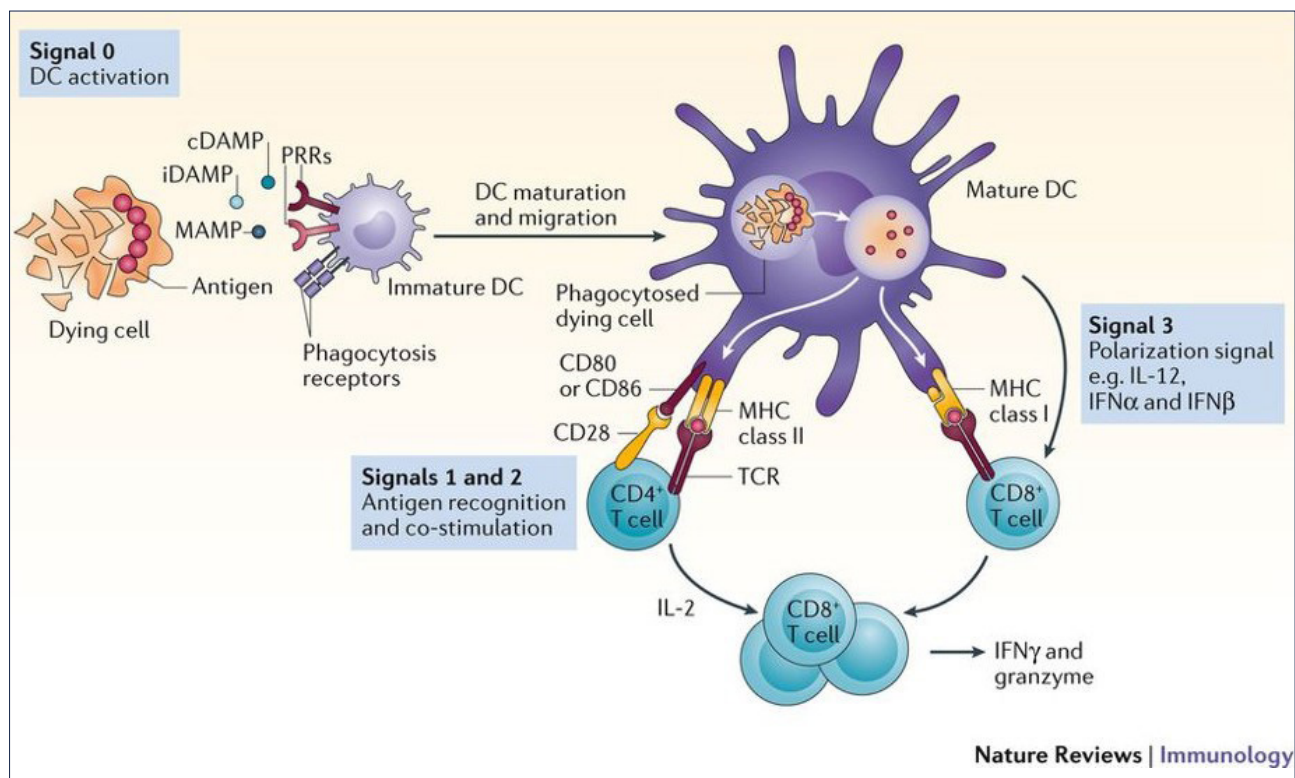
When the TcR, associated with CD3 and CD4 or CD8 molecules, binds to the antigen-MHC complex on an antigen presenting cell, cellular activation signals are transmitted from the complex of TcR/CD3. These TcR activation signals must be accompanied by co-stimulatory signals via CD28 and other co-stimulatory molecules or by cytokines. TcR signalling alone results in anergy or apoptosis. Activation of antigen presenting cells leads to expression of costimulatory molecules including CD40, CD80, CD83 and CD86. Cytokines within the inflammatory milieu and signalling from toll-like receptors (TLR), that recognise foreign pathogen associated molecular profiles, activate the antigen presenting cell to enable effective co-stimulation of T cells.

Innate immune responses and the activation of adaptive immune responses

Adaptive immune responses depend on the initial recognition of pathogens. There are several pathways for recognition, including TLR 1-10, intracellular cytoplasmic sensors (including RIG-I like receptor, STING and cGAS) and various innate lymphoid cells (ILCs). For antigen presenting cells, the initial sensing of such pathogens or cell damage is mediated by pattern recognition receptors on the dendritic cells and myeloid cells. These start the maturation and migration of the antigen processing cells as well as the upregulation of antigen processing by the DC and the upregulation and expression of MHC II on the surface of the DC. Following this, the DC can efficiently present antigens to naive T cells, which will then become effector or memory T cells. (Figure 3)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Figure 3. Innate immune responses and the initiation of adaptive immunity



Note: The first step in the initiation of an antigen specific immune response is the maturation and migration of DCs, which is initiated by signals delivered by pattern recognition molecules and phagocytosis receptors which are part of the innate immune system. These signals, designated signal 0, can be delivered by DAMP (Danger associated molecular patterns) MAMP (Microbial associated molecular profiles) or by molecules derived from dying cells. The DC has TLRs that mediate these signals. The maturing DCs take up antigens by phagocytic receptors and C type lectin receptors, process the antigens and present them on MHC I and MHC II molecules (referred to as signal 1), as well as express costimulatory molecules (referred to as signal 2). These signals lead to stimulation of CD4+ T cells, which produce cytokines that further activate CD4+ and CD8+ T cells (signal 3 for T cell activation). The types of cytokines produced by CD4+ T cells are responsible for determining the type of T cell response that will be produced.

Source: Yatim N, Cullen S, Albert ML Dying cells actively regulate adaptive immune responses, Nature Review Immunology 2017; 17:262-275 Used with permission

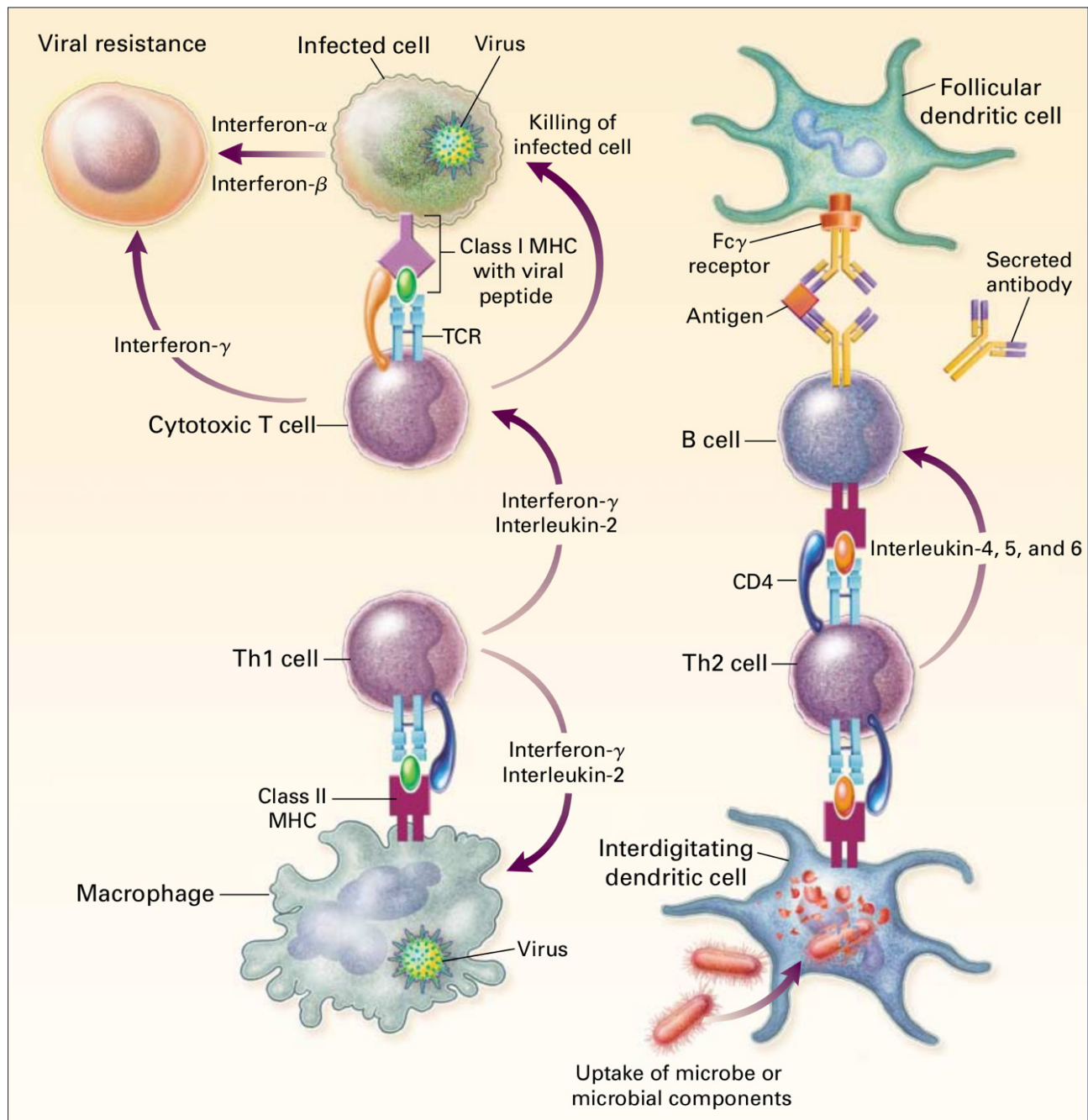
T cell effector responses

Upon recognition of cognate antigens binding to the TcR expressed on the cell surface, T cells become activated and develop into effector T cells. CD4+ effector T cells function as helper cells. This help is mediated by the secretion of cytokines which influence the function of surrounding cells. CD4+ T cells can be broadly divided into sub-populations defined by the pattern of secreted cytokines and surface expression of chemokine receptors that controls their migration to lymphoid and other tissues. CD4+ T cells, in addition to broad classification as helper, cytotoxic or regulatory cells, can be described by their stage of maturation as naïve (including recent thymic emigrants), effector memory, central memory, transitional memory, terminally differentiated or stem cell memory. These stages of maturation differ in longevity and in patterns of migration, which are largely defined by their surface markers including particularly chemokine receptors and β integrins.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

With cognate interactions, naïve T cells initially develop into non-polarised Th0 memory cells, and with subsequent stimulation develop into type 1 helper (Th1), type 2 helper (Th2) and type 17 helper (Th17) T cells, depending on cytokines present in the cellular micro-environment in which they develop. Th1 lymphocytes secrete interleukin (IL)-2 and interferon-gamma (IFN gamma), but not IL-4, -5 or -6 whereas Th2 lymphocytes secrete IL-4, -5, -6 and -10, but not IL-2 or IFN gamma (Figure 4).

Figure 4. An overview of CD4+ and CD8+ lymphocyte responses



Note: T cells characteristically possess TcR that recognise processed antigen presented by MHC molecules, as shown on the left side of the figure. Most cytotoxic T cells express cell-surface CD8 and recognise processed intracellular viral antigens, which are presented as peptides by MHC-I molecules, and kill infected

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

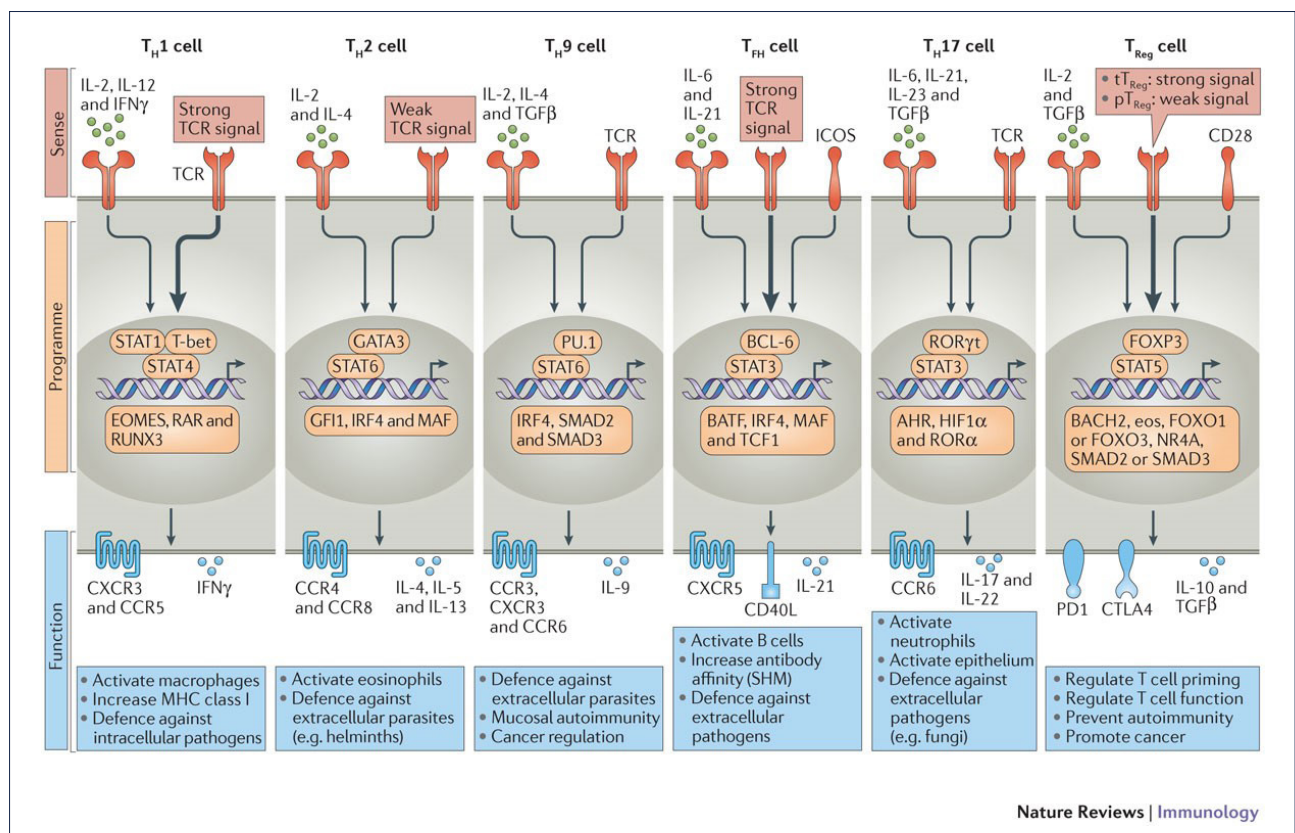
cells, thereby preventing or restricting viral replication. Activated cytotoxic T cells secrete interferon-gamma that, together with interferon-alpha and interferon-beta produced by the infected cells themselves, sets up a state of cellular resistance to viral infection. As shown on the right side of the figure, helper T cells are generally positive for CD4 molecules, recognise processed extracellular antigen presented by MHC-II molecules on antigen presenting cells, and can be divided into two major populations. Type 1 helper (Th1) T cells secrete interferon-gamma and interleukin-2, which activate macrophages and cytotoxic T cells to kill intracellular organisms. Type 2 helper (Th2) T cells secrete IL-4, -5, and -6, which help B cells secrete protective antibodies. B cells recognise antigen either directly or in the form of immune complexes on follicular dendritic cells in germinal centres of lymphoid tissue.

Source: Delves PJ, Roitt IM. The immune system. Second of two parts. N Engl J Med 2000; 343:108-17. All rights reserved. Used with permission.

Th1 cytokines support cell-mediated immune responses whereas Th2 cytokines generally support antibody responses. CD4+ T cells may also function as Treg cells, which develop in the thymus (central Tregs) or within the peripheral lymphoid tissue. Each of these populations has specific nuclear factors controlling their development (77) (Figure 5).

Figure 5. Lymphocyte differentiation and diversity

Not really a better more recent overview of responses in the immunity



CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Note: Thymus-derived naïve CD4+ T cells differentiate into different sub-populations of CD4+ T cells during interaction with antigen presenting cells. Depending on the strength of TcR signalling, the particular transcription factors, the anatomical site and cytokine predominance in the micro-environment in which they encounter antigen presented by DC, they differentiate into effector or memory cells, with the phenotype determined by specific nuclear factors required for development of each subset. The effector cells express chemokine receptors that control their migration and produce specific cytokine mediators that determine their specific function.

Source: DuPage, M., and J.A. Bluestone. 2016. Harnessing the plasticity of CD4+ T cells to treat immune-mediated disease. *Nat Rev Immunol.* 16:149-163. Used with permission.

CD8+ T cells

CD8+ effector T cells are predominantly cytotoxic lymphocytes (CTLs). After binding to antigen on the surface of an infected cell, CTLs kill infected cells by inducing apoptosis by one of two means. Firstly, CTLs may insert perforins into the membrane of an infected cell, facilitating the passage of granzymes which promote apoptosis by direct activation of the intracellular caspase pathway. Alternatively, CTLs may bind to Fas (a protein which is expressed on the surface of the infected cell) via the Fas ligand (which is expressed on the surface of the CTL). This binding subsequently promotes apoptosis of the infected cell. CD4+ T cells also have the capacity to be CTLs under the regulation of CD8+ T cells. These cytolytic CD4+ T cells induce cell death by a fas-mediated mechanism that depends on CD137 (BB-1). The development of CD8+ CTL requires interactions with CD4+ T cells.

CD4+ T cell memory populations

An essential feature of an adaptive immune response is the establishment of immunological memory. Each of the populations of CD4+ T cells, defined by their cytokine production and chemokine receptors (figure 5), can be further defined by the stage of development. Naïve T cells either become effector or memory T cells following their encounter with cognate antigen and DC. This occurs in the lymph node where naïve T cells entering from the blood through high endothelial venules (HEV) and encounter their cognate antigen carried from the tissue as processed antigens on antigen presenting cells. Following clonal expansion and conversion of naïve T cells to memory T cells, specific changes in the T cell phenotype ensure that the T cells recirculate into peripheral tissues and have a superior quantitative and qualitative response upon subsequent encounter with antigens.

Memory and naïve cells can be distinguished by cell surface markers. They express different isoforms of the CD45 molecule; CD45RA on naïve cells and CD45RO on memory cells, although naïve cells are more accurately defined by multiple surface markers (CCR7+, CD28+ and CD62L+). Effector memory cells re-express the CD45RA isoform but can be distinguished from naïve cells in that effector cells do not express CD62L or CCR7. Within the memory CD4+ T cell populations there are subpopulations recognised by the surface expression of specific molecules, including CD27 and the chemokine receptor CCR7, which is critical in migration of T cells into the lymph node and peripheral tissues. Cells expressing the chemokine receptor CCR6 migrate into gut and peripheral tissues whereas CXCR3 is critical for the migration and T-cell killing at sites of inflammation and virus infection. (120)

Memory CD4+ T cells control the development of B cells and the production of high affinity antibodies. (Figure 5) Loss of CD4+ T cells is thus a critical factor in the failure of adaptive immune responses to HIV infection.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Chemokines and T cell circulation

Chemokines derive their name from being chemotactic cytokines. Their principal biological function is to regulate and direct the trafficking of cells to sites of inflammation rich in foreign antigens. Broadly, the chemokine family is divided into four subgroups: CC, CXC, C and CX3C where C represents two terminal cysteine residues and X represents the number of intervening amino acids between the two terminal cysteine residues. This structural classification also has biological significance where CXC chemokines, also referred to as alpha-chemokines, are inflammatory chemokines that attract neutrophils whereas CC chemokines, also referred to as beta-chemokines, are homeostatic chemokines principally involved in homeostatic recirculation and in attracting lymphocytes and monocytes into immune responses.

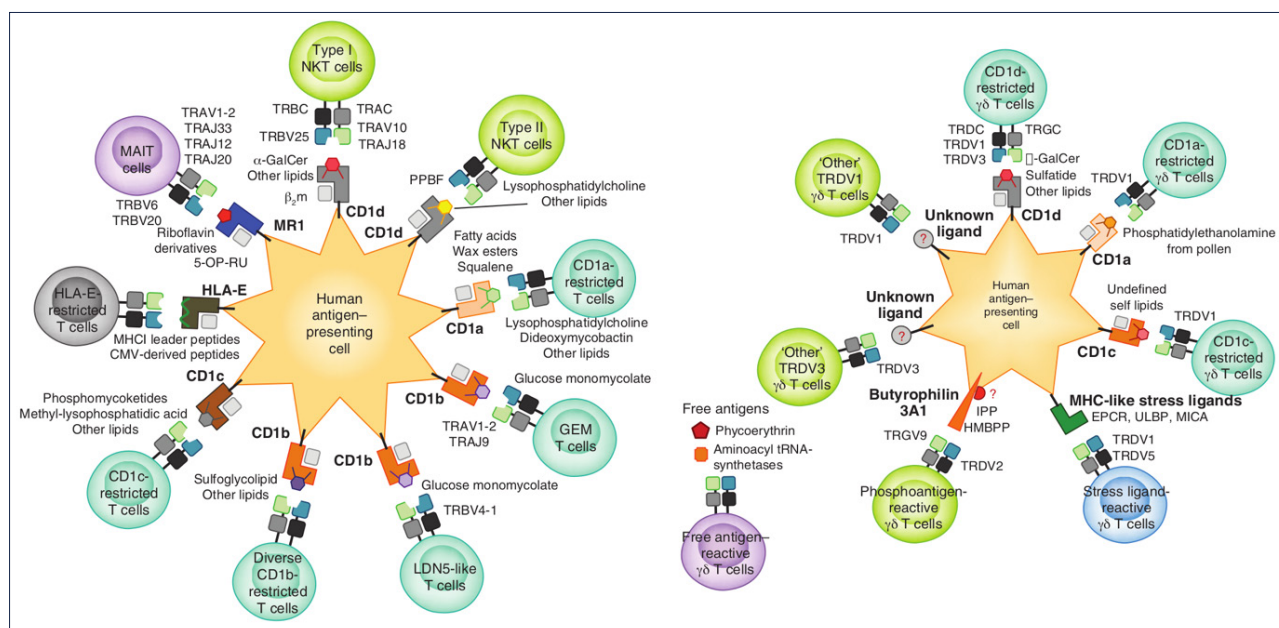
Chemokines bind to specific chemokine receptors on the surface of cells. Most of the chemokine receptors belong to the seven-transmembrane-spanning, G-protein-linked rhodopsin receptor family. (13) Chemokine receptors primarily bind to chemokines within the one class of chemokines and are classified as being either CC chemokine receptors (CCR) or CXC chemokine receptors (CXCR). Chemokine/chemokine receptor pairs of particular significance in HIV pathogenesis are: macrophage inflammatory protein-1 alpha (MIP-1 alpha, CCL2), MIP-1beta (CCL3) and 'regulated on activation, normal T cell expressed and secreted' (RANTES, CCL5), which are natural ligands for CCR5 the coreceptor for HIV, and stromal derived factor-1 (SDF- 1, CXCL12), which is the natural ligand for CXCR4. Polymorphisms in these receptor/ligands have been demonstrated to influence HIV transmission and disease progression (see section on [Natural history of HIV infection](#)).

Innate lymphoid cells and NK cells

The signals for development of particular CD4+ T cell subsets depends on the TcR signal strength, antigen presenting cell function and the cytokines in the environment. There is a parallel system of development of specific innate lymphoid cells (ILCs) designated ILC1, ILC2 and ILC3 that correspond in terms of cytokine production to Th1, Th2 and Th17 CD4+ T cells. (Figure 6) (57) These ILCs are predominantly tissue resident and have few if any circulating equivalents. Included among these ILC are cells that have been defined by their invariant TCR including Mucosa associated Invariant T cells (MAIT cells). These cells represent the cellular equivalent of the TLR and recognize microbial products or metabolites on antigen presenting cells. MAIT cells and ILC are lost in HIV infection. Natural killer cells (NK cells) are also lymphocytes that mediate innate immune responses against virally-infected cells but are capable of circulating to tissues; they exist as CD56 bright KIR- IFN γ producing and a CD56 dim KIR+ cell expressing low IFN γ and the cytotoxic molecules perforin and granzyme.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Figure 6. Innate lymphoid cell receptors and ligands



Note: A) Innate lymphoid cells are restricted by a limited range of TCRαβ and an “antigen” presented in their HLA restricting element on dendritic cells. MAIT cells are restricted by specific TCR on their surface, the MR1 molecule on antigen presenting cells and the microbial riboflavin metabolite 5-OP-RU. B) Innate lymphoid cells restricted by TCRγδ recognize a range of MHC restricted molecules with a range of ligands binding to the MHC including lipid such as α-Galactosylceramide restricted by CD1d recognized by NKT cells.

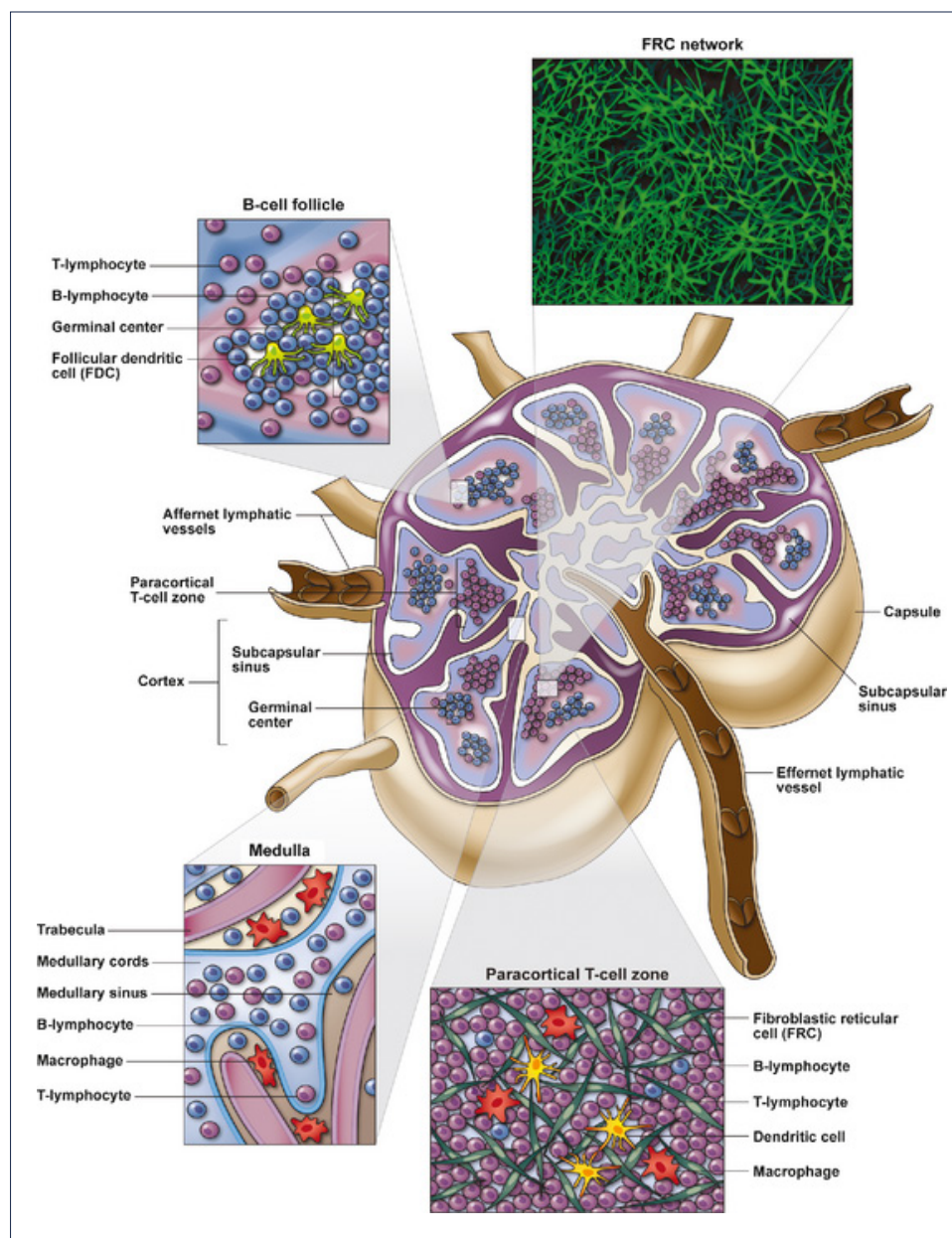
Source: Godfrey DI, Uldrich AP, McCluskey J, Rossjohn J, Moody DB. The burgeoning family of unconventional T cells. *Nature Immunology*. 2015 Nov; 16:1114–23. Used with permission

Lymph node architecture

The lymph node is a specialised lymphoid organ that facilitates the development of both humoral and cellular adaptive immune responses by providing a site for interaction between recirculating naïve T and B cells and antigen carrying DC migrating from tissues via afferent lymphatics. It is divided into an outer cortex and an inner medulla. The cortex contains B cell-enriched follicles that contain specialised foci called germinal centres. The germinal centres are the site of expansion of antigen-specific B cells and are involved in the generation of antibody responses, in particular the development of B cells with high affinity antigen receptors, known as B cell receptors (BCRs), which consist of immunoglobulin molecules expressed on the cell surface. This occurs through a process of affinity maturation and somatic hypermutation of immunoglobulin genes in B cells. Follicles contain DCs, follicular B lymphocytes, follicular helper CD4+ T cells (TFH) cells and a non-haematopoietic population of follicular DC (FDC) that provide a repository of immune complexes, including HIV-containing immune complexes in people with HIV infection. (29,84) The T-cell enriched cortical regions between the follicles are known as the interfollicular regions. These thymus-dependent interfollicular regions are enriched in naïve T cells and are critical for the development of cellular immune responses. They are the site of initial activation of naïve T cells during DC-T cell interactions. The T-cell enriched regions contain antigen-presenting interdigitating DC derived directly from blood or, by migration via afferent lymphatics, from tissue. They also contain CD4+ and CD8+ T cells and some naïve B cells. The collagen matrix and fibroblastic reticular cells provide a scaffolding of the lymph node but in HIV infection there is progressive lymph node fibrosis which is a critical factor in CD4+ T cell loss (Figure 7). (83)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Figure 7. Lymph node architecture



Note: Antigen migrates to the lymph node from infected tissues via the afferent lymphatics as free antigen or processed in tissue and carried by DC. Naive T cells enter from blood and interact with DC in the cortical T cell zones. B cells interact with T cells and DC in the T cell regions and then migrate into the B cell follicle where they expand to produce antigen-specific memory B cells and plasmablasts, which migrate to the bone marrow and differentiate into plasma cells and produce antibodies. FDCs in the germinal centres of the B cell follicle provide a reservoir of antigen/antibody immune complexes. T cells, B cells and plasmablasts migrate from the lymph node via the medulla and the efferent lymphatic vessels. Antigen-specific

memory or effector B cells or T cells, activated in the lymph node, can then migrate to tissue sites of infection or inflammation. The collagen matrix and fibroblastic reticular cells network provide the scaffold of the lymphoid tissue.

Source: Estes JD. Pathobiology of HIV/SIV-associated changes in secondary lymphoid tissues. Immunol Rev 2013; 254:65–77. Used with permission.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Immunological aspects of HIV pathophysiology

Most people with HIV infection initially develop HIV-specific immune responses comprising HIV-specific CD8+ and CD4+ T cells and HIV-specific B cells and antibodies. These responses are suboptimal and ultimately fail in the majority of people, primarily because of viral immune evasion mechanisms. The preservation of strong HIV-specific antibody and cellular immune responses in people with non-progressive HIV infection does come at the expense of immune activation (see below – Long-term non-progression and elite controllers). This suggests that strategies to restore and maintain host immune responses will be important in the long-term management of patients with HIV disease and for cure strategies. Effective HIV-specific immune responses will also be necessary for the success of prophylactic and therapeutic HIV vaccines.

HIV-specific CD8+ T cell responses

CD8+ T cells recognise a variety of peptides from all HIV proteins including reverse transcriptase, envelope, core (gag) and the accessory proteins Vif and Nef, although CD8+ T responses are predominantly directed against epitopes encoded by the gag and env genes. CD8+ T cells recognise divergent HIV strains with greater frequency than HIV-specific CD4+ T cells. (110) The control of HIV can be shown to be associated with CD8+ T cell responses. Evidence for a direct role for CD8+ T cell responses in the control of HIV and simian immunodeficiency virus (SIV) infection is derived from animal models of macaques infected with SIV where depletion of CD8+ T cells results in rapid rebound of SIV viraemia. (131) Conversely, the induction of effector CD8+ memory T cells can control SIV infection. (112)

Measurement of CD8+ T cell responses

CD8+ T cell responses against HIV can be measured by a variety of assays (See section on Immunological diagnostics). Traditional chromium-release assays were used to detect antigen-specific CD8+ T cell killing of labelled targets. These assays require cell culture and are labour intensive. Other assays to detect antigen-specific T cells use flow cytometry and granule release assays, tetramers of MHC peptide, or intracellular cytokine production. Cytokine production can also be detected via enzyme-linked immunospot assay (ELISPOT). Potential discrepancies between the numbers of antigen-specific CD8+ T cells detected by tetramer staining and those detected by functional assays, such as chromium-release or intracellular cytokine staining, should be appreciated. Chromium-release assays require multiple ex vivo cell divisions and then detection by functional analysis. This may underestimate actual numbers of antigen-specific CD8+ T cells as these cells may readily apoptose ex vivo. Tetramer assays, on the other hand, may over-estimate CD8+ T cell responses by detecting cells with a TcR binding a specific antigen-MHC complex, which exhibit low cytokine production or cytolytic activity. Other methods for measuring CD8+ T cell-mediated killing include CD107a degranulation, fluorescence-based target elimination and caspase cleavage assays, each with advantages and disadvantages.

Role of CD8+ T cells in the pathogenesis of HIV disease

CD8+ T cells play an important role in delaying HIV disease progression. HIV disease progression is associated with a decline in HIV-specific CD8+ T-cell activity in some patients and slow progression of HIV disease is associated with strong CD8+ T-cell activity, upregulation of perforin expression and with polyfunctionality.

Furthermore, an inverse correlation between CD8+ T responses and plasma viral loads suggests a protective role for CD8+ T cells. (51) More direct evidence of a protective role of CD8+ T-cell responses in HIV infection comes from animal models. Monkeys subjected to CD8+ T-cell depletion cannot control plasma viraemia

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

during primary SIV infection. (38) Furthermore, CD8+ T cell depletion during chronic SIV infection leads to profound increases in plasma viraemia (131) and adoptive transfer of CD8+ T cells at the time of infection reduces the viral reservoir. (12)

Human leukocyte antigen associations

The association between HLA genotype and HIV disease progression underscores the importance of CD8+ T-cell responses in HIV disease pathogenesis. (108) HIV-specific CD8+ T cells recognise viral peptides when they are presented on the surface of virally-infected cells in association with HLA- I molecules. Different HLA molecules present different peptides. This variation thus influences the quality of the immune response. For example, HLA-B27 and HLA-B57 are associated with slow HIV disease progression. (139) Even a single amino acid change within HLA-B35 is associated with differences in HIV disease progression. (97) Studies on the evolution of viral reverse transcriptase and HLA types have demonstrated that HIV will adapt to HLA type at a population level. (3,144) Homozygosity of MHC-I molecule genes produces a more restricted CD8+ T cell response than heterozygosity, and has been associated with faster HIV disease progression. (35)

An increase in HIV viral load has been associated with mutations in immunodominant epitopes of peptides eliciting CD8+ T-cell responses, commonly referred to as immune escape. Viral control depends on both the HLA, the nature of the TcR and function of the T cell. (43) In an individual, adapted and non-adapted epitopes differ in their recognition by CD8+ T cells but the presence of CD8+ T cells recognizing adapted epitopes can facilitate DC mediated transfer of virus between CD4+ T cells. (46) This maintains persistence of HIV infected cells even in the presence of CTL responses.

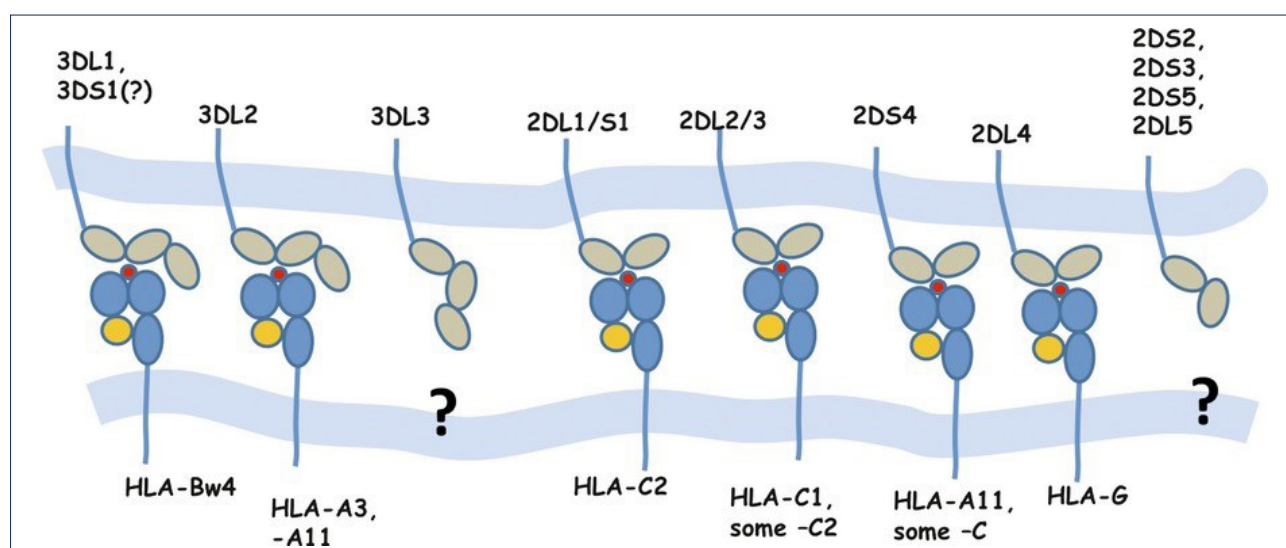
The mechanism by which HLA molecules influence disease outcome differs at different stages of HIV disease. (96) For example, HLA-B57 is associated with an early effect in reducing CD4+ T-cell decline and has a persistent effect throughout the disease course. HLA-B27 has no benefit in the early decline in CD4+ T cell counts to < 200/μL but is important later in delaying disease progression. People with HLA-B35 have an accelerated loss of CD4+ T cells early in the disease course but CD4+ T-cell loss is not different to that seen in people with other HLA genotypes at later stages of disease. At least some of these effects are related to the generation of CTL, early suppression of viral replication and the fitness of escape mutants. (94) Although a small number of specific HLA alleles were initially described as impacting HIV viral load and disease outcome, most alleles can be shown to influence HIV viral load in an additive way. (18)

HLA and KIR

While HLA-I molecules are important in the CD8+ T cell response, NK cells also contribute to viral clearance by responding to the absence or reduced expression of specific HLA-I molecules on virally infected cells. To recognize aberrant virus-infected cells, NK cells express both inhibitory and stimulatory molecules known as Killer Immunoglobulin Receptors or KIR (these molecules belong to the immunoglobulin superfamily of molecules). Polymorphic genes encode a range of KIR (Figure 8) and different haplotypes of KIR genes have been associated with differences in control of HIV replication and HIV disease outcome. (35) The haplotypes containing 2DS activating receptors have been associated with elite control of HIV. The interaction between KIR and HLA-C is important as it represents the most frequent HLA molecule recognized by KIR and its expression is correlated with HIV control in different populations in large genome wide association studies(8) The importance of HLA-C in control of HIV infection is evident in the HIV vpu downregulation of HLA-C in latently infected cells. (14) Such down regulation can be recognized by activating KIR. Successful combinations of HLA-KIR have been shown to control HIV in African populations. (35)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Figure 8. HLA-I and Killer Immunoglobulin Receptors (KIR)



Note: Specific interactions between different KIR molecules on CD8+ T cells and NK cells and MHC-I molecules on target cells. HLA-C2 = HLA-C allotypes with Asn77/Lys80. HLA-C1 = HLA-C allotypes with Ser77/Asn80. Bw4 = HLA allotypes with the serologically defined Bw4 motif.

Source: Martin MP, Carrington M. Immunogenetics of HIV disease. Immunological Reviews. 2013; 254:245–64. Used with permission

Temporal change in CD8+ T-cell responses during HIV progression.

In the majority of people with HIV infection, HIV-specific CD8+ T cell responses are generated soon after the peak of viral replication during primary HIV infection. Indeed, the initial decrease in HIV viral load during primary infection is attributed to the generation of CD8+ T-cell responses. (149) Detection of HIV-specific CD8+ T cell responses precedes the detection of HIV-specific neutralising antibodies.

Up to 10% of CD8+ T cells present during primary HIV infection are HIV-specific. (149) In infections by other viruses, such as cytomegalovirus (CMV) and Epstein Barr virus (EBV), the proportion of virus-specific CD8+ T cells during chronic infection can be greater than 10%. The breadth of HIV-specific CD8+ T-cell responses in acute infection influences disease progression. Monoclonal expansion of HIV-specific CD8+ T cells in patients with acute HIV infection is associated with a poor prognosis and a broad response favours control. Moreover, once the viral set point is reached following primary infection, there is an inverse relationship between the breadth of HIV-specific CD8+ T-cell responses and HIV viral load. (51)

HIV-specific CD8+ T-cell responses are detected in chronic phases of HIV disease in most patients with a frequency of up to 2% of total CD8+ T cells in blood (41) and lymph nodes. (58) Antigen-specific CD8+ T cells have two fates. Some cells become terminally differentiated effector cells. Effector cells occur in large numbers but are not long-lived and die by apoptosis. In contrast, other CD8+ T cells become long-term memory cells that are in low numbers but are likely to persist. The CD8+ T-cell effector pool is continuously replenished from the CD8+ long-term memory T-cell pool. In turn, the CD8+ long-term memory T-cell pool is replenished from continued antigen stimulation of the naïve CD8+ T-cell pool. The expansion of CD8+ T cells is in large part dependent on continued antigen stimulation. This may explain why HIV-specific CD8+ T cells decline in parallel with HIV viral load reduction following combination antiretroviral therapy (cART). (134)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

When cART is implemented in the earliest stages of HIV infection, there is a very low frequency of infected cells and aborted production of CD8+ T cells (5) and subsequent failure of control of HIV recrudescence after cART interruption. (55)

These observations highlight the problem of effective antiviral immune responses: a dependence on prolonged viral antigen exposure, which increases the viral reservoir. The failure of CTL clearance of residual latent virus infection in patients on suppressive cART depends on both the accumulation of viral escape mutants and the reduced HIV viral load attenuating the CTL responses. (69) Treatment interruption, however, is not effective in increasing CTL or viral control.

HIV-specific CD8+ T-cell functional abnormality

HIV-specific CD8+ T cells demonstrate a number of functional defects. (151) CD8+ T cells are deficient in perforin, which is associated with poor ex vivo killing of targets when compared with CMV-specific CD8+ T cells in the same people. (7) Low levels of perforin have also been observed in CD8+ T cells from lymph nodes of people with HIV infection. (6) Studies of elite controllers and long term non-progressors have provided insights into the factors that control effective immune responses to HIV; perforin production and polyfunctionality, in terms of broader range of cytokine production, being particularly important. Differences in maturation and expression of CD27 and CD28 may also be important and it has been found that most HIV-specific CD8+ T cells are CCR7-CD45RA- (pre-terminally differentiated) compared with CMV-specific CD8+ T cells which are CCR7-CD45RA+ (terminally differentiated). (41) Failure of CD8+ T cells to mature could be the consequence of impaired CD4+ T-cell help. Disease progression after immune escape in HLA-B*5701-restricted epitopes is associated with the development of reduced perforin production and loss of polyfunctional T cells. (29) Furthermore, HIV proteins specifically impair CD8+ T cell responses. Firstly, Nef and Tat decrease HLA class I expression on infected cells. Secondly, Nef increases Fas ligand (FasL) expression on virally infected cells leading to FasL- Fas interaction leading to apoptosis of CD8+ T cells. Finally, Nef inhibits apoptosis in the infected cell by blocking intracellular signalling events downstream of Fas.

Non-cytolytic CD8+ T-cell responses

CD8+ T cells from people with HIV infection can inhibit the replication of HIV in tissue culture by a non-cytolytic mechanism. (18) This activity has been attributed to the secretion of a cell-associated factor (CAF). CAF inhibits HIV replication by non-lytic mechanisms and does not impair the function of the infected cell; it does not alter the activation status of the CD4+ T cell or cause CD4+ T cell proliferation; it acts independently of MHC restriction; it is active against many strains of HIV-1, HIV-2 and SIV. CAF inhibits viral transcription by binding to HIV long-terminal repeat (LTR) of viral DNA (60) interrupting the ability of HIV Tat to accelerate HIV transcription. The CAF inhibition of the transcription complex to reduce HIV expression is the core characteristic. (18)

CAF activity correlates with clinical disease progression. High levels are seen in early HIV disease or non-progression. Patients with advanced HIV disease have low levels of CAF and a limited number of longitudinal studies have demonstrated that the loss of CAF is associated with disease progression, which resolves in people on cART.

While alpha-defensin and beta-chemokines have some CAF characteristics (58), the exact nature of CAF remains unknown. Alpha-defensins and beta-chemokines are produced by cells other than CD8+ T cells, which was not a characteristic of the original description of CAF. A number of putative genes have been shown to be differentially expressed in CD8+ T cells showing high CAF activity. (19)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

HIV-specific CD4+ T-cell responses

HIV-specific CD4+ T-cell responses are generated during acute HIV infection in the vast majority of people with HIV infection but are markedly reduced or lost in the chronic stages of HIV disease. Suboptimal CD4+ T-cell help is central to the immunodeficiency of HIV disease. Preferential infection of HIV-specific cells may offer one explanation for poor HIV-specific CD4+ T cell responses. (74) Similar infection of antigen-specific T cells by HIV has been observed in people who received an HIV vaccine including the Ad5 adjuvant. (123) The depletion of CD4+ T-cells responding to HIV means that any immunological interventions to expand HIV-specific CD4+ T-cells will need to block HIV infection with cART.

Measurement of CD4+ T-cell responses

A variety of in vitro assays are available to measure CD4+ T-cell responses. Traditionally, CD4+ T-cell responses were measured using lymphocyte proliferation assays. In these assays, CD4+ T cells are mixed with HIV antigen and 3H-thymidine. CD4+ T cells which recognise HIV antigens proliferate and incorporate 3H-thymidine. The 3H-thymidine incorporation gives a qualitative measure of antigen-specific CD4+ T cell responses.

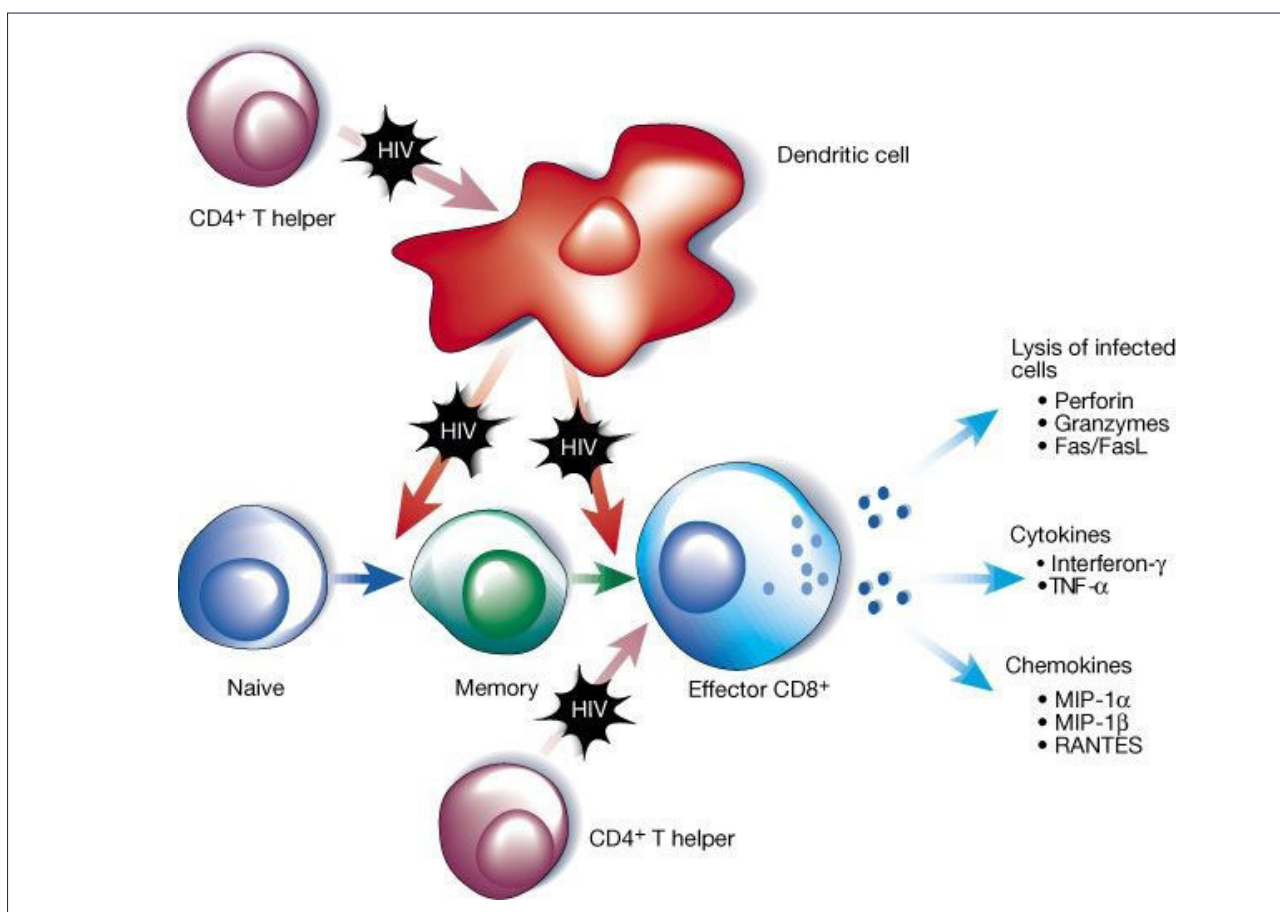
Alternatively, CD4+ T-cell responses can be measured by the detection of cytokine production following stimulation with HIV antigens. This may be measured either by ELISPOT assay or by intracellular staining and flow cytometry. These assays give qualitative and quantitative results. In contrast to CD8+ T-cell responses, measurement of CD4+ T-cell responses by tetramer assays has limited availability because of lower affinity of peptide binding to MHC-II molecules compared to MHC-I molecules. Another method for detection and isolation of antigen specific CD4+ T cells uses the expression of OX40 (CD134) and CD25 shortly after antigen stimulation as a marker of antigen-activated cells. (8)

Role of CD4+ T-cell depletion and dysfunction in HIV pathogenesis

Loss of effective CD4+ T-cell responses has detrimental consequences for both CD8+ T cell and B-cell responses against HIV. CD4+ T-cell help is crucial for priming CD8+ T cells, (66) maintaining CD8+ T cell memory (Del Cornò et al., 2005), and maturing CD8+ T cell function (Figure 9). CD4+ T cells provide this help through the production of local cytokines, such as IL-2 and IL-15, which stimulate CD8+ T-cell activity. CD4+ T cells also enhance co-stimulatory pathways between antigen-presenting cells and cytolytic CD8+ T cells via upregulation of CD40L expression. CD40L is expressed on activated CD4+ T cells. CD40L is crucial in triggering DC to produce IL-12 which, in turn, is central to the initiation of CD8+ T-cell responses. Some viruses can bypass this step by activation of the DC directly but HIV reduces innate signalling, including interferon signalling in myeloid DC. Activation of CD8+ T cells by DC then depends on providing DC-T cell signalling by plasmacytoid DCs that can be directly activated by HIV and produce high levels of IFNα and other type I interferons (66), which can then activate the myeloid DC and initiate CD8+ T cell responses. HIV can interrupt this process both by reducing plasmacytoid DC numbers and function and by blocking innate signalling pathways in myeloid DC.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Figure 9. The relationship between CD4+ helper T-cell function and CD8+ T-cell activity



Note: CD4+ T cells are important for priming dendritic cells to initiate CD8+ T cell responses. They help maintain memory T cells and are important in maturation of CD8+ T-cell function. All of these actions are impaired by HIV infection. In addition, HIV can directly impair dendritic cell function. FasL= Fas ligand; MIP= macrophage inflammatory proteins; RANTES= regulated on activation normal T cell expressed and secreted; TNF= tumour necrosis factor.

Source: McMichael AJ, Rowland-Jones SL. Cellular Immune responses to HIV. Nature 2001; 410:980-7. Used with permission.

Temporal change in CD4+ T-cell responses during HIV progression

HIV-specific CD4+ T-cell responses are generated early following infection with HIV and are detectable in people treated early in acute infection. (10) In contrast, HIV-specific CD4+ T-cell responses are low or absent in most people with chronic HIV disease, including those on effective cART, but are detectable in people with long-term non-progressive disease. While HIV-specific CD4+ T-cell responses have been detected in most people with established HIV disease, they have fewer HIV-specific than CMV-specific CD4+ T cells, suggesting a limited HIV-specific CD4+ T-cell response. The decline in HIV-specific CD4+ T-cell responses is a fundamental process in HIV disease progression.

Several factors are thought to contribute to the impairment of HIV-specific CD4+ T-cell responses in progressive HIV disease. These include virus-induced anergy, antigen-induced cell death, direct infection and

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

pyroptosis or apoptosis of CD4+ T cells. HIV Tat down regulates HLA-II expression and therefore may lead to viral induced anergy by impairing antigen recognition. (74,137) An inverse correlation between HIV-specific CD4+ T-cell responses (10) and plasma HIV viral load suggests that HIV-specific CD4+ T-cell responses are protective. However, a causal relationship has not been proven. HIV-specific CD4+ T-cell responses decrease following control of HIV replication with cART, possibly because of reduced antigen presentation. (11) HIV-specific CD4+ T-cell responses are preserved, however, in people who commence cART at low HIV viral loads. (8) There is also abnormal production of T-cell subsets from naïve T cells during HIV infection. (62)

CD4+ T cell defects in HIV disease

Progressive HIV disease is characterised by quantitative and qualitative defects in CD4+ T cells manifesting as a decline in both CD4+ T-cell numbers and function. The proximal cause of CD4+ T cell loss in HIV disease is a perturbation of CD4+ T-cell homeostasis. This perturbation results from both an increase in the destruction of mature effector memory CD4+ T cells and decreased replacement of these cells with precursor cells, including central memory CD4+ T cells and immature progenitors. Other factors contributing to the loss of CD4+ T cells in people with HIV infection include generalised immune activation leading to enhanced T-cell proliferation and death, direct cytopathic effects of HIV and altered trafficking with redistribution of CD4+ T cells to lymphoid organs, including the gut lymphoid tissue. A number of factors contribute to the impaired function of CD4+ T cells in people with HIV disease. These include reductions in the proportion of naïve CD4+ T cells, restriction of T-cell receptor repertoire and HIV-induced anergy.

Quantitative defects in CD4+ T cells

CD4+ T-cell homeostasis refers to the process of balance between cell production and destruction resulting in maintenance of stable CD4+ T-cell numbers. Processes which result in new CD4+ T-cell production are referred to as entry pathways and processes which result in the destruction of CD4+ T cells are referred to as exit pathways. These processes are usually tightly regulated, but perturbation of this process leads to CD4+ T cell decreases in people with HIV disease (Figure 2). Predominant entry pathways include CD4+ T-cell production by proliferation of peripheral CD4+ T cells or by differentiation from progenitors via thymic (or extrathymic) pathways. The predominant exit pathways include enhanced proliferation and cell death and HIV-mediated CD4+ T-cell destruction. Over time in untreated people, exit pathways predominate, resulting in a median CD4+ T-cell decline at a rate of 84 cells/μL per year. (154)

Alterations to entry pathways

Increased CD4+ T cell proliferation

Untreated HIV infection is characterised by marked increases in immune activation and lymphocyte proliferation, which exceed that observed in people without HIV infection by at least two- to three-fold. During HIV infection, naïve CD4+ T cells live about 618 days and CD8+ T cells about 271 days. Memory CD4+ T cells live about 53 days and CD8+ T cells about 43 days. This is about 3-fold shorter than healthy controls and after commencing cART the lifespan remains half that of controls. The augmented proliferation is predominantly observed in memory CD4+ (and CD8+) T cells, which proliferate rapidly in comparison to naïve T cells. (150) Although gut derived microbial products may be a predominant driver of proliferation (see Immune activation below) other causes of peripheral lymphocyte proliferation include: HIV-antigen specific expansion; stimulation of T cells by cross-reactive antigens; and cytokine mediated bystander activation. (114) Activation-induced apoptosis leads to eventual decline in CD4+ T-cell numbers, if not compensated for by other entry pathways (see below). Increased lymphocyte proliferation induces anergy (see below)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Reduced CD4+ T cell differentiation from progenitor cells

Contrary to previously held beliefs that the thymus is not active in adults, many reports demonstrate that substantial thymic output persists even into late adulthood. (75) However, the role of the thymus in adults with HIV infection is poorly understood. Thymic function may be measured by imaging (e.g. CT scan) or measurement of T-cell receptor excision circles (TREC, i.e. episomal circular DNA products produced following T-cell receptor gene rearrangement during thymic development) in blood T cells. When peripheral CD4+ T cell proliferation is taken into account, these measures of thymic function suggest that thymic function is reduced in people with HIV disease. While thymic size is decreased in people with advanced HIV disease, people with moderate HIV-related immune deficiency have more thymic tissue than age-matched controls without HIV infection. Furthermore, the amount of thymic tissue correlates with the rate of increase in naïve CD4+ T cells following initiation of cART. (157) These findings suggest that increased production of naïve CD4+ T cells by the thymus in people with early HIV disease initially compensates for the loss of CD4+ T cells secondary to increased peripheral turnover. However, thymic function wanes over time, perhaps because of viral factors discussed below, which leads to a net decrease in the size of the CD4+ T-cell pool.

Alterations to exit pathways

HIV-induced CD4+ T-cell loss in blood and tissues

HIV induces cell death in both infected and uninfected bystander CD4+ T cells by cytopathic, apoptotic and immune processes. Mechanisms underlying HIV-induced CD4+ T-cell loss are outlined in Table 1.

Despite a marked increase in CD4+ T-cell turnover in HIV disease, direct HIV cytopathic effect on CD4+ T cells in blood has been difficult to demonstrate. Studies of gastrointestinal tract lymphoid cells, however, have shown a rapid and profound loss of CD4+ T cells in acute HIV infection in humans (Mehandru et al., 2004) and SIV infection in primates. (9) Memory CD4+ T cells are lost primarily in the lamina propria of the gut mucosa. (25) This happens as early as days 4 to 14 of acute infection. Less than 20% of the cells are lost by direct infection or by CTL activity. The predominant mechanism of cell loss is a bystander effect by gp120 induced FasL-mediated apoptosis and is specific for CD4+ T cells. CD4+ T-cell depletion in the gut has been demonstrated at all stages of HIV disease and accounts for a significant and sustained loss of total body CD4+ T cells. (90) The gut depletion does not occur in long term non-progressors who maintain CD4+ T cells and suppress HIV replication. (52)

Much of the CD4+ T cell loss seen in HIV infection has been attributed to pyroptosis (71), a process of cell death mediated by caspase 1 and associated with production of IL-1b and IL-18. Peripheral blood CD4+ T cells are not susceptible to pyroptosis (51) suggesting that this pathway is most active in tissue CD4+ T cells. Most of this loss is attributed to abortive infection and triggering of innate pathways by incomplete DNA transcripts. The effect of cART on depletion of CD4+ memory T cells in the gastrointestinal tract is variable, although reconstitution is more effective following treatment in primary infection, (102,67) and reconstitution of gut Th17 cells that maintain mucosal integrity may also occur with therapy. (86)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Table 1. Mechanism of CD4 cell destruction in HIV disease

Cell	Process	Mechanism
Infected	Cytopathology	Disruption of cell membrane syncytia formation Accumulation of unintegrated viral DNA
	Apoptosis	Env and Vpr-induced apoptosis, Tat-induced Fas expression
	Immunological	HIV-specific CTL
		NK cell killing
Bystander	Cytopathology	Syncytia formation
	Apoptosis	Tat and Nef increase FasL expression
	Immunological	Autoimmune processes, ADCC

ADCC = antibody-dependent cellular cytotoxicity; CTL = cytotoxic T lymphocyte.

Adapted from McCune JM. The dynamics of CD4+ T-cell depletion in HIV disease. Nature 2001; 410:974-79.

Redistribution of CD4+ T cells

Alterations to physiological pathways of lymphocyte trafficking may account for some changes observed in the peripheral blood of people with HIV infection. CD4+ T cells are sequestered in lymphoid tissues, including lymph nodes, of people with untreated HIV infection. Antigenic stimuli within lymph nodes also result in the activation and retention of CD4+ T cells within the lymphoid tissues. Increased inflammation, including chemokine expression, and fibrosis in the lymph nodes of people with untreated HIV disease may contribute to this phenomenon. The initial phase of CD4+ T cell increase following initiation of cART is thought to represent the corresponding redistribution of CD4+ T cells from lymphoid tissues into the peripheral blood.

Qualitative defects in CD4+ T cell function in HIV disease

Memory and naïve T cells

In addition to the quantitative defects, there are many qualitative defects in CD4+ T cells in progressive HIV disease. There is a decrease in the proportion of naïve CD4+ T cells

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Immunological control of HIV infection in specific patient groups

Highly exposed but persistently seronegative individuals

The observation that HESN people remain HIV antibody-negative despite repeated exposure to HIV suggests that mechanisms exist to protect humans from HIV infection. Putative immunological and genetic associates of protection from HIV infection in HESN individuals have been identified in cohort studies of infants born to mothers with HIV infection, exposed health-care workers, and sexual partners of people with HIV infection, including sex workers in areas of high HIV prevalence. In these studies, HIV infection is excluded by the absence of HIV DNA and the inability to culture virus from peripheral blood mononuclear cells.

A number of protective mechanisms have been proposed. Specific characteristics of the mucosal immune system that prevent HIV infection include the presence of a low inflammatory responses in the mucosa. Low levels of activated cells may be because of poorly activated innate cells (28) or suppressive myeloid cells and regulatory T cells. In addition, the presence of HIV-specific immunity has been shown by the production of IgA neutralizing antibodies in mucosal secretions of HESN sex workers. (57)

Exposure to HIV in a subset of people may stimulate an effective circulating HIV-specific CD8+ T-cell response. HIV-specific CTLs have been identified in 30% of HESN men who have sex with men, heterosexual partners of people with HIV infection, infants of mothers with HIV infection, health-care workers following needlestick injuries containing HIV infected blood, and sex workers. (46,53,46,142) While HIV-specific CTLs persist for up to 34 months following HIV exposure, (17) repeated exposure to HIV is thought to be necessary for their maintenance. Longitudinal studies have demonstrated that HIV-specific CTLs wane during periods of reduced HIV exposure. Indeed, HIV seroconversion has been reported in sex workers during periods of reduced HIV exposure and waning HIV-specific CTLs despite previously strong HIV-specific CTL responses. (142)

Interestingly, CD8+ T cells of HESN people recognise CTL epitopes rarely recognised by CD8+ T cells of people with HIV infection. (141) Moreover, cross-clade HIV-specific CTL recognition of conserved epitopes has been demonstrated in some people. HLA restriction has been demonstrated for HESN sex workers. In a case control study, it was shown that the cells controlling infection were regulatory T cells, suggesting that the primary protection was in reducing activated target cells in the site of entry.

Non-cytolytic HIV-specific T cell responses may also play a role in preventing HIV infection in HESN people. HIV-specific CD4+ T-cell proliferative responses occur in up to 75% of the people in the cohorts described above. (53,103) Furthermore, increased production of beta-chemokines, which may limit HIV entry into susceptible cells, occurs in HESN people, (93,101) as does non-cytolytic CD8+ T cell-mediated HIV suppression. (92) The detection of HIV-specific antibody responses in HESN people is described in some but not all studies. Local factors including serpin, trappin-2 (126) and innate immune responses including low PRR have been found to be present in HESN people. HIV-specific IgA antibodies have been found in the vaginal fluid of HESN women participating in a microbicide trial. Host genetics may have a role in HIV transmission but chemokine receptor polymorphisms account for only a small percentage of HESN people. In particular, CCR5 Δ 32 homozygosity has been reported in up to only 3% of HESN people. (101)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Long-term non-progressors and elite controllers

Many studies have examined factors associated with slow progression to advanced HIV disease and have identified heterogeneous groups designated long-term non-progressors (LTNP). These may include slow progression because of defective virus (e.g. deletion of the nef gene) or because of favourable host factors. Individuals who maintain an undetectable HIV viral load in the absence of cART (approximately 1 in 300 individuals) have been called elite controllers. (20)

Adaptive and innate immune responses appear to be more important than viral factors in elite controllers. The virus replicates efficiently in vitro and sequence analysis shows no demonstrable genome defects. HLA antigens associated with a better prognosis, including HLA-B57 and -B27 are found more frequently in elite controllers. Although there is no detectable virus, elite controllers do show a gradual loss of CD4+ T cells. (124) Elite controllers also have a lower level of immune activation and lower plasma lipopolysaccharide (LPS) levels than viraemic individuals but levels are higher than that observed in people without HIV infection. Finally, recent studies have shown that survival of central memory T cells is enhanced in elite controllers compared with people with HIV infection on cART, suggesting that elite controllers have a greater capacity to replenish HIV-infected effector memory T-cells and maintain normal T-cell numbers. The detection of DNA by the intracellular sensor cGAS is effective in conventional DC of elite controllers, which leads to type I IFN and upregulation of interferon stimulated genes (ISG). This results in effective CD8+ CTL production. Recent work has suggested that the germinal centre and the B cell follicles may be the critical reservoir for persistent productive infection in elite controllers. (91)

Post-treatment controllers

A group of patients maintaining low or undetectable HIV viral load following discontinuation of cART for primary HIV infection has been identified in the VISCONTI study. This group of patients does not have the genetic factors associated with control of HIV replication in elite controllers and has reduced immunological responses to HIV by antibodies and T cells. Preservation of central memory CD4+ T cells has been demonstrated in this group of patients. (45) Modelling of the HIV viral load in such patients suggests that this may represent a state where the viral reservoir is reduced below the level required to initiate further infection or to restimulate immune responses. (59) It is unclear how frequent this early control of HIV by cART may be in patients on long-term therapy after early initiation of treatment.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Escape of HIV from host immune responses

Multiple mechanisms exist by which HIV evades specific immune responses. These escape strategies are mutational or constitutive, and result in the evasion of cellular and antibody responses. (8)

Mutational escape

HIV-specific CTLs kill HIV-infected cells following recognition of viral peptides presented in association with MHC-I molecules on the surface of virally infected cells. Epitope deletion in HIV envelope, secondary to viral mutation, occurs in primary infection and later stages of HIV disease, and results in the loss of antigen recognition by HIV-specific CTLs. (106,62,107) Multiple lines of evidence suggest that mutational escape plays an important role in HIV disease pathogenesis. Viral mutants which have escaped HIV-specific CTLs are more frequently found in mothers who transmit HIV to their infants than in non-transmitting mothers. Furthermore, following autologous transfusion of HIV-specific CTL clones directed at a single HIV epitope, viral mutants evolve that lack the targeted epitope and thus escape control of the transfused HIV-specific CTLs. (148) Viral escape from HIV-specific CTLs is associated with a poorer clinical outcome. (148) At the population level, escape from CTL determines the distribution of viral sequences so that the predominant sequences are those that have escaped from the predominant HLA alleles in the population. HIV escape from antibody responses has also been demonstrated, but is less well studied than escape from HIV-specific cytotoxic T cells. Emergence of viral mutants which resist neutralisation by autologous HIV-specific antibodies has been demonstrated in people with symptomatic primary infection. (2)

Neutralising antibodies have been found in some people with long-term slowly progressive HIV disease, but these antibodies lose their capacity to neutralise HIV over time. Serum fails to neutralise concurrent viral isolates present in people with long-term infection, despite neutralisation of earlier isolates. Broadly neutralising antibodies are now considered to be the result of viral escape from neutralising antibodies. These observations suggest viral isolates continually evolve to resist the humoral immune response. (22)

Constitutive escape

HIV has developed other means to evade HIV-specific immune responses. First, post-integration viral latency protects the infected cell from immune surveillance, as viral antigens are not expressed on the cell surface. These latently infected cells produce infectious HIV following subsequent cellular activation. Second, a number of HIV proteins interfere with critical cellular processes that facilitate the host immune response. Specifically, the HIV tat protein impairs antigen processing by interfering with proteasome function and downregulating MHC-II molecule expression while the HIV Nef protein downregulates the expression of CD4 and MHC-I molecules. (137,68) Finally, HIV proteins, specifically Nef, induce apoptosis of HIV-specific CTLs by increasing the expression of FasL, resulting in apoptosis of Fas-expressing CTLs. This process is referred to as back-killing. (101)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Immune activation in the pathogenesis of HIV disease

Mucosal changes and microbial translocation

Enterocytes of the gut epithelium show evidence of apoptosis very early after HIV infection, with a peak 14 days following infection. This apoptosis is accompanied by increased epithelial proliferation and the development of regenerative villous enteropathy, which is characterised by villous atrophy plus micro-abscesses. This process is driven both by T cell activation and failure of mucosal regeneration. (102) The compromised mucosal integrity may lead to an increase in circulating bacterial products, such as LPS, as described in graft-versus-host disease and inflammatory bowel disease. Gut permeability is increased 2 to 10 fold in people with HIV infection. (24) Chronic HIV disease is associated with increased plasma levels of LPS, a marker of gram negative microbial products, compared with seronegative people and those with early HIV disease. Plasma levels of LPS detected in people with chronic HIV infection were also correlated with other markers of systemic immune activation including HLA-DR and CD38 expression on CD8+ T cells, and plasma levels of IFN α and soluble CD14 (sCD14). LPS binds to monocytes via CD14, which is released as sCD14 by activated macrophages. (Douek) Plasma levels of intestinal fatty acid binding protein (I-FABP) also correlate with microbial translocation and inflammation (154) as does the levels of tryptophan metabolites. (130) Microbial products may lead to enhanced immune activation by: increase in cytokine production by antigen presenting cells (IFN α and IL-15); increase in the production of cytokines IL-2, IL-4, IL-7 and IL-15 by lymph node cells; and direct activation of plasmacytoid DC. Direct ligation of TLR by bacterial products activates CD4+ and CD8+ T cells to express CD38, CD69 and to drive CD4+ T cells into cycle. TLR2 ligands have been shown to directly induce susceptibility to HIV infection, particularly by CCR5 using HIV-1. Thus, microbial translocation may also increase viral replication and induce T cell loss by indirect mechanisms. Early use of cART reduces GIT infection and immune activation. (67)

Immune activation in non-pathogenic and pathogenic SIV infection of non-human primates

Further data on the role of immune activation in HIV disease pathogenesis come from African green monkey and sooty mangabey monkey models. Both these animals are infected naturally with SIV, and develop high SIV viral loads but do not lose CD4+ T cells or show development of AIDS. (26) In contrast, SIV infection of rhesus macaques leads to high SIV viral loads, CD4+ T cell depletion and the development of AIDS as found with HIV infection in humans. Levels of immune activation differ but even in those cases where sooty mangabey monkeys have persisting CD4+ T cell depletion there is no clinical disease. Interestingly, in sooty mangabey monkeys there is a rapid depletion of the gut-associated CD4+ T cells in common with pathogenic infection. (104)

Immune activation in non-AIDS HIV disease and deaths

Immune activation may not only lead to CD4+ T cell decline and impaired host immune responses against opportunistic infections but may also lead to serious non-AIDS events. Chronic immune activation may lead to atherosclerotic vascular disease of the heart and brain, osteoporosis and renal disease that have become increasingly apparent since antiretroviral therapy reduced the incidence of most opportunistic infections and AIDS-related malignancies by up to 80%.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Immune-based therapies for the treatment and prevention of HIV infection

Rationale

Antiretroviral therapy alone, by suppressing viral replication, results in marked but incomplete restoration of cell-mediated immunity. Moreover, HIV-specific immune responses decline in people taking cART. In some individuals receiving cART, restoration of total CD4+ T cells is also impaired despite excellent virological control. Current cART strategies are limited by toxicity, cost, adherence, resistance and the need for continuous therapy. The incomplete recovery of cell-mediated immune function following cART is related to: persistent immune activation; loss of HIV-specific immune responses; persistent HIV-induced immunodeficiency; and HIV-associated anergy. Immune-based therapies may prove to be useful adjuncts to cART in augmenting and accelerating improvements in cell-mediated immune function.

The data from the monkey models, including African green and sooty mangabey monkeys, suggest that evolution of host factors has allowed the persistence of SIV as a non-lethal infection. (26) This adaptation seems to have occurred in the presence of high SIV viral load and results in reduced immune activation and apoptotic loss of T cells. (76) Non-immunological factors control retroviral replication, including the APOBEC system and the TRIM5alpha system. (48) These represent innate mechanisms that control retroviral infection including genomic repetitive elements and endogenous retrovirus. (49) A whole genome analysis showed no association with acquisition of HIV other than the effect of CCR5Δ32. (100) By this same approach, disease progression was related most strongly to the well-known HLA-B57 association. The protective change was also linked to an endogenous retroviral element (PC5), an HLA-C related determinant and an RNA polymerase subunit gene. (89)

Therapeutic vaccines for boosting HIV-specific immunity

Strategies to restore and maintain HIV-specific immune responses may be critical in the long-term control of HIV disease. Controversy persists regarding the essential components of the immune responses needed to prevent disease progression or to clear virus in patients on cART, the identity of immunogenic epitopes that will stimulate broad immune responses, and the identity of in vitro correlates of immune protection. The success of boosting HIV-specific immune responses will require the stimulation of both CD4+ T and CD8+ T cell responses; the stimulation of broad responses directed towards multiple epitopes by polyfunctional T cells; and the concurrent use of cART to limit HIV replication. A recent CMV vector vaccine used in SIV infection of non-human primates looks the most promising of the existing vectors. (111)

Approaches to boosting HIV-specific host immune responses by the use of CTL expanded in vitro have been unsuccessful. (148) However, expansion of CTL and CD4+ T cells in vivo using DC vaccination is clearly effective in reducing viral load. (36) Simpler therapeutic vaccination strategies that use exogenous or endogenous antigens are being developed. In contrast, the hope that intermittent cessation of cART might potentially regenerate HIV-specific immune responses has been discarded because of the clear reduction in survival and lack of clear efficacy of this strategy. Similar approaches to induce high level neutralising antibody have some potential application.

Use of immune modulators, including cytokines, to reduce immune activation and improve CD4+ T cell recovery has had only a modest effect compared to cART and does not have a clear role at present (Tables 2 and 3).

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Table 2. Immune modulating cytokines that may have a therapeutic role in HIV management

Cytokine	Immune effect	References
IL-2	Increase HIV-specific responses (CAF) Increase antigen presentation	(Abrams et al., 2009)
IL-7	Increase thymus-mediated T lymphocyte differentiation and homeostatic T cell proliferation Reduced colonic and systemic inflammation	(Imamichi et al., 2011; Levy et al., 2009) (Sereti et al., 2014)
IL-10	Decrease pro-inflammatory cytokine production	(Villacres et al., 2012; Pott et al., 2007)
IL-12	Increase HIV and non-HIV CTL responses	(Kalams et al., 2013)
IL-15	Increase effector memory CD4+ T cells Increase CTL perforin expression Increase T cell replication and virus production	(White et al., 2007) (Manganaro et al., 2018)
IL-16a	Increase responsiveness to IL-2 Decreased activation-induced apoptosis	(Cruikshank et al., 1996; Parada et al., 1998) (Center et al., 2000)
IL-21	Increase CTL perforin expression Decrease Treg production by TGF-beta Increase TH17 cells.	(White et al., 2007; Pallikkuth et al., 2013; Attridge et al., 2012) (Ortiz et al., 2016)
GM-CSF	Increase macrophage anti-HIV activity Vaccine adjuvant	(Overton et al., 2014) (Herasimtschuk et al., 2014)
KGF	Increase production of IL-7 by thymic epithelial cells	(Jacobson et al., 2014; Herasimtschuk et al., 2013)
Growth Hormone	Increase thymic tissue Reduction in lipoatrophy.	(Lindboe et al., 2016)
IFNα	Reduction in Type I IFN reduces viral load in animal models, though effects of IFN depend on stage of disease in SIV infection	(Zhen et al., 2017; Sandler et al., 2014)

a These cytokines also have direct anti-HIV effects as suggested by inhibition of HIV replication in vitro. CAF = cell-associated factor; CTL = cytotoxic T lymphocyte; IL = interleukin; Th1 = type 1 helper, KGF = keratin growth factor; TGF = transforming growth factor.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Table 3. Pharmaceutical agents that decrease immune activation associated with HIV infection

Agent	Mechanism of action and rationale	References
Corticosteroids	Decrease pro-inflammatory cytokine production Decrease activation induced lymphocyte death	(Kasang et al., 2012; Wallis et al., 2003)
Cyclosporin	Decrease target cells by decreasing IL-2 production, cellular activation and proliferation Decrease viral maturation by interaction with immunophilins	(Rizzardi et al., 2002; Markowitz et al., 2010; Lederman et al., 2006)
Hydroxyurea	Decrease cellular proliferation by decreasing intracellular nucleotide concentration. No clinical benefit.	(Benito et al., 2007; Bloch et al., 2006)
Mycophenolate	Decrease lymphocyte proliferation to antigenic stimuli Increase apoptosis of activated lymphocytes	(Kaur et al., 2006)
Thalidomide	Decrease production of TNF-alpha Reduces CCR5 and CXCR4 upregulation by HIV	(Wohl et al., 2002; Juffermans et al., 2000)
Rapamycin	Acts through inhibition of mTOR to reduce cell activation, apoptosis and autophagy	(Nicoletti et al., 2011)
Statins	Atorvastatin reduces immune activation by decreasing T cell signalling. Pravastatin does not have this effect.	(Overton et al., 2014; De Wit et al., 2011; Eckard et al., 2014)
Hydroxychloroquine	Hydroxychloroquine and chloroquine act on TLR signalling in pDC to reduces immune activation. Limited or no effects on CD8+ T cell activation or CD4+ T cell recovery in antiretroviral therapy-treated patients and CD4+ T cell depletion in untreated patients. Prevention of infection by reducing mucosal immune activation	(Paton NI et al., 2012; Murray et al., 2010)(Routy et al., 2015; Piconi et al., 2011) (Lajoie et al., 2018)
Aspirin	Reduced inflammation at mucosal surface. reduces HIV infection	(Lajoie et al., 2018)
Cyclooxygenase-2 (COX-2) inhibitors	Reduced LPS-induced upregulation of COX-2	(Pettersen et al., 2011; Kvale et al., 2006)
Ruxolitinib	Inhibits cytokine activation by Jak 1,2 inhibition	(Gavegnano et al., 2017)
Tofacitinib	Inhibits cytokine expression by Jak1,3 inhibition	(Gavegnano et al., 2017)
anti-IFNAR	Reduce type 1 interferon-induced cell death and immune activation	(Cheng et al., 2017)

a Because of effects in nucleotides, these agents may augment effects of antiretroviral agents.

TNF = tumour necrosis factor.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Eradication of HIV cellular reservoirs and HIV cure

Immune-based therapies were initially trialled as alternatives or adjuvants to cART, particularly in patients with CD4+ T cell depletion. Subsequently immune modulators have been used to reduce the immune activation associated with HIV infection and, in particular, gut bacterial translocation. Most recent work has focused on the use of immune modulators as a mechanism to facilitate the clearance of HIV in cure strategies.

Latent HIV infection

After suppression of HIV replication and viraemia with cART, there is persistent reservoir of latent HIV infection, predominantly within memory CD4+ T cells (50) and to a limited extent in myeloid cells including, monocytes and dendritic cells in the gut. (38) This CD4+ T cell reservoir is likely to be maintained by replication of the infected cells rather than low level HIV replication. (61) The reservoir of HIV has been difficult to accurately measure as much of the integrated virus is defective and not all the intact virus can be activated by T cell activation or proliferation (28)

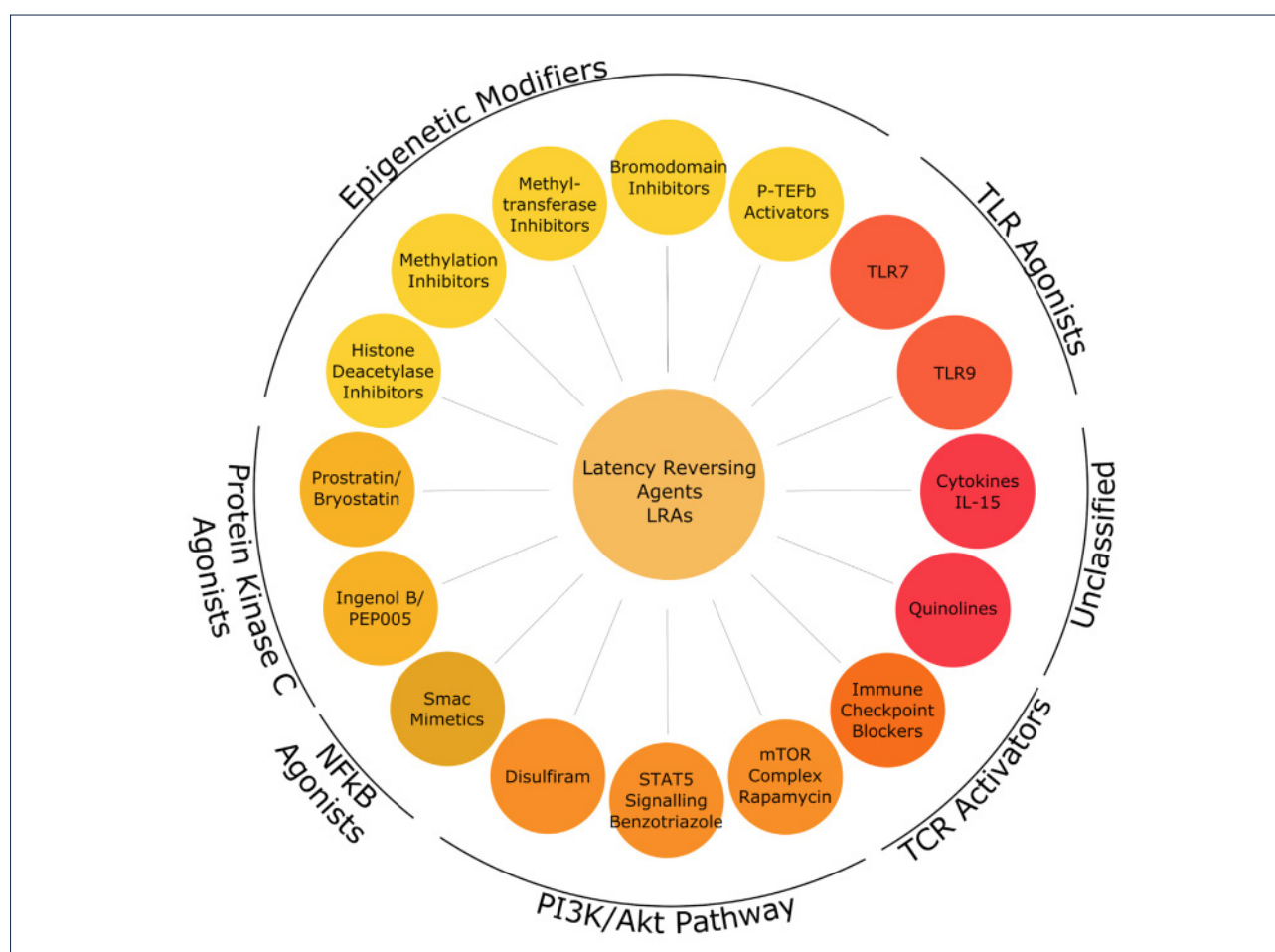
Since latency represents the major barrier to eradication of HIV infection, strategies to activate HIV transcription in latently infected T cells and increase anti-HIV immune responses are under investigation. This strategy designated 'kick and kill' involves activation ('kick') of HIV replication and the subsequent 'kill' of infected cells by a viral cytopathic effect or immune-mediated killing. (65) Most of the initial work has involved the application in clinical trials of latency reversing agents (LRA) that could activate virus expression from latency in vitro.

Latency reversing agents

Early clinical trials using inhibitors of histone deacetylase that could activate HIV from latency in vitro, such as sodium valproate (184), did not show any effect and subsequent work with more potent inhibitors, such as vorinostat, (182,183) panabinostat (185) and romidepsin (155) has shown that virus replication can be demonstrated in patients on therapy but that this replication is not associated with a significant increase in plasma HIV viral load or decrease in the size of viral reservoirs. More recent strategies have used an expanded range of different LRAs (Figure 10) and preclinical work has also used modulators of apoptosis to increase the virally mediated or immune mediated killing of HIV-infected cells. (146)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Figure 10. Latency reversing agents in development and clinical trials



Note: The classes of compound acting to increase HIV expression from latency are shown in circles within the different mechanistic classes. All are classified here according to the pathway of mediating increased HIV expression. A number of the classes also have an immunological effect and activate CTL (IL-15, Immune checkpoint blockers), or innate immunity (TLR7, TLR9).

P-TEFb = positive transcription elongation factor b; TLR = Toll-like receptor; mTOR = mechanistic target of rapamycin; STAT5 = signal transducer and activator of transcription 5; IL-15 = interleukin-15.

Source: Kim Y, Anderson JL, Lewin SR. Getting the “Kill” into “Shock and Kill”: Strategies to Eliminate Latent HIV. *Cell Host & Microbe*. 2018 Jan 10;23(1):14–26. Used with permission

Lack of effective killing may reflect changes of CTL killing in the presence of HDACi (69) or lack of activity of the current immune-based therapies. (30) The range of LRAs and their combinations has expanded rapidly with the development of in vitro and ex vivo models of latency that can be used to test the efficacy of these agents in virus reactivation. However, the gold standard remains cells isolated from virally suppressed HIV infected individuals. Use of cytokines, such as type I IFNs, IL-2, IL-7, IL-15 may potentially lead to reduction in reservoir size but larger definitive studies are still needed. Particularly promising is the use of TLR agonists that activate innate immunity leading to decreased viral DNA and viral reservoirs.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Boosting anti-HIV immune responses

Specific stimulation of CTL to improve killing of HIV-infected cells has focused on the use of therapeutic vaccination, including DC vaccines, (98) and the use of cytokines, such as IL-7 and IL-15, alone or concurrently with therapeutic vaccines. The use of immune checkpoint blockers such as antibodies to CTLA-4 and PD-1 that can restore antiviral immunity is now being evaluated in clinical trials. Boosting immune responses with immune checkpoint inhibitors has been shown to be effective in cancer immunotherapy. (146) Finally, CTLs can be engineered by introducing TCRs specific for HIV to produce chimeric antigen receptor-T cells (CAR-T cells). A more versatile and likely effective approach uses T cells engineered to recognize the T cell by an HIV-specific antibody, which avoids the need to individualize the CTL TCR for specific MHC recognition. These convertible CAR-T cells (cCAR-T cells) bind to the target cells by a modified monoclonal antibody that crosslinks the cytotoxic T cell to the HIV infected cell. (117)

Summary

Despite the efficacy of cART, immune-based therapies may have a complimentary role for both immune reconstitution and HIV cure. These interventions may augment CD4+ T cell numbers and cell-mediated immunity in the presence of viral suppression with cART. While the clinical benefits of immune-based therapy remain to be determined, augmentation of antibody-mediated control through potent neutralisation and ADCC, as well as T cell-mediated immune responses through use of immunomodulators, such as immune checkpoint blockers and CAR-T cells, may play a role to limit viral replication, reduce the risk of drug resistance and eradicate HIV reservoirs in people taking cART.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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3. Diagnostic & Monitoring Tests

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Virological tests

More recent Australian clinical guidance on HIV Testing is available.

Read the guidance: <https://unifiedhiv.wpenginepowered.com/hiv-testing-policy/introduction/>

Virological tests for diagnosing and monitoring HIV infection

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Last reviewed: May 2019

Introduction

The diagnosis of human immunodeficiency virus-1 (HIV-1) and human immunodeficiency virus-2 (HIV-2) infection is usually made by the detection of circulating antibodies in blood. Antibodies are identified by the use of a screening test (standard test), usually an enzyme immunoassay (EIA), followed by definitive diagnosis using test strategies that include supplemental EIAs, nucleic acid tests and a Western Blot assay (reference test). Reference testing strategies and algorithms are designed to provide the greatest positive predictive value through a combination of tests. In some situations, such as pre-seroconversion (acute infection) or neonatal infection, detection of HIV antibodies may be unreliable. In these cases, diagnosis of infection may require tests that detect HIV directly – whether by quantitating plasma HIV RNA or HIV proteins (p24 antigen), or by detection of HIV DNA in blood mononuclear leucocytes. In 2005, screening tests became available that detect both HIV antibody and p24 antigen in a single test, which improved the detection of individuals presenting with acute HIV infection. Combined antibody and antigen tests are so called fourth generation tests and are widely used as screening (standard) tests to detect antibodies to both HIV-1 and HIV-2. HIV-2 is endemic in West Africa and in some countries with historical socioeconomic links with West Africa (e.g. France, Spain, Portugal, and former Portuguese colonies such as Brazil, Angola, Mozambique, and parts of India). HIV-2 is not prevalent in the Australasian Pacific region but has been reported particularly in individuals with links to HIV-2 endemic countries. HIV-2 is similar to HIV-1 in its structure, genomic organisation, route of transmission and ability to cause acquired immune deficiency syndrome (AIDS). Because the viruses are closely related there is significant serological cross-reactivity in antibody tests so the use of specific HIV-2 Western Blot assays and nucleic acid tests are used to confirm the diagnosis.

HIV antibody and antigen testing

HIV antibody enzyme immunoassay

Because of its rapidity, sensitivity and low cost, the enzyme immunoassay (EIA) is the standard screening tool for HIV infection(1). Synthetic and native HIV antigens, fixed on a solid phase, are exposed to and bound by HIV antibodies in test serum. These antibodies are then detected by a second antibody to human IgG, with a sensitivity of more than 99.5%. Most commercially available EIAs are automated and allow for high throughput testing. For example, most laboratories in Australia use testing instrument platforms that enable continuous loading of specimens with results being available within 1 hour. The EIA also detects antibodies against a broad range of HIV types and subtypes, and is continually updated to include newly described HIV-1 subtypes.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Test results arising from the screening (standard) HIV test are classified as reactive or non-reactive (negative) or occasionally invalid. Reactive screening test results must undergo further testing at a designated Reference laboratory to confirm whether the reactivity is true or false. Initially reactive screening results are generally not reported until the confirmatory tests are completed. Test results obtained from the patient sample are compared with a cut-off value which classifies a test as being reactive or negative. In most cases, if a sample is found to be negative by the screening (standard) test no further testing is performed and the result is issued. If acute HIV infection is suspected, other more sensitive tests such as p24 antigen or nucleic acid tests may be indicated. A positive antibody test is usually observed within 3 to 6 weeks following infection. Reactivity on the fourth generation antibody and antigen combination test may be observed several days earlier than antibody-only tests (2-4 weeks).⁽²⁾

The weeks between HIV infection and seropositivity are termed the window period and are associated with high levels of circulating HIV RNA, and potentially more efficient HIV transmission. Direct detection of HIV nucleic acids by molecular amplification tests such as polymerase chain reaction (PCR) or serological detection of HIV p24 antigen is usually possible before the detection of HIV antibodies. These direct detection virological tests are indicated in suspected cases of primary infection or seroconversion illness or having a high-risk exposure in the previous 6 weeks and suspected of having acute HIV infection.

False-positive test results are rare and the specificity of most EIAs is above 99.8%. Factors associated with false-positive EIA results are not well characterised and may include antibodies to human leukocyte antigen (HLA) class II antigens, autoantibodies and immune complexes, malaria, recent vaccination and acute viral infections, but also laboratory/technical errors in testing procedure and specimen handling. Therefore, although a negative enzyme-linked immunosorbent assay (ELISA) result, repeated at 3 months, effectively rules out a diagnosis of HIV infection, an initially reactive EIA result is not indicative of infection unless confirmed by supplemental tests including a positive Western Blot assay or nucleic acid test.

HIV rapid tests

The use of HIV rapid tests has gained popularity since their availability in the late 1980s. Rapid HIV tests were first introduced in Australia in 2013 despite being widely available in other countries for many years. These devices are screening tests intended to be performed in settings near or at the side of the patient (hence the name point-of-care HIV tests) and have rapidly become a convenient and highly acceptable form of testing that may lead to increased uptake and frequency of testing when compared with conventional clinic- and laboratory-based testing.⁽³⁾ Introduction of rapid HIV tests in some countries has been driven by the lack of laboratory infrastructure mainly in resource limited settings but more recently through a growing recognition of the public health benefits of promoting and improving access to individuals who may not otherwise engage in conventional testing pathways. Point-of-care HIV tests generally involve alternate sample types including finger prick capillary blood or oral fluids and provide results in 10 – 30 minutes by visual reading of reactivity to the HIV antigen and the internal control lines. In Australia, it is a requirement that all reactive HIV point-of-care tests be confirmed by conventional diagnostic laboratory tests.

The Australian regulator requires rapid HIV tests to have a clinical sensitivity of 99.5% for whole blood, serum or plasma and 99% for oral fluid tests (based on testing performed outside of the seroconversion window period for the device) and a clinical specificity of at least 99% for detection of HIV infection.⁽⁴⁾

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

While many rapid tests for HIV infection demonstrate a high level of sensitivity and specificity, it is recognised that most have limitations when compared with conventional tests. The most common limitation is the prolonged window period when detecting the presence of HIV antibodies by simple lateral flow technology. It has also been recognised that operators of rapid HIV tests should undergo comprehensive training in their operation, understand the limitations of the tests and use appropriate key messages and language in the delivery of test results.

Examples of rapid HIV tests are shown in figures 1A-D



Figure 1A. Trinity Unigold HIV-1 antibody test

(NR: valid non-reactive test;
R: valid reactive test)

Note two lines C: internal procedural control and T: test line detects presence of HIV antibodies



Figure 1B. Alere Determine HIV-1 and HIV-2 antigen and antibody Ag/Ab combination test

This test presents three lines (control; Ag and Ab)

Test strip marked 10B is a valid reactive test showing control line, antibody (Ab) and weak reactivity to antigen (Ag) lines.

Test strip marked 11A is a valid non-reactive test showing a control line indicating the test is valid, but no reactivity is visible in the Ag or Ab test areas.

Source: NSW State Reference Laboratory for HIV, St Vincent's Hospital Sydney Limited.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Figure 1C. ATOMO HIV Self Test antibody test



Sample with a HIV negative test result



Sample with a HIV reactive test result

Source: Atomo Diagnostics

The Atomo HIV Self Test is a single-use, immunochromatographic, rapid in-vitro diagnostic test for the detection of antibodies to Human Immunodeficiency Virus Type 1 (HIV-1) and Type 2 (HIV-2) in whole blood.

The Atomo HIV Self Test is intended to be used by untrained lay users in a private setting as a self test to aid in the diagnosis of infection with HIV-1 and HIV-2 from samples of fresh, whole blood obtained through a finger stick blood collection technique. The device requires a sample size of 10uL.

The Atomo HIV Self Test is comprised of a test strip inside a plastic cartridge. The test is performed by placing a small drop of blood on the test strip and then applying drops of test fluid (diluent). When the test is completed, two lines can appear on the strip. The control line will only become visible if the test has been performed correctly. The test line will only become visible if the applied sample contains antibodies to HIV.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Figure 1D. Orasure OraQuick Advance HIV 1 / 2 test



The Orasure device is the only product on the Australian market that detects HIV-1 and HIV-2 antibodies in oral fluids as well as plasma/serum or whole blood from venepuncture or fingerstick. While the test is available as over the counter self-testing applications in other countries (such as USA) it is not available in Australia for home or self-testing.

HIV-1 Western Blot assay

The Western Blot assay involves detection of antibodies in patient sera that react with a number of different HIV proteins. These proteins are separated into bands of distinct molecular

weight using protein gel electrophoresis. After transfer (blotting) to a solid membrane, proteins that bind HIV antibodies in test sera can be identified. Antibodies to different HIV-1 proteins appear in a defined order. First, antibodies to the structural gag proteins, the precursor (p55), p24 and p18, appear. These antibodies are closely followed by antibodies to the envelope glycoproteins – the precursor gp160, the extracellular gp120, the transmembrane gp41 – and then the polymerase components p31, p51 and p66. Antibodies to the smaller regulatory and accessory HIV proteins encoded by Vpr, Vpu, Vif, Rev, Tat and Nef may also be seen.

The Western Blot test is classified as negative if there is no reaction of the patient's serum with any HIV protein bands. An individual is classified as seropositive for HIV antibodies according to specific criteria. There is a lack of consistent interpretation criteria defined by the different peak organisations Centers for Disease Control and Prevention [CDC], World Health Organization [WHO], Consortium for Retrovirus Serology Standardization (CCRS), which has led to confusion about classification of HIV seropositive samples. Generally, a positive Western Blot result is defined by the detection of antibodies to all of the three main groups of HIV proteins – envelope (gp160, gp120 or gp41), gag (p24, p55) and polymerase (p68 or p51). The WHO criterion for a positive Western Blot is a minimum of two envelope glycoproteins. Samples that do not meet the criteria for seropositivity but demonstrate reactivity to some viral proteins are classified as indeterminate. Previously, HIV Reference Laboratories in Australia interpreted Western Blots according to National Serology Reference Laboratory criteria, where there were four groups of indeterminate Western Blots profiles each corresponding to the likelihood of HIV infection with reactivity profiles containing antibodies to envelope glycoproteins being the most specific or most likely to be associated with true HIV infection.

In some countries, including the USA, the HIV-1 Western Blot test is being replaced by HIV-1/2 confirmatory assays such as the *Bio-Rad Geenius™* HIV 1/2 Confirmatory Assay. Any indeterminate result is then referred for nucleic acid-based testing. In Australia however, reference laboratories are experienced in interpretation of Western Blot results and many experts believe it is important to retain a native HIV viral protein assay in the testing strategy to safeguard against possible false-negative results arising from HIV genetic diversity if nucleic acid-based tests are used. However, there is great interest in the pathology sector regarding emerging nucleic acid tests for HIV diagnosis.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

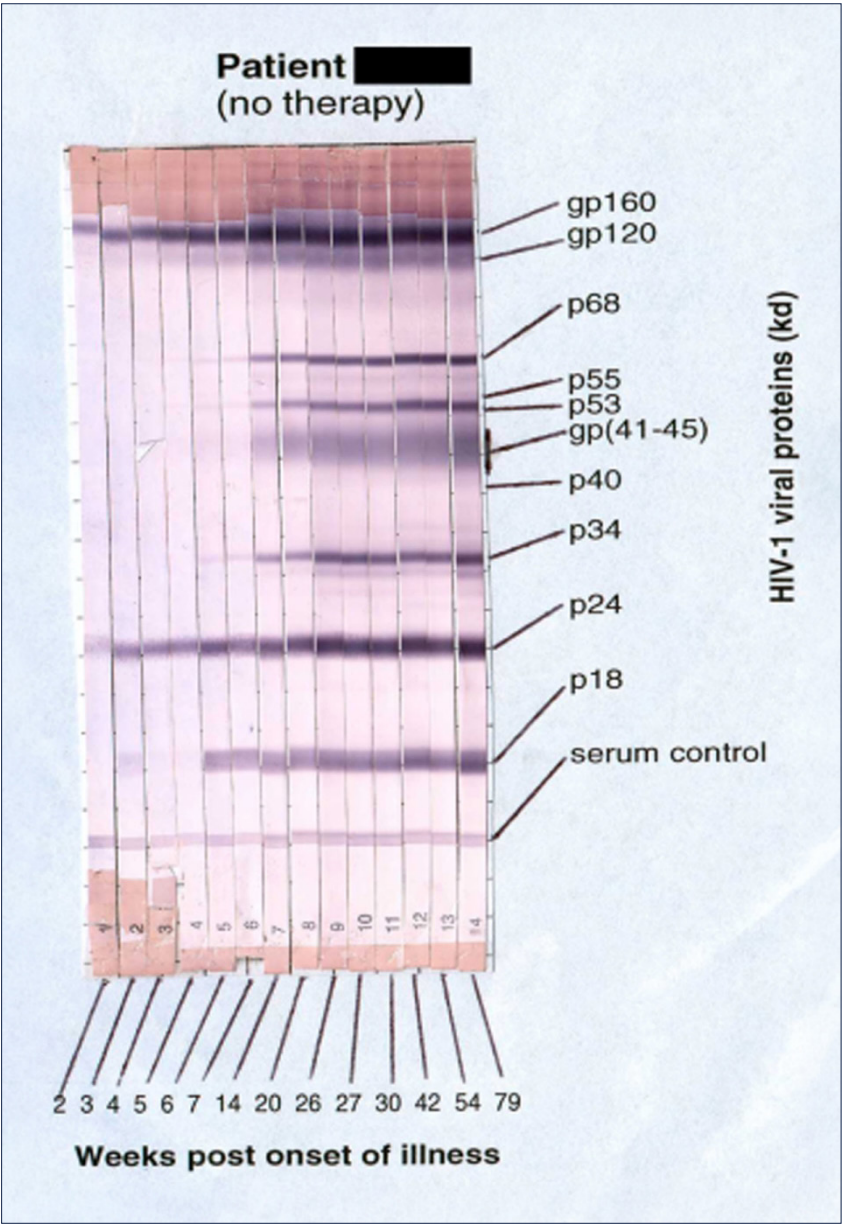


Figure 2. Typical appearance of an evolving HIV-1 Western Blot in HIV infection (seroconversion)

Note: serial Western Blot test strips exposed to serum from the patient demonstrating the typical stepwise appearance of bands to the specific viral antigens over time.

Source: NSW State Reference Laboratory for HIV, St Vincent's Hospital Sydney Limited.

An indeterminate Western Blot assay should be followed by repeat HIV serology tests after 4 to 6 weeks, to exclude an evolving HIV antibody response. During seroconversion (changing from seronegative to seropositive) the evolving pattern of antibody/viral protein bands is dynamic with additional bands occurring in days to weeks following infection. The application of tests that directly detect the presence of viral nucleic acid or protein (p24) may be used, especially when the index of suspicion is high. A positive result in one or more such assays leads to a presumptive diagnosis of HIV infection, pending the development

of a Western Blot assay which meets positive criteria for HIV antibodies. Negative results from one or more of these assays, and a non-evolving indeterminate Western Blot assay, exclude HIV infection and indicate that the initial reactivity on the screening test is non-specific or false. These results are frequently called biological false positives (BFP).

HIV-2 antibodies

HIV-2 infection is rare in Australia and antibodies to HIV-2 proteins in most sera from people with HIV-2 infection will cross-react with HIV-1 proteins in Western Blot assays. Specific HIV-2 Western Blot assays can be used to confirm HIV-2 infection and distinguish it from HIV-1. However, the cross-reactivity between HIV-1 and HIV 2 is often significant making it difficult to conclusively differentiate the infections. There have been reported cases of misdiagnosis of HIV-2 in cases of HIV-1 infection due to this cross-reactivity.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

HIV quantification

HIV RNA quantification (or viral load) is a critical tool in the management of HIV disease. Detection of HIV RNA can help provide a positive diagnosis of HIV infection in certain clinical situations, such as acute or neonatal infection, where standard serological testing is inappropriate or unclear. Quantification of HIV RNA levels allows and predicts the rate of HIV disease progression^{(5) (6)} and is the major laboratory tool for monitoring the response to antiretroviral therapy.

An increasing number of commercially available assays may be used as an aid in the diagnosis of HIV-1 infection, including acute or primary infection. The presence of HIV-1 RNA in plasma or serum of patients without antibodies to HIV-1 is indicative of acute or primary HIV-1 infection. Manufacturers are making claims to support the use of these assays as a supplemental test for specimens that have repeat reactive results with approved HIV immunoassays. There is a trend toward using approved tests to confirm HIV infection in serological test where antibodies are detected.

Nucleic acid quantification

Different technologies are used to quantitate HIV RNA but all have now achieved a sensitivity of 20-50 copies of HIV RNA per millilitre (mL) of plasma. In acute HIV infection, plasma HIV RNA levels may be used to assist in the confirmation of acute or primary infection before the appearance of HIV antibodies detected by an EIA or Western Blot assay. Most true-positive results will show very high levels (10^5 to 10^6 copies/mL) of circulating HIV RNA, consistent with uncontrolled viraemia. False-positive results occur in less than 10% of cases; these usually involve low RNA levels (less than 104 copies/mL) and are usually not reproducible.^{(7) (8)} A number of manufacturers of HIV viral load tests still do not make claims that support the use of these tests for diagnosis of HIV infection.

Real time PCR assay

Conventional nucleic acid-based quantification methods are being replaced in some laboratories with one of a number of real time PCR assays that have become available. The Roche COBAS™ AmpliPrep/ COBAS TaqMan™ HIV-1 test combines automated sample preparation for HIV-1 RNA purification using the AmpliPrep, and real-time PCR amplification and detection using the COBAS AmpliPrep TaqMan™ system. Similar to the Roche COBAS™ Amplicor test, this assay targets dual conserved regions in HIV-1 and uses fluorescently-labelled probes to detect the amplified products in real time. The advantages are a wider dynamic range and greater sensitivity.^{(9) (10)} Earlier versions of HIV viral load assays using single target amplification test systems were prone to variability in the levels of HIV-1 RNA reported to be caused by genetic diversity of HIV-1 and mutations and mismatches in the primer and probe target areas. The introduction of dual targets in highly conserved regions of the HIV-1 genome has reduced this variability and allows for greater equivalence in reported RNA results from patients with HIV infection with different subtypes.

A comparison of different HIV-1 viral load methods is shown in Table 1, along with a diagrammatic representation of the genomic structure of HIV-1, for information, in Figure 3.

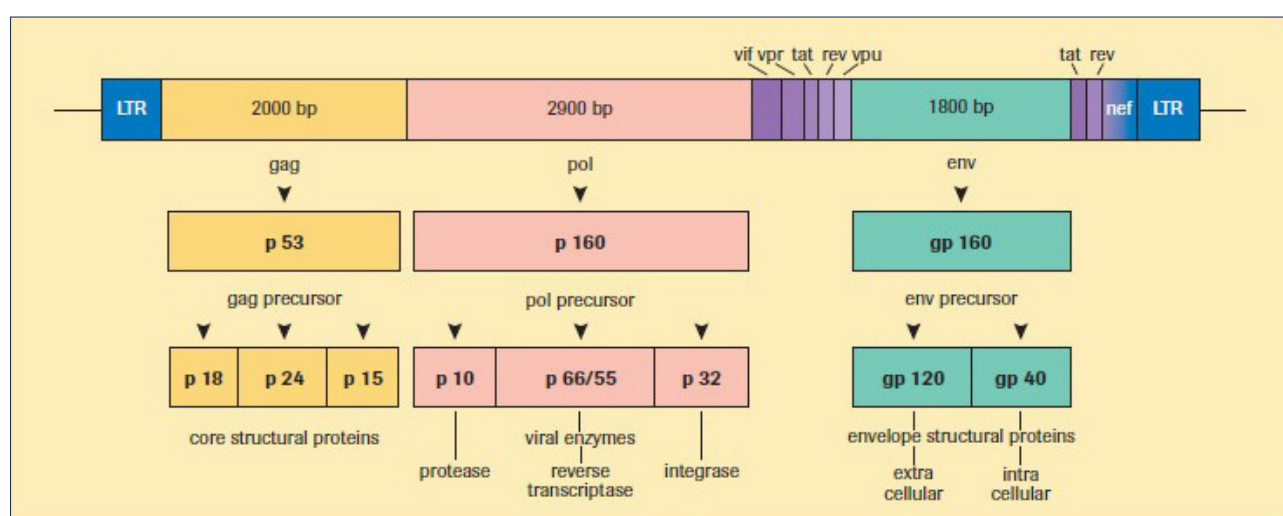
CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Table 1. Comparison of four commercial HIV-1 viral load methods

HIV Viral Load Method	Assay Target/s	Measuring Range (cp/mL)
Roche	<i>gag</i> and LTR	20 – 1 X 10 ⁷
Abbot	Integrase	40 – 1 X 10 ⁷
Qiagen	LTR	34 – 4.5X10 ⁷
Hologic	<i>pol</i> and LTR	30 – 1 X 10 ⁷

Source: NSW State Reference Laboratory for HIV, St Vincent's Hospital Sydney Limited.

Figure 3. Genomic structure of HIV-1



The Abbott RealTime HIV-1 assay, for use on the m2000 system, uses a unique partially double-stranded probe that targets the HIV-1 *pol*. The probe strands are labelled with a fluorophore (reporter) at the 5' end, and a quencher moiety at the 3' end of the shorter, complementary strand. In the presence of target *pol* sequences, the reporter probe preferentially binds, and upon release of the shorter quencher probe, fluoresces. Assay performance characteristics from Abbott Laboratories show that the assay has a 5-log₁₀ linear range, assay specificity of 100% (n=259), 95% probability of detecting samples with a viral load of 25 copies/mL, and recognition of subtype panels from group M (A-H), group O, and group N. (11) (12) (13) (14) (15) (16)

The Hologic Aptima HIV-1 Quant Dx assay (Aptima assay; Hologic Inc., San Diego, CA) employs transcription-mediated amplification (TMA) and real-time detection for rapid, high-throughput testing of viral load on the Panther platform. Target amplification via TMA, utilizes two enzymes, MMLV (Moloney murine leukemia virus) reverse transcriptase and T7 RNA polymerase to amplify two regions of HIV-1 RNA (*pol* and LTR). Detection is achieved using single-stranded nucleic acid torches that are present during the amplification of the target and that hybridize specifically to the amplicon in real-time. Each torch has a fluorophore and a quencher. When the torch is not hybridized to the amplicon, the quencher is in close proximity of the fluorophore and suppresses the fluorescence. When the torch binds to the amplicon, the quencher is moved farther away from the fluorophore and it will emit a signal at a specific wavelength when excited by a light source. As more torches hybridize to an amplicon a higher fluorescent signal is generated. Assay performance characteristics from Hologic show that the assay has a 6-log₁₀ linear range, assay specificity of 100% (n=630), 95% probability of detecting samples with a viral load of 30 copies/mL, and recognition of subtype panels from HIV-1 groups M, N and O. (38)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

HIV DNA PCR

The HIV DNA assay detects both unintegrated and integrated forms of HIV DNA present in circulating peripheral blood mononuclear cells. There are a number of newly emerging qualitative assays able to detect both HIV DNA and RNA (total nucleic acid) for supplementary reference testing and diagnostic testing strategies. The main clinical use of these assays is in the qualitative detection of HIV in situations where serological testing is inappropriate (e.g. pre-seroconversion, or neonatal infection where results may be confounded by the presence of maternal antibodies) or where serological testing has been disputed or is inconclusive (e.g. indeterminate Western Blot assay result). The HIV DNA PCR test is highly sensitive (greater than 99%, detecting one copy of HIV DNA per 10,000 to 100,000 cells) and specific (98%), but has not replaced serology either as a screening test or as a diagnostic test in isolation. HIV DNA testing is the preferred test for early infant diagnosis when neonates are born to HIV seropositive mothers.

HIV DNA PCR and HIV RNA reverse transcriptase (RT)-PCR techniques were commonly used in laboratory research, however they have made a rapid transition to routine clinical practice. Amplification may be performed on various genomic regions of interest, and the products used in such analyses as HIV subtype determination, phylogenetic analysis, detection of genetic mutations, and prediction of viral tropism and drug resistance.[\(17\)](#) [\(18\)](#)

HIV antigen testing

Assays are available to directly detect the major structural core protein HIV-1 p24 (designated p24 because the molecular weight of the protein is 24 kilodaltons). While initially examined for utility as an assay to monitor HIV viral load,[\(19\)](#) [\(20\)](#) it is no longer considered to be appropriate for viral load testing due to a lack of sensitivity. [\(21\)](#) [\(22\)](#) The p24 assay is widely used by reference laboratories in Australia, but is not commercially available in the USA and as such does not appear in recommended CDC testing algorithms. HIV-1 p24 antigen is particularly useful in diagnosis of acute HIV infection as a supplemental test when antibody tests may be negative, inconclusive or indeterminate. While nucleic acid tests offer superior sensitivity and specificity for the earliest detection of HIV infection, dedicated specimens are required for nucleic acid tests while HIV-p24 can still be performed on the primary serum sample submitted for antibody screening. The presence of HIV-1 p24 in newly identified sera or in sera which exhibit negative or inconclusive HIV-1 antibody tests should be confirmed by neutralisation with anti-p24 antisera.

In 2005, the so-called fourth generation HIV screening tests were developed. These tests detect HIV-1 p24 antigen and both HIV-1 and HIV-2 antibodies in a single test. They have been rapidly adopted globally as preferred screening tests for HIV infection and allow for the routine detection of recently acquired infections where antibody-only tests may be unreliable.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

HIV tissue culture

Tissue culture allows HIV to be expanded and propagated in vitro by its culture with donor peripheral blood mononuclear cells in the presence of stimulatory factors such as interleukin 2 (IL-2). Coculturing of patient peripheral blood mononuclear cells, or cells from other body compartments suspected to be infected with HIV, with stimulated donor peripheral blood mononuclear cells is an alternative method for the detection of very low levels of virus. Culture supernatants are assayed for the presence of p24 or reverse transcriptase, which generally appear over 1 to 2 weeks. The efficiency of the process falls dramatically with lower HIV viral load, although it can be improved by using techniques such as the removal of inhibitory CD8 cells from the patient and donor peripheral blood mononuclear cells, stimulation with phytohaemagglutinin or IL-2. The tissue culture technique is expensive and time-consuming and must be performed only within a laboratory with appropriately certified biocontainment. For viral detection and isolation in clinical situations, tissue culture has now been replaced by the methods outlined above and is never performed as a routine test. However, it remains a mainstay of laboratory practice, where it is used for the maintenance and analysis of viral strains.

Antiretroviral drug resistance testing

HIV shows a high rate of genomic evolution due to the error-prone nature of RT (which introduces random sequence changes into newly produced viral RNA)(23), the high rate of viral production, and the rapid turnover of productively infected cells. For these reasons HIV strains rapidly develop resistance to antiretroviral monotherapy through the acquisition of mutations in RT, envelope or protease genes that confer resistance of enzymatic function to the effects of the drug on the enzyme. The principle behind combination antiretroviral therapy (cART) is to achieve a low level of viral replication and thus a reduced opportunity for the introduction of advantageous mutations into newly produced viruses. Strains that have mutated to become resistant to one therapeutic agent may also have abnormally lowered replicative capacity (fitness), making the acquisition of mutations to further agents less likely.

The resistance profile of a viral strain can be estimated by examination of the nucleic acid sequence of the target genes for evidence of known resistance mutations, or directly assessed by tissue culture of the virus (full length or cloned into a common viral backbone) in the presence of a panel of antiretroviral drugs. Treatment may then be altered in the knowledge that a patient is carrying a virus resistant to one or more agents. Studies have demonstrated improved virological outcomes in patients whose therapeutic choices have been guided by the use of resistance testing(24) (25) (26) (27) (28) (29) (30) and the use of resistance testing is regarded as standard of care in Australia, western Europe and the USA.(31) (32)

There are a number of commercially available methods for determining the resistance profile of an HIV isolate. The most common is genotypic resistance testing, which is the only assay routinely available in Australia and is supported by the Medicare Benefits Schedule (MBS). Samples submitted for genotypic antiretroviral resistance testing should be accompanied by a request for a plasma HIV RNA level and a treatment history to aid in the interpretation of test results.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Antiretroviral drug resistance genotyping

Assessment of the HIV genotype (i.e. the nucleic acid sequence) involves the isolation of viral RNA followed by the RT-PCR amplification of portions of the target genes. These amplification products are then sequenced using standardised automated DNA sequencing procedures. Ultracentrifugation of a plasma sample with a low HIV viral load (1000 – 2000 copies/mL) will pellet free virus for RNA extraction and sequencing. Test sequences are compared with a wild-type control reference strain (i.e. no prior exposure to antiretroviral agents) for annotating differences in the predicted amino acid sequences. Mutations that have been associated with resistance to antiretroviral drugs are then identified by comparison with a database of known codon (genetic code) mutations. Resistance mutations are usually reported as primary (generally associated with phenotypically detectable drug resistance) or secondary (mutations generated after the primary mutation, and which may confer varying levels of resistance). The nomenclature of mutations is the wild-type amino acid (using the 20 letter amino acid code)/the amino acid position in the protein/the mutant amino acid e.g. for a change from the wild- type methionine residue at position 46 of protease to isoleucine is denoted M46I. Mutations that involve the insertion of amino acids follow similar nomenclature with the additional amino acids following the residue position. Tables 2 and 3 show HIV resistance mutations to the classes of antiretroviral agents.

Caution must be exercised in the interpretation and use of resistance genotyping data. Two major factors contribute to the complexity of this process: the contribution of minor species and mutational complexity. It is important to realise that genotypic resistance testing gives a snapshot of the dominant viral forms circulating in the plasma at the time of testing. Viral variants with different resistance profiles may circulate at low levels or be present latently in proviral DNA. These may rapidly re-appear and become dominant once the selective pressure of antiretroviral therapy changes. Only minor species that are circulating at substantial levels (above about 20%) may be detected and reported. For this reason, genotypic resistance data must always be interpreted in the light of a thorough history of treatment and previous resistance testing.

Mutations are associated with drug resistance on the basis of in vitro or in vivo data. These data are not always clear and the publication of new evidence means the assignment of mutation to phenotype is being continuously updated. The substantial sequence variability between HIV strains means that it can be difficult to distinguish naturally occurring viral variants from selected mutations that confer an evolutionary advantage, particularly if this advantage is small or secondary to the existence of a primary mutation. When in doubt, consultation with the laboratory performing the assay is strongly indicated.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Table 2. HIV antiretroviral drug resistance mutations: nucleoside/nucleotide reverse transcriptase inhibitor (NRTI) and non-nucleoside/nucleotide reverse transcriptase inhibitor (NNRTI) mutations

Major Nucleoside RT Inhibitor (NRTI) Resistance Mutations												
	Non-TAMs					TAMs						MDR
	184	65	70	74	115	41	67	70	210	215	219	69 151
Cons	M	K	K	L	Y	M	D	K	L	T	K	T Q
3TC	<u>VI</u>	R										Ins M
FTC	<u>VI</u>	R										Ins M
ABC	VI	R	E	<u>VI</u>	<u>E</u>	L			W	FY		Ins M
TDF	***	<u>R</u>	E		F	L		R	W	FY		Ins M
ZDV	***	***	*	*		L	N	R	W	FY	QE	Ins M

Bold underline: High-level reduced susceptibility or virological response. **Bold:** Reduced susceptibility or virological response. Plain text: Reduced susceptibility in combination with other NRTI-resistance mutations. Asterisk: Increased susceptibility.

TAMs: Thymidine analog mutations. Selected by AZT and d4T and facilitate primer unblocking. Non-TAMs prevent NRTI incorporation.

MDR: Multidrug resistance mutations. T69 insertions occur with TAMs. Q151M occurs with non-TAMs and the accessory mutations A62V, V75I, F77L, and F116Y.

M184VI: The most common NRTI-resistance mutations. Although they cause high-level in vitro resistance to 3TC/FTC, they are not contraindications to 3TC/FTC because they increase TDF and AZT susceptibility and decrease viral replication fitness.

Additional mutations: K65N similar but weaker than K65R. K70GQNT similar to K70E. T69D and V75MT reduce susceptibility to d4T and ddI, which are not shown because they are no longer recommended for HIV treatment. T215SCDEIVALN (T215 revertants) emerge from T215YF in the absence of NRTIs. E40F, E44DA, D67GE, V118I, and K219NR are accessory TAMs. D67, T69, K70 deletions have not been well studied. They usually occur in combination with K65R and/or Q151M.

References: hivdb.stanford.edu/s/nrtinotes

Major Non-Nucleoside RT Inhibitor (NNRTI) Resistance Mutations								
	100	101	103	106	181	188	190	230
Cons	L	K	K	V	Y	Y	G	M
DOR	I	EP		<u>AM</u>	CIV	<u>LCH</u>	<u>SE</u>	<u>L</u>
EFV	<u>I</u>	<u>EP</u>	<u>NS</u>	<u>AM</u>	CIV	<u>LCH</u>	<u>ASEQ</u>	<u>L</u>
ETR	<u>I</u>	<u>EP</u>			<u>CIV</u>	L	<u>ASEQ</u>	<u>L</u>
RPV	<u>I</u>	<u>EP</u>			<u>CIV</u>	<u>L</u>	<u>ASEQ</u>	<u>L</u>
NVP	<u>I</u>	<u>EP</u>	<u>NS</u>	<u>AM</u>	<u>CIV</u>	<u>LCH</u>	<u>ASEQ</u>	<u>L</u>

Bold underline: High-level reduced susceptibility or virological response. **Bold:** Reduced susceptibility or virological response. Plain text: Reduced susceptibility in combination with other NNRTI-resistance mutations.

Abbreviations: Doravirine (DOR), efavirenz (EFV), etravirine (ETR), rilpivirine (RPV), nevirapine (NVP).

Additional Mutations: A98G (DOR, EFV, ETR, NVP, RPV); E138GQKR are nonpolymorphic mutations associated with intermediate/high-level RPV resistance. E138A is a polymorphic mutation associated with low-level RPV resistance. P225H (DOR, EFV); F227C is associated with high-level DOR resistance and intermediate resistance to the remaining NNRTIs; F227L (DOR, NVP), L234I (DOR), Y318F (DOR, NVP).

Synergistic combinations: V179D+K103R reduce NVP and EFV susceptibility >10-fold. Y181C+V179F cause high-level ETR and RPV resistance.

ETR genotypic susceptibility score (package insert): Y181IV (3.0); L100I, K101P, Y181C, M230L (2.5); V90I, E138A, V179F, G190S (1.5); A98G, K101EH, V106I, V179DT, G190A (1.0); <2.5 susceptible; 2.5 to 3.0 intermediate; >3.0 high-level. V90I, A98G, V106I, E138A, V179DT, G190A/S have little effect on ETR susceptibility alone.

References: hivdb.stanford.edu/s/nnrtinotes

Source: adapted from Stanford University HIV Drug Resistance Database. For most current details of interpretation, please refer to <http://hivdb.stanford.edu>

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Table 3. HIV antiretroviral therapy resistance mutations: protease inhibitor and integrase inhibitor mutations.

Major Integrase Inhibitor (INSTI) Resistance Mutations										
	66	92	118	138	140	143	147	148	155	263
Cons	T	E	G	E	G	Y	S	Q	N	R
BIC	K	Q	R	KAT	SAC			HRK	H	K
DTG	K	Q	R	KAT	SAC			HRK	H	K
EVG	AIK	Q	R	KAT	SAC		G	HRK	H	K
RAL	AIK	Q	R	KAT	SAC	RC		HRK	H	K

Bold underline: High-level reduced susceptibility or virological response. **Bold:** Low-level reduced susceptibility or reduced susceptibility or virological response. Plain text: Reduced susceptibility in combination with other INSTI-resistance mutations.

Abbreviations: Bictegravir (BIC), dolutegravir (DTG), elvitegravir (EVG), raltegravir (RAL).

Additional mutations: L74MI, T97A, V151I, E157Q, G163KR are common polymorphic accessory DRMs. H51Y, F121Y, S153YF, S230R are additional nonpolymorphic mutations associated with reduced susceptibility to one or more INSTIs. E92GV, Y143HKSGA, P145S, Q146P, Q148N, V151AL, and N155ST are rare nonpolymorphic IN mutations that reduce RAL and/or EVG susceptibility. Mutations outside of IN in the polypurine tract have been reported to reduce INSTI susceptibility in two persons.

References: hivdb.stanford.edu/s/instinotes

Major Protease Inhibitor (PI) Resistance Mutations											
	32	46	47	48	50	54	76	82	84	88	90
Cons	V	M	I	G	I	I	L	V	I	N	L
ATV/r	I	IL	V	VM	<u>L</u>	VTALM		ATFS	<u>V</u>	<u>S</u>	M
DRV/r	I		VA		V	LM	V	F	V		
LPV/r	I	IL	VA	VM	V	VTALM	V	<u>AETFS</u>	V		M

Bold underline: High-level reduced susceptibility or virological response. **Bold:** Reduced susceptibility or virological response. Plain text: Reduced susceptibility in combination with other PI-resistance mutations.

Abbreviations: atazanavir (ATV), darunavir (DRV), lopinavir (LPV), 'r' (ritonavir).

Additional mutations: L10F, V11I, K20TV, L23I, L33F, K43T, F53L, Q58E, A71IL, G73STCA, T74P, N83D, and L89V are common nonpolymorphic accessory resistance mutations. L10F, V11IL, L33F, T74P, and L89V are accessory resistance mutations associated with reduced DRV/r susceptibility. D30N and N88D are nonpolymorphic resistance mutations selected by NFV. L10RY, V11L, L24F, M46V, G48ASTLQ, F53Y, I54S, V82CM, I84AC, N88TG are rare nonpolymorphic variants.

Hypersusceptibility: I50L (each PI except ATV); L76V (ATV).

References: hivdb.stanford.edu/s/pinotes

Source: adapted from Stanford University HIV Drug Resistance Database. For most current details of interpretation, please refer to <http://hivdb.stanford.edu>

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Resistance phenotyping

Phenotypic drug resistance is considered the gold standard test for drug susceptibility and directly measures the competency of a virus isolate to grow in various concentrations of antiretroviral drugs. Phenotypic drug resistance assays are not routinely performed due to availability, lengthy turn-around time for results and cost. Nucleic acid sequences from the various target genes of HIV are extracted from patient plasma HIV RNA and are inserted into the backbone of a laboratory clone of HIV or used to generate pseudotyped viruses that express the patient-derived HIV genes of interest. Replication competence of the pseudotyped viruses at increasing drug concentrations is monitored by expression of a reporter gene and is compared with replication of a reference wild-type HIV strain. The antiretroviral drug concentration that inhibits viral replication by 50% is calculated, and the ratio of the IC₅₀ (inhibitory concentration) of test and reference viruses is reported as the fold increase in resistance. The addition of phenotypic to genotypic testing is generally preferred for persons with known or suspected complex drug-resistance mutation patterns, particularly to protease inhibitors (PIs)(33).

Genotypic determination of HIV-1 CCR5/CXCR4 tropism

HIV-1 uses one of two coreceptors for entry into cells: CCR5 and CXCR4. CCR5 inhibitors, block the CCR5 receptor, but not the CXCR4 coreceptor, reducing viral entry, replication and therefore plasma viral load. CCR5 inhibitors, of which maraviroc is the only one licensed, are only effective if a patient's HIV uses CCR5 as its coreceptor.(34) (35) If any proportion uses CXCR4, there will be no meaningful response to maraviroc. Therefore, the patient must be documented as having HIV that only uses CCR5 within the 3 months before the commencement of maraviroc.

Viral coreceptor usage is determined primarily by sequencing the section of the envelope gene encoding the V3 loop of the HIV-1 gp120 viral envelope protein. Previously, viral tropism has been determined by a phenotypic assay (Trofile®) which was expensive, required a significant blood volume and had a lengthy turn-around time. More recently, genotypic assays that use viral RNA from plasma or viral DNA from white blood cells have been developed and validated. These assays work like a genotypic resistance assay. The viral RNA or DNA is extracted, amplified and sequenced. This sequence is then examined by the Geno2Pheno (G2P) algorithm.

The G2P algorithm provides a statistical estimate of the likelihood that the virus binds to CXCR4. This process generates a false-positive rate, which is reported along with the tropism result. The lower the false-positive rate the more likely the patient's HIV uses CXCR4. The higher the false-positive rate, the more likely the virus uses CCR5. Currently, the consensus position is to use a false-positive rate of 20% as the break-point for determining whether a virus binds CCR5 or CXCR4. As even a minor proportion of HIV using CXCR4 will compromise the activity of any CCR5 inhibitor such as maraviroc, the test is performed in triplicate and the result with the lowest false-positive rate determines the result reported. That is, for a virus to be reported as CCR5-using each of the three results must have a false-positive rate above 20. If any result is below 20, then the virus is reported as being CXCR4-using.

The plasma viral RNA G2P assay has undergone the most rigorous validation and is the test of choice for any viraemic patient. The pro-viral DNA G2P assay should be used only in patients who have viral loads of less than 2000 copies/mL because there is substantially less clinical experience with this test and the results generated are more variable.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Ethylenediaminetetraacetic acid (EDTA) anticoagulant treated whole blood is required. If a RNA-based tropism is ordered, a HIV viral load test must also be ordered on the same sample, as the test only works in patients with HIV RNA levels of 2000 copies/mL or above, and will not be performed when the viral load is lower.

The turn-around time for results is approximately 2 weeks, similar to that for genotypic resistance assays. The report will give the overall result as either:

- Analysis of sequences of V3 loop of the HIV-1 envelope gene does not detect the presence of a substantial sub population of CXCR4 using virus. CCR5 inhibitors are likely to be effective or
- Analysis of sequences of V3 loop of the HIV-1 envelope gene suggests the presence of CXCR4 using virus. CCR5 inhibitors are unlikely to be effective

The report will include the G2P results for the triplicate assays, including the false-positive rate and the interpretation of each of the triplicates performed.

Once a CXCR4-using virus has been detected, the test should not be ordered again. It is not appropriate to start a CCR5 inhibitor in a patient with a history of a CXCR4-using virus. Therefore, as the virus only evolves from CCR5 to CXCR4 use, once a virus has been labelled CXCR4-using, it will always be CXCR4-using, and a CCR5 inhibitor is not recommended. To start maraviroc a patient must have carriage of a CCR5-using virus within 3 months of the start date.

HLA-B*57:01 allele genotyping for assessing the risk of abacavir hypersensitivity reaction.

Abacavir hypersensitivity reaction (AHSR) affects 4-8% of patients with HIV-1 infection within the first 6 weeks of starting abacavir. It is usually characterised by fever, rash, abdominal pains and lethargy. Symptoms related to abacavir hypersensitivity reaction deteriorate with continued therapy and improve within 72 hours of abacavir discontinuation. Rechallenging with abacavir after a hypersensitivity reaction usually results in recurrence of symptoms within hours and with the potential to be fatal.(36)

GlaxoSmithKline and Western Australian investigators have independently found a strong association between an HLA type and the risk of developing abacavir hypersensitivity. Martin et al. (37) showed a strong association between carriage of the 57.1 ancestral haplotype of major histocompatibility complex (MHC) genes and abacavir hypersensitivity in HIV patients using recombinant haplotype mapping. They found the occurrence of the *HLA-B*57:01* allele and a haplotypic variant of the *Hsp70-Hom* allele represented a highly predictive susceptibility marker for abacavir hypersensitivity. Genetic tests involving *HLA-B*57:01* alone or in combination with the *Hsp70-Hom* M493T variant reduced the prevalence of definite abacavir hypersensitivity in the population predominantly of European origin from 8% to 0.4%. When using *HLA-B*57:01* alone, an estimated 1.6% of the tested population would be inappropriately denied access to abacavir, however, testing for the presence of both *HLA-B*57:01* and the *Hsp70-Hom* M493T variant would reduce this percentage to 0.4%. On the basis of many such studies it is recommended that *HLA-B*57:01* screening occur before commencement of abacavir-containing regimens and that *HLA-B*57:01* –positive patients should not be prescribed abacavir.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

A retrospective study by GlaxoSmithKline of patients with abacavir hypersensitivity reaction also found a strong association between the hypersensitivity reaction and HLA-B*57:01. They identified a strong association between a point mutation (SNP) in the tumour necrosis factor- α (TNF- α) gene and abacavir hypersensitivity reaction. However, this association is thought to be a secondary rather than a primary association as the HLA-B57 and TNF- α SNP genes are linked.

Molecular assays have been developed to identify the *HLA-B*57:01* allele associated with abacavir hypersensitivity reaction. The EUROArray HLA-B57:01 Direct assay provides molecular genetic determination of HLA-B*57:01 alleles in human genomic DNA. The test provides fast and simple HLA-B*57:01 detection, encompassing all currently known HLA-B*57:01 alleles in one test reaction. The procedure is performed directly on whole blood samples and does not require a separate DNA isolation. Genomic DNA of blood cells is prepared for PCR by diluting the blood with the extraction solution provided in the test kit and incubating it for one minute. In the first reaction step, a section of the HLA-B gene and a β -globin gene fragment as positive control are amplified from the thus produced extract or, alternatively, from a patient genomic DNA sample using the polymerase chain reaction (PCR). All PCR products are labelled with a fluorescence dye as they are produced. In the second reaction step, the products are analysed using a microarray containing immobilised probes which are complementary to the amplified DNA. The specific binding (hybridisation) of the fluorescing PCR product to the corresponding microarray spot is detected using a special microarray scanner (by EUROIMMUN). If an *HLA-B*57:01* allele is present in a patient DNA sample, a fluorescence signal is generated at the specific HLA-B*57:01 spots. The spot signals are evaluated automatically using the EUROArrayScan software.[\(39\)](#)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Immunological tests used to monitor HIV infection and disease

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Last Reviewed: September 2019

Introduction

In addition to clinical and virological staging of HIV infection, patients should be staged immunologically as this provides prognostic information for the patient. This is currently undertaken by measuring blood lymphocyte subpopulations using flow cytometry assays, which detect cells expressing surface markers that have been identified by binding of labelled antibodies. For example, T cells express CD3 (part of the T cell receptor for antigens) and can be divided into subpopulations with different functions according to co-expression of CD4 or CD8 molecules with subpopulations of CD4+ and CD8+ T cells identified on the basis of expression of markers of activation or immunological memory. In healthy individuals, the proportions and numbers of these lymphocyte subpopulations remain relatively fixed but may be altered in disease states, such as HIV infection, which is characterised by CD4+ T cell depletion.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Routine monitoring of blood lymphocyte subpopulations in people with HIV infection

In patients with HIV infection not receiving antiretroviral therapy (ART), the blood CD4+ T cell count or proportion (CD4+ T cells as a percentage of total lymphocytes) should be monitored because they relate to the extent of HIV disease and guide the use of prophylactic antimicrobial therapy to prevent opportunistic infections. However, there is limited value in regularly monitoring CD4+ T cell counts in patients who achieve persistent suppression of HIV replication (HIV RNA <200 copies/mL) and a CD4+ T cell count >300/mL once ART is established, unless non-HIV related causes of CD4+ T cell depletion, such as radiotherapy or immunosuppressive therapy, are introduced. (1) Guidelines on using CD4+ T cell counts to monitor people with HIV infection are provided at [ASHM Adult HIV Guidelines](#).

Assessing T cell CD4/8 ratios may have clinical utility in HIV-infected individuals, particularly those with suppressed HIV replication on ART, because they reflect the effect of both the number of CD4+ T cells and CD8+ T cell activation and expansion related to reactivation of infections with viruses such as cytomegalovirus, which has been linked to an increased risk of HIV co-morbidities. (2) In addition, examination of other lymphocyte subpopulations may provide additional information about HIV disease progression or immune reconstitution on ART. For example, increased proportions of activated T cells are a strong predictor of HIV disease progression independent of CD4+ T cell counts (3,4) and may predict CD4+ T cell recovery on ART. (5) Also, the number or proportion of naïve CD4+ T cells or recent thymic emigrants in patients receiving ART are an indicator of immune reconstitution related to production of new CD4+ T cells. (6,7) Finally, assessing memory B cells may provide information about the cause of defects of antibody production sometimes encountered in patients receiving ART. (8) However, the information obtained from assessing these other lymphocyte subpopulations is not routinely needed to make treatment decisions

The methods used to assess lymphocyte subpopulations in the blood of patients with HIV infection are summarised in Table 1.

Table 1. Methods used to detect and enumerate lymphocyte subsets

Cell type	Lymphocyte markers	Method
CD4+ ('helper') T cell	CD4+	Flow cytometry
CD8+ ('cytotoxic') T cell	CD8+	
Naïve CD4+ or CD8+ T cell	CCR7+, CD45RA+	
Central memory CD4+ or CD8+ T cell	CCR7+, CD45RA-	
Effector CD4+ or CD8+ T cell	CCR7-, CD45RA+	
Effector memory CD4+ or CD8+ T cell	CCR7-, CD45RA-	Flow cytometry
Activated CD4+ or CD8+ T cell	CD38+, HLA-DR+	
Recent thymic emigrant T cell	TRECs	PCR
B cell	CD19+	Flow cytometry
Memory B cell	CD27+	

TRECs: T cell receptor excision circles PCR: Polymerase chain reaction

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Assessment of HIV-specific T cells

In addition to measuring the blood count or proportion of total CD4+ T cells or CD4+ T cell subpopulations, it is also possible to assess the proportion of blood T cells that specifically respond to HIV antigens. Whilst this type of test is not used in the routine clinical setting, it has utility in research settings for understanding immunological responses against HIV and particularly in assessment of HIV vaccine candidates. Table 2 summarise the assays used to identify HIV-specific T cells.

Table 2. Assays used to detect HIV-specific T cells

Assay	CD4	CD8	Quantitative	Functional	Interpretation
Tetramer binding, using flow cytometry ¹	√ ²	√	√		Number of T cells recognising specific HIV antigens
ELISPOT assay ³	√	√	√	√	Number of T cells capable of producing cytokines following recognition of HIV antigens
Intracellular cytokine production, using flow cytometry ⁴	√	√	√	√	Number of T cells capable of producing cytokines following recognition of HIV antigens
Cr51 release assay ⁵		√	√	√	Number of T cells able to kill cells expressing HIV antigens (CTLs)
Degranulation assay, using flow cytometry ⁶		√	√	√	Number of T cells able to degranulate following recognition of HIV antigens
Lymphoproliferation assay ⁷	√			√	Number of CD4+ T cells able to proliferate following recognition of HIV antigens

¹ Tetrameric HLA-peptide complexes detect T cells that express a T cell receptor complex which specifically recognises a given peptide presented by a given human leukocyte antigen molecule.

² Less developed for CD4+ T cells as tetramers harder to create, specific CD4+ T cell frequency lower and reduced MHC class II and T cell receptor affinity.

³ T cells are exposed to HIV antigens. Cells recognising these antigens produce cytokines such as interferon-gamma (IFN-gamma). Secreted IFN-gamma is captured by specific antibodies coating the well. Cells are then removed by washing and bound IFN-gamma is detected by colorimetric techniques.

⁴ T cells are exposed to HIV antigens. Cells recognising these antigens produce cytokines such as IFN-gamma. Cell membranes are then made permeable to permit fluorescent monoclonal antibodies to enter cells, which bind to the cytokine of interest. The cytokine-containing cells are then enumerated by flow cytometry.

⁵ Autologous B cells are transformed to express HIV antigens on their cell surface. These cells are pulsed with 51Chromium (51Cr) which remains intracellular. CD8+ T cells are then mixed with autologous B cell targets. HIV-specific cytotoxic T lymphocytes lyse target cells and thus release 51Cr which can then be measured.

⁶ T cells are exposed to HIV antigens. CD8+ T cells recognising these antigens degranulate, which can be detected by CD107a expression on cell surface by flow cytometry.

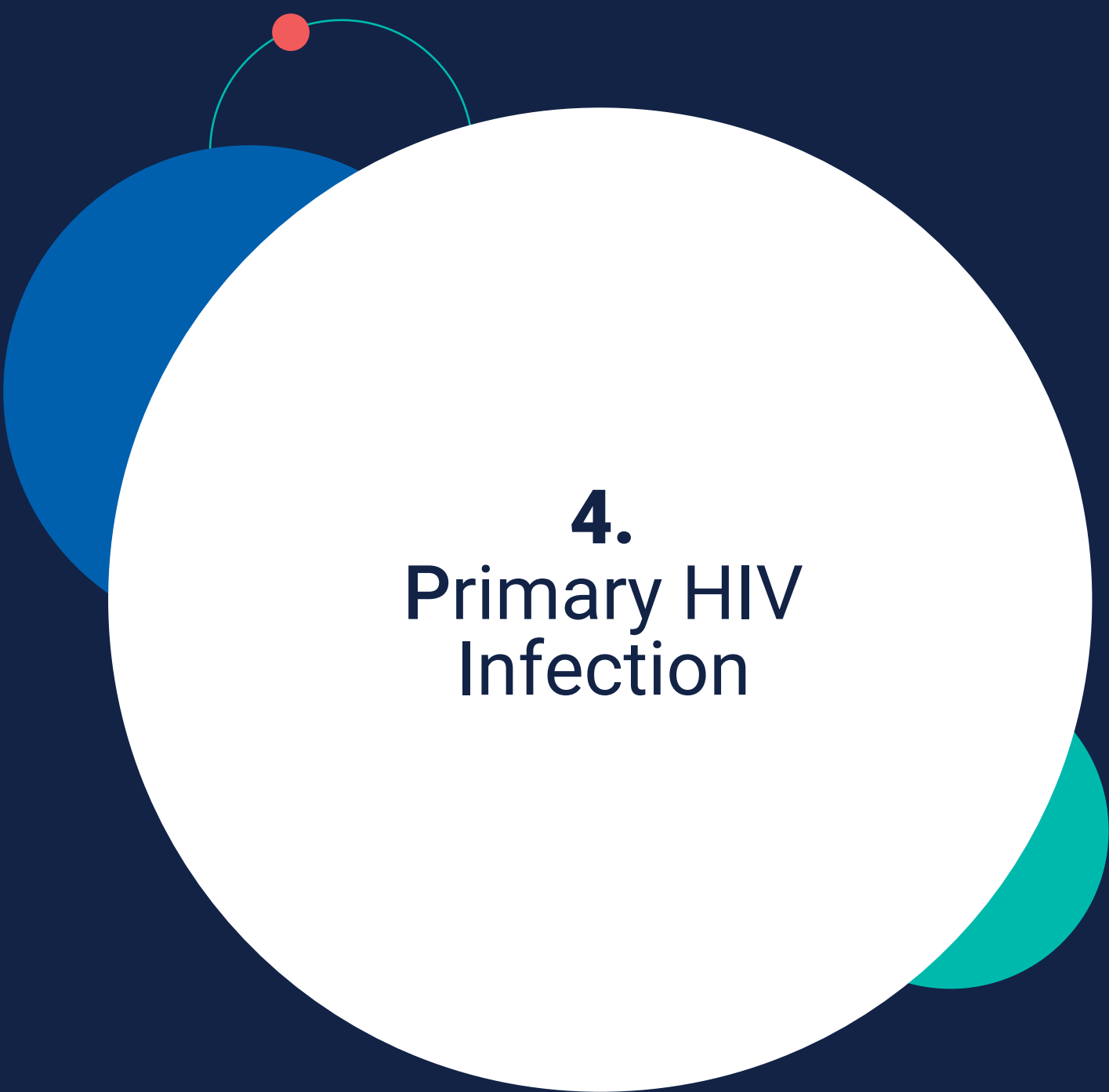
⁷ Lymphoproliferative assay – CD4+ T cells are mixed with HIV antigens and 3H-thymidine. CD4+ T cells which recognise HIV antigens proliferate and incorporate 3H-thymidine. The stimulation index reported compares the amount of 3H-thymidine incorporated into cells exposed to HIV antigens compared with those exposed to control antigens.

ELISPOT: enzyme-linked immunospot assay CTL: cytotoxic T lymphocyte.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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An abstract graphic featuring a large white circle in the center, partially overlapping a blue circle to its left and a teal circle to its right. A thin teal arc with a red dot is positioned above the white circle. The background is a dark blue gradient.

4. Primary HIV Infection

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Primary HIV Infection

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Introduction

Primary HIV infection (PHI) usually refers to the critical six-month period following the acquisition of HIV. This period, immediately following initial infection, is associated with a highly dynamic series of virological and immunological events, which have been demonstrated to impact the long-term course of untreated infection, including severity and rate of disease progression. It is now recognised as the ideal time to commence anti-retroviral therapy (ART). Clinically, the initial stages of infection are characterised by a 'mononucleosis-like' illness that is non-specific and generally mild but with characteristic clinical manifestations. Recognition of these signs and symptoms provides a clue to diagnosis, providing an opportunity for subsequent rapid initiation of ART.

The early weeks following HIV infection may also be variously referred to as acute seroconversion illness, acute HIV infection, or the acute retroviral syndrome. Clinicians must have a high index of suspicion for PHI in people who are known to have a high-risk of acquiring sexually-transmissible or blood-borne virus infections and/or people that present with consistent symptoms, as well as the clinical acumen to arrange appropriate screening and diagnostic testing.

Early diagnosis in this critical period is of great importance, both from a public health perspective, with rates of transmission highest during PHI, and for the individual, as early initiation of ART is now well established to be beneficial by positively modifying long-term disease outcomes and by limiting both immune damage and the size of the viral reservoir with reduction of onwards transmission.

Pathogenesis of primary HIV infection

The weeks following HIV infection are a highly dynamic period, with a series of virologic and immunologic events having occurred prior to the onset of clinical manifestations of PHI and the emergence of positive findings on diagnostic tests. An exceedingly high plasma HIV viral load and rapid loss of CD4+ T cells in all tissue compartments accompany the clinical manifestations of PHI. Resolution of symptoms is associated with the development of an anti-HIV immune response and early control of viraemia. (1)

HIV infection occurs most commonly at the genital or anal mucosa via the dendritic cells and macrophages that populate these tissues. (2) The virus uses its envelope protein, gp120 to bind initially to CD4 and then subsequently to one of two co-receptors, CCR5 or CXCR4, on the cell surface of dendritic cells and macrophages. These events lead to conformational changes in the associated transmembrane protein in gp41, leading to fusion of viral and target cell membranes followed by endocytosis of the virus into the cell. Infection is typically established by virus that utilises the co-receptor CCR5 for cellular entry, which is particularly abundantly expressed by cells in the mucosal immune system. Individuals who are homozygous for a non-functional allele of CCR5, referred to as CCR5 (delta), are therefore highly resistant to infection. (3)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Dendritic cells may harbour the virus with or without being productively infected. Via their normal role as antigen presenting cells, these cells travel to regional lymph nodes and, through the hijacking of the normal physiological function of antigen presentation to T cells, transfer virus to multiple CD4+ T cells, rapidly amplifying the infection within lymph nodes and other secondary lymphoid structures in the mucosa, where virus is detectable within 2 days. (1, 4) This triggers both an antibody and T cell response with the resultant preferential infection of follicular CD4+ T cells within lymph nodes. Once virus-infected cells enter the lymphatics, there is rapid onset of viraemia, and dissemination to multiple organs, including the spleen and central nervous system. (5)

Cell-mediated immune responses against HIV

In contrast to the rapid depletion of CD4+ T-cells in early HIV infection, CD8+ T cells increase rapidly, up to tenfold, during this period. Cytotoxic T lymphocyte (CTL) responses of CD8+ T cells are critical in controlling viral replication in early HIV infection, through lysis of infected cells, leading to plasma viraemia being reduced to a 'set point' level, representing the balance between viral replication and immune control (Figure 1). This early viral set point, which occurs at 3-6 months post infection, has been shown to be highly predictive of the later course of the disease-free period until the onset of AIDS. (6-8) Interestingly, most of the CD8+ T cells are not specific to HIV antigens, and those that are respond to a small number of epitopes in a hierarchical immunodominance pattern. Although this response broadens over time, the CTL response later in infection seems to be less effective in controlling the disease, perhaps due to accumulation of immune escape mutations in the virus over time.

HIV selectively infects and destroys memory CD4+ T cells in early infection, with rapid depletion of these cells in the lymphoid tissues, gut and genitourinary tracts⁹. If not reversed early, this damage leads to distortion of the architecture within lymphoid tissues and then fibrosis, which is difficult to reverse. This results in impairment of immune responses not only to HIV, but to other antigens as well, eventually leading to the profound immunodeficiency of AIDS. Nevertheless, a robust CD4+ T cell response in PHI occurs simultaneously with, or even before, the CD8+ T cell response and is associated with maintenance of effective immunity. (10) The role of helper CD4+ T cells is likely performed through cytokine release, maximizing of CTL responses via interferon-gamma and interleukin-2 (IL-2) and prevention of T cell exhaustion via IL-21. (11, 12) The ability of CD4+ T cells to provide effector function declines as cell numbers deplete. However, in elite controllers, those rare individuals capable of persistently suppressing HIV replication in the absence of ART, the effectiveness of the CTL response is linked to preservation of the CD4+ helper T cell response. (10)

Some infected CD4+ T cells become resting cells before the virus causes cell death. This allows the integrated virus to become latent, establishing a viral reservoir that can be reactivated at a later time point. This reservoir is established within the earliest days of primary infection and persists for the lifetime of the patient, but can be limited in its size by early initiation of ART. (13)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

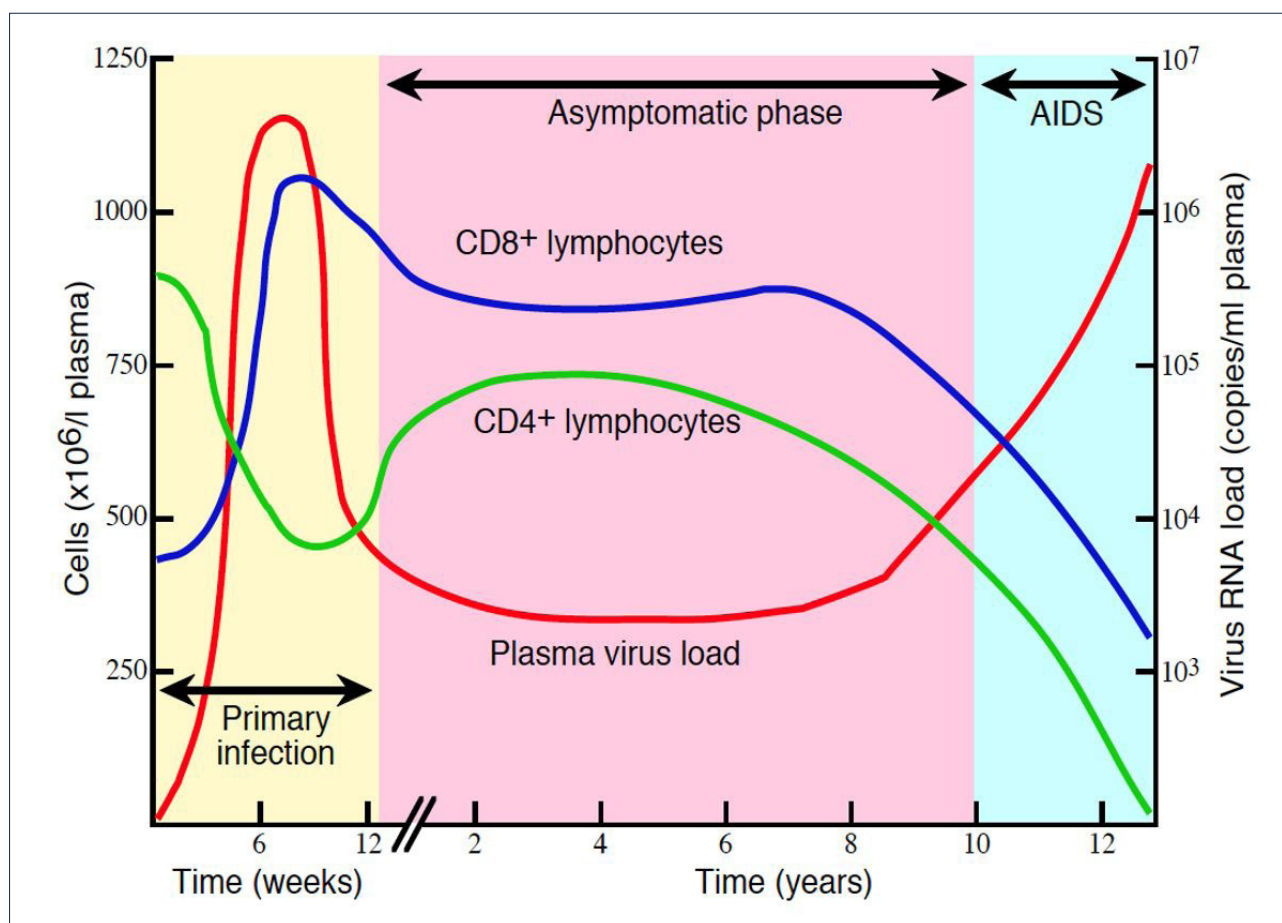


Figure 1. Time course of viral load, CD4+ and CD8+ T cell counts during HIV Infection. Adapted from "Cytotoxic T lymphocyte responses to human immunodeficiency virus: control and escape." Sewell et al, 2000, Stem Cells, 18(4): 230-44. ISSN: 10665099.

Clinical manifestations of primary HIV infection

It is difficult to precisely determine what proportion of people with PHI experience symptoms, though this is reported to be in the range of 23-92% of infected individuals. (14) The presence of symptoms during PHI is predictive of long-term outcomes, with greater severity associated with more rapid disease progression. (15, 16) Often these symptoms are non-specific in nature and may not be of sufficient severity for an affected individual to seek medical care, however severe illness leading to hospitalisation may be seen. The usual time from exposure to illness is 2-4 weeks, (17, 18) though delayed seroconversion of up to 10 months has been observed. (19) Typically, the illness will be self-limiting, lasting approximately 3 weeks, however in up to 20% of cases, opportunistic infections can occur due to the transient lymphopenia of acute infection. Oral or oesophageal candidiasis is most common and *Pneumocystis jirovecii* pneumonia, cryptosporidiosis, herpes zoster and cytomegalovirus (CMV) disease have also been reported. (14, 20, 21)

The originally described triad of symptoms associated with PHI includes fever, pharyngitis and lymphadenopathy. Fever is most common and is typically associated with headache and oral ulceration. Examination will typically reveal an erythematous and oedematous oropharynx without exudate. Painful mucocutaneous ulcers may also be seen, which may also be present in the oesophagus or anus or on the genitalia, with the important

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

differential diagnosis being disease caused by co-existent sexually transmitted infections, such as ano-genital herpes or syphilis. Lymphadenopathy develops in the second week of illness, commonly involving the axillary and cervical nodes and tends to decrease in size following the acute presentation, however it may persist well after resolution of other symptoms. In the absence of fever, other symptoms may include myalgia, lethargy, rash, diarrhoea, and weight loss. Rarely, neurologic involvement can occur, in particular patients may present with aseptic meningitis, encephalopathy, myelopathy, or peripheral nervous system involvement. (22-24)

It is important to consider co-infection with other viral, bacterial or fungal pathogens, which may complicate the clinical presentation. Co-infection with other viruses such as cytomegalovirus, hepatitis B or C viruses, herpes simplex virus or other sexually transmitted infections such as chlamydia, gonorrhoea or syphilis must be considered in the diagnostic work-up. (25)

HIV rapid testing

Fourth generation HIV immunoassays and NATs have enabled identification of people with PHI prior to the development of HIV-specific antibodies, however these methods entail blood collection and laboratory testing and may be inconvenient for the person being tested. Point-of-Care (POC) or rapid tests, first introduced into Australia in 2018, are screening tests performed independent of the laboratory. These tests may utilise saliva or finger-prick capillary blood and provide results within 10-20 minutes through visual interpretation. These tests have clear benefits in resource-limited settings in the absence of formal laboratory support. They also have utility in developed countries, making testing more accessible and applicable to the significant minority of individuals tested for HIV who never return to receive their test results. Such individuals represent a significant public health risk, particularly in the highly infectious period of PHI. (39, 40)

Although the rapid tests available in Australia are required to demonstrate a high level of sensitivity and specificity prior to approval for use, it is important to be aware of their limitations, particularly in the setting of PHI, where the window period of rapid tests may be prolonged compared with formal laboratory testing. It was demonstrated that if POC testing alone was to be performed in high-risk individuals in Australia, there is a potential for failing to detect a significant proportion of PHI at the earliest opportunity. (41) Careful consideration of their use should therefore be undertaken when patients present with symptoms suggestive of PHI. It is a requirement that all reactive POC tests should be confirmed by conventional diagnostic laboratory tests, including those conducted in community-based and outreach testing settings.

Nevertheless, there has been a recent recommendation by the WHO toward replacing laboratory-based HIV diagnosis (especially via western blotting immunoassays) with simpler POC testing, especially in developing countries. This is based on a body of evidence suggesting that the performance of POC tests is comparable to that of laboratory-based tests and that their use enables both positive and negative determinations to be made much more quickly. (42) This allows management to be instituted more rapidly, with consequent public health benefit.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Antiretroviral drug resistance testing in primary HIV infection

Resistance of HIV to antiretroviral drugs is an important cause of treatment failure, which is covered in detail in the section entitled *Virological tests for diagnosing and monitoring HIV infection*. Acquisition of drug resistance mutations depends on the interplay between factors such as patient adherence to treatment, drug potency, genetic barrier to resistance, host genetics, and specific mutations contributing to viral drug resistance and replicative capacity. (43) Rates of drug resistance vary significantly between populations, but the rates of transmitted mutations are still shown to be significant in representative studies. (44) In ART-naïve patients, studies have shown that the presence of drug resistance mutations may reduce the efficacy of first-line or subsequent regimens, increasing the risk of developing further resistance, and is associated with more rapid disease progression. (45-47) Although rates of drug resistance in transmitted virus are currently low in Australia, (48) it is the recommended standard of care that HIV drug resistance testing is undertaken at the time of all new diagnoses of HIV infection, including during PHI, not only to guide choice of ART but also to provide important public health surveillance information regarding population rates of transmitted drug-resistant variants.

Management of primary HIV infection

Upon diagnosis of PHI, there must be clear communication to the patient, in combination with counselling regarding the importance of safe practices to prevent further spread of infection. During the months following PHI, there is an extremely high HIV viral load in the blood and genital tract. Individuals with PHI contribute disproportionately to HIV transmissions; the probability of sexual transmission has been shown to be up to 26 times higher in the early stage of HIV infection compared to established infection. (49, 50) There is evidence that early diagnosis coupled with effective counselling can significantly reduce the probability of further transmission. (51) It has been demonstrated that reduction of HIV viral load through early initiation of ART leads to much lower risk of transmission between sexual partners. (52, 53)

Despite the difficulty in identifying patients with PHI, guidelines now reflect the significant body of evidence suggesting that ART should be commenced as soon as possible for all persons with HIV, regardless of symptomatology or CD4+ T cell count at diagnosis. There is demonstrable benefit for the individual (54) and from a public health perspective. Combination ART has well established efficacy, with the vast majority of individuals able to achieve undetectable HIV viral load within 3 months and maintain long-term viral suppression with preservation of immune function. (55) Randomised-controlled trial data have demonstrated that individuals with primary infection who do not commence ART progress more rapidly, in terms of decline of CD4+ T cell count, than those that do commence ART. (56) Furthermore, a major international randomised trial demonstrated that commencement of ART early, with high CD4+ T cell counts had significant benefits when compared to the approach of waiting until the CD4+ T count drops below 350/μL. The study examined outcomes including serious AIDS-related events such as AIDS-related cancers or infections, as well as serious non-AIDS-related events, such as cardiovascular disease, and found significantly lower rates of all events in the early initiation group. (57)

Even when started during PHI, ART is continued indefinitely upon initiation. Previous studies have evaluated the utility of discrete courses of ART in early infection, followed by a period of treatment interruption, and have shown no clear benefit over continuous therapy. Furthermore, a CD4+ T cell count-guided interruption of treatment approach has been clearly found to be associated with increased morbidity and mortality compared to continuous therapy. (58, 59) These studies were conducted with the aim of minimising patient exposure to ART in order to minimise toxicity, however it is important to note that the toxicity profile of modern combination ART is minimal in comparison to that of previous treatment regimens.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Ideally, the choice of ART regimen should be guided by the results of drug resistance testing, however treatment can be initiated prior to the availability of such results if this would preclude initiation of ART within the ideal target of two weeks from diagnosis. Regimens are chosen as per Australian guidelines, which are based on the United States Department of Health and Human Services guidelines, with consideration of potential adverse effects, childbearing potential, pill burden, dosing frequency, drug-drug interaction potential, and comorbid conditions. In the majority of cases a combination of three drugs is used, including an integrase strand inhibitor (INSTI) as first-line, in combination with two nucleoside reverse transcriptase inhibitors (NRTIs). A boosted protease inhibitor (PI) or non-nucleoside reverse transcriptase inhibitor (NNRTI) can be used as an alternative to an INSTI if required. Importantly, abacavir-containing regimens should not be initiated until the results of HLA*B5701 testing are known.

ART has evolved from regimens with high pill-burden and inconvenient dosing schedules, to the modern era of fixed-dose single-tablet regimens. Furthermore, dual drug regimens, and long-acting injectable therapies have recently entered clinical practice and can be considered for select individuals.[\(60, 61\)](#)

Conclusion

Primary HIV infection is a critical period in which the virological and immunological events that take place, even before the onset of clinical symptoms, may determine the long-term outcome of disease. Early recognition of symptoms, especially in people deemed to be high-risk individuals, is critical. Understanding the pathophysiology of PHI allows appropriate selection of diagnostic tests in the acute period. Early diagnosis allows prompt institution of ART, which has highly significant health benefits in the individual, and is fundamental to the concept of treatment as prevention of further transmission, conferring significant public health benefit.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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5. HIV-infectious Disease & Cancer

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Respiratory tract infections in patients with HIV infection

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Last reviewed: October 2019

Introduction

Respiratory complaints amongst people with HIV infection are common with a wide range of aetiologies, although the majority will be caused by common viral or bacterial infections. This chapter aims to cover the spectrum of bacterial, fungal and viral organisms, with an emphasis on a diagnostic approach and treatment. Mycobacterial and cryptococcal infections will be covered elsewhere.

The approach to respiratory disease in patients with HIV involves a synthesis of symptoms, signs, epidemiological risk factors, knowledge of the patient's degree of immunodeficiency, chest radiography and sputum sampling. More specialised investigations such as lung-function testing, computed tomography (CT) of the chest, bronchoscopy or lung biopsy may be required to make a diagnosis. Multiple disease processes may affect the respiratory system in human immunodeficiency virus (HIV) infection (Table 1) and multiple pathological processes can occur simultaneously, especially in advanced immunodeficiency.

Opportunistic infections and cancers of the respiratory tract no longer predominate as the cause of respiratory symptoms in the era of combination antiretroviral therapy (cART) and trimethoprim-sulphamethoxazole prophylaxis, with great reductions in the incidence of *Pneumocystis jirovecii* pneumonia and bacterial pneumonia.(1) Non-infective respiratory disorders such as chronic airflow limitation and lung cancer may be increasing, as survival improves.(2) It is important therefore to consider the differential diagnosis of symptoms according to level of immunodeficiency and treatment with cART. The onset of respiratory symptoms after the initiation of cART in an immunocompromised patient suggests the possibility of an immune reconstitution inflammatory syndrome.(2)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

General approach to the assessment of respiratory tract infections

The degree of immunodeficiency, as indicated by the blood CD4+ T cell count, provides a guide to the differential diagnosis of respiratory tract disease in HIV patients (Table 1).

Table 1. Pathogens causing respiratory tract disease in patients with HIV infection at different CD4+ T cell counts

CD4+ T cell count (cells/mL)	Bacterial	Fungal	Viral	Protozoan	Malignant
Any	<i>Mycobacterium tuberculosis</i> <i>Streptococcus pneumoniae</i> <i>Haemophilus influenzae</i> <i>Moraxella catarrhalis</i>		Upper respiratory tract viruses (RSV, metapneumovirus, parainfluenza, coronaviruses) Influenza virus		Non-Hodgkin lymphoma
< 200 ¹	<i>Pseudomonas aeruginosa</i> Gram negative enterobacteriaceae <i>Rhodococcus equi</i> <i>Staphylococcus aureus</i> <i>Nocardia spp.</i> <i>Legionella spp.</i>	<i>Pneumocystis jiroveci</i>			Kaposi sarcoma
< 100 ¹		<i>Cryptococcus neoformans</i> <i>Aspergillus spp.</i> <i>Candida spp.</i> <i>Coccidioides immitis</i> <i>Histoplasma capsulatum</i> <i>Penicillium marneffeii</i>		Toxoplasma gondii	
< 50			CMV HSV		

Adapted from Hanson et al, 1995, Salami AK, 2006

1. Other risk factors, such as intravenous drug use and corticosteroid therapy, may increase susceptibility to infection at higher CD4+ T cell counts.

MAC – *Mycobacterium avium* complex; CMV – cytomegalovirus; HSV – herpes simplex virus

People with significant immunodeficiency (ie. CD4+ T cell count < 200/μL or < 14% of total lymphocyte count) are at increased risk of opportunistic infections, including *Pneumocystis jiroveci* pneumonia (PJP) (previously *Pneumocystis carinii* pneumonia [PCP])(3). Bacterial pneumonia can occur at any CD4+ T cell count but occurs more frequently in immunodeficient people than in those with a preserved CD4+

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

T cell count, often in association with bacteraemia. Non-Hodgkin lymphoma and tuberculosis (TB) can occur at any level of immunodeficiency, although TB is more likely to involve extrapulmonary sites in immunodeficient patients. More severe immunodeficiency (CD4+ T cell count < 100/μL) is associated with an increased risk of *Toxoplasma gondii* pneumonitis and cryptococcal pulmonary pathology. At this level of immunodeficiency, staphylococcal and gram-negative bacterial pneumonia occur more frequently than in people with CD4+ T cell counts > 100/μL. Infections with *Streptococcus pneumoniae* and *Haemophilus* spp. also occur. In the profoundly immunodeficient person (CD4+ T cell count < 50/μL) both cytomegalovirus (CMV) and *Mycobacterium avium* complex may be associated with pneumonitis, usually in the context of disseminated disease. It is important to remember that all opportunistic infections may rarely occur at higher CD4+ T cell counts, especially in the setting of asplenia or antiretroviral therapy. In a follow-up study of the SMART study, risk of opportunistic infections or cancer, including pulmonary diseases, and death was associated with uncontrolled HIV replication even at higher CD4+ T cell counts.(4) The use of multiplex PCR on respiratory tract secretions has shown the important role of viruses in acute febrile respiratory illness in patients with HIV infection, especially with higher CD4+ T cell counts and on cART, a finding which may lead to the more judicious use of antibiotics.(5) However, co-pathogens such as *Pneumocystis jirovecii* were found on bronchoalveolar lavage (BAL) fluid analysis in patients at lower CD4+ T cell counts, making it difficult to determine the contribution of respiratory viruses.(6)

Clinical history

Symptoms

Certain features in the patient's history may be suggestive of one disease process over another. Typically, PJP is a subacute illness of fatigue, fever and dry cough of several weeks duration. In comparison, symptoms of short duration (hours to days), including chest pain, abrupt onset of fever and rigors and a productive cough are more consistent with bacterial (e.g. pneumococcal) pneumonia. Dyspnoea may occur in a range of infective pathological processes but may also be the only symptom of non-infective conditions, such as cardiomyopathy, ischaemic heart disease or pulmonary hypertension.

Prophylactic therapies

Immunodeficient patients who are taking prophylaxis for *Pneumocystis* infection are nine times less likely to develop PJP than those not taking prophylaxis(7). Prophylactic treatment with cotrimoxazole (sulphamethoxazole/trimethoprim) is likely to reduce the incidence of bacterial infections as well as PJP and reactivation of *T. gondii* infection. In low income countries with a high prevalence of malaria and severe bacterial infection, cotrimoxazole prophylaxis reduces anaemia and improves growth in children with HIV infection.(8) Second line prophylaxis for PJP with dapsone or inhaled pentamidine is associated with a small risk of treatment failure for PJP.(9) Atovaquone is non-inferior to dapsone for secondary prophylaxis and has fewer side effects.(10) Prophylaxis for MAC with macrolide antibiotics may also decrease the incidence of pneumonia.(11) Persons with a positive tuberculin skin test (TST; > 5 mm) who have not received treatment for latent TB have a 14% risk of developing active TB over a 2-year period and should therefore be considered for isoniazid prophylaxis.(12) The data on gamma interferon release assays, such as Quantiferon Gold or ELISPOT testing, in the setting of HIV are more limited, but it is likely a positive test has the same significance. It is uncertain if there is a clinical benefit of isoniazid treatment for latent TB infection when defined by a positive gamma interferon release assay if the TST is < 5 mm (see section on *Mycobacterium tuberculosis*). Annual influenza vaccination is recommended as patients with HIV may be more likely to contract influenza and experience severe disease requiring hospitalisation.(13)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Epidemiological risk factors

People who have resided in or travelled to countries with a high prevalence of TB are at increased risk for TB. A contact or occupational history may also be useful in suggesting the possibility of TB. A past history of incomplete treatment of TB may suggest drug-resistant TB. Travel to areas endemic for the dimorphic fungi may be important: *Histoplasma capsulatum* is endemic in areas of the USA (especially the Mississippi and Ohio River valleys), Latin America, West Indies, Eastern India, and Africa. *Coccidioides immitis* is hyperendemic in some parts of the southwest of the USA, Northern Mexico, and in Central and South America. Other illnesses with respiratory symptoms where a travel history might be important include melioidosis, *Talaromyces marneffe* infection (formerly *Penicillium marneffe* causing penicilliosis), strongyloidiasis and Salmonella infection. Persons with HIV infection who inject drugs are more likely to develop bacterial pneumonia (4, 14) and invasive bacterial infection such as endocarditis, caused by organisms such as *Staphylococcus aureus*. Smoking is an important risk factor for bacterial pneumonia as well as bronchitis, chronic airflow limitation and carcinoma of the lung in people with HIV infection, as in the general population. Marijuana smoking has been associated with Aspergillus infection. (15) Men who have sex with men are more likely to develop Kaposi sarcoma (KS), in proportion to their risk of HHV8 carriage, although isolated pulmonary disease without mucocutaneous lesions is uncommon. (16) Antiretroviral treatment itself may be a cause of respiratory symptoms, e.g. dyspnoea caused by nucleoside analogue-induced lactic acidosis, hypersensitivity reaction to abacavir (now largely eliminated by HLAB5701 testing).

Physical examination

The physical examination may be normal in HIV patients with PJP, aside from tachypnoea and a dry cough, although fine crackles may be present. Signs of consolidation suggest bacterial, mycobacterial or fungal disease. Examination for extrapulmonary features should be undertaken, as disseminated disease processes may present with pulmonary symptoms. Cardiovascular signs should be assessed as pulmonary hypertension, endocarditis, cardiomyopathy and pericardial effusions may also cause breathlessness. Signs associated with immunodeficiency should be elicited (e.g. oral candidiasis) as these may influence the differential diagnosis in the absence of a current CD4+ T cell count. The skin should be examined for the presence of KS and the cutaneous lesions of cryptococcosis. The presence of neurological signs may suggest disseminated toxoplasmosis, and drowsiness may occur in cryptococcosis. Hepatosplenomegaly may be present in people with *Mycobacterium avium* complex infection, non-Hodgkin lymphoma or CMV infection.

Investigations

Blood tests

Most standard biochemical and haematological tests are not helpful in the diagnosis of respiratory symptoms in advanced HIV disease. However, peripheral blood neutrophilia and left shift may occur in bacterial pneumonia and cryptococcal disease. Neutropenia may suggest an increased likelihood of bacterial or fungal infection. Measurement of the degree of impairment of gas exchange with arterial blood gas analysis is important, as the degree of hypoxaemia may change the management of certain diseases (e.g. steroid therapy in PJP). In cases of suspected cryptococcal disease, the titre of serum cryptococcal antigen is used as evidence of disseminated disease. Bacterial blood cultures should be obtained as well as mycobacterial blood cultures in immunodeficient patients, given the elevated rates of bacteraemia.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Chest radiograph

The chest radiograph may reveal the presence of focal consolidation suggestive of bacterial, tuberculous or cryptococcal disease or lymphoma typical radiological pattern of TB, with upper lobe disease and cavitation, may not be seen in immunodeficient people. Pleural effusions may be caused by KS or the range of diseases which also cause consolidation. The presence of a pleural effusion makes the likelihood of PJP quite low, although in advanced HIV disease, multiple disease processes may co-exist. The presence of a pneumothorax makes PJP more likely, although other disease processes may rarely cause a bronchopleural fistula and be associated with a pneumothorax. Cavitating disease is likely to be caused by TB or infections by bacteria, fungi, *Nocardia* spp., and some non-tuberculous mycobacteria. Diffuse infiltrates with a reticular or granular pattern are suggestive of PJP, but many other diseases may have a similar radiographic pattern. A normal chest radiograph does not exclude PJP or cryptococcosis where extrapulmonary disease is the major manifestation (6) (see Table 2 and Table 3).

Table 2. Differential diagnosis of chest radiograph abnormalities

	PJP	Bacteria	TB	Fungi	NHL	KS	MAC	CMV
Normal	Yes		Yes	Yes		Yes		
Focal consolidation/infiltrate	Yes	Yes	Yes	Yes	Yes			
Miliary	Uncommon		Yes	Yes				
Diffuse or multifocal	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Reticular or granular		Yes	Yes	Yes	Yes			Yes
Nodular	Uncommon	Yes	Yes	Yes	Yes	Yes		
Cystic lesions	Yes			Yes				
Cavities	Uncommon	Yes	Yes	Yes				
Pneumothorax		Yes	Uncommon	Uncommon				
Lymphadenopathy			Yes	Yes	Yes	Yes	Yes	
Pleural effusions		Yes	Yes	Yes	Yes	Yes		

CMV = cytomegalovirus; KS = Kaposi sarcoma; MAC = *Mycobacterium avium complex*; TB = tuberculosis; NHL = non-Hodgkin lymphoma; PJP = *Pneumocystis jirovecii* pneumonia.

Adapted from Table 13.5 in Morris A, Huang L. Evaluation and management of respiratory complications of HIV infection. In: Crowe S, Hoy J, Mills J, editors. Management of the HIV-infected patient. London: Martin Dunitz; 2002:217.

Other investigations

Other investigations for a suspected respiratory tract infection in HIV patients are shown in Table 3. Sputum from all patients presenting with a productive cough should be sent for microscopy and culture. Sputum investigations should routinely include Gram stain, bacterial and fungal culture and sensitivity testing. Although not all specimens need to be examined for mycobacteria, a low threshold for testing sputa for acid-fast bacilli and mycobacterial culture should be maintained. An induced sputum should be collected where the clinical likelihood of PJP is high, provided adequate negative-pressure facilities exist. The sample is assessed for the presence of *P. jirovecii* by immunofluorescence, Giemsa or silver stains and a result is usually available within 2 hours. Quantitative real time PCR testing for *Pneumocystis* has a negative predictive value of nearly 100%.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Supplemental investigations such as bronchoscopy increase the diagnostic yield for *P. jirovecii* infection and may facilitate other diagnoses as well. *P. jirovecii* cysts or DNA may still be detected in bronchoalveolar lavage fluid after several days of therapy with cotrimoxazole. A high-resolution CT scan that does not reveal 'ground glass' changes makes the diagnosis of PJP unlikely. (17) The absence of these findings suggests that alternative pathology to PJP should be considered. Where a pleural effusion has been detected, a diagnostic pleurocentesis is warranted. Pulmonary nodules should be biopsied if sputum sampling, bronchoscopy and less invasive investigations are negative (e.g. serum cryptococcal antigen or bone marrow biopsy in the setting of pancytopenia).

Table 3. Recommended investigations in respiratory illness

Routine investigations
Full blood count and differential
CD4+ T cell count
Expectorated sputum examination – bacteriology, <i>P. jirovecii</i> immunofluorescence, PCR, acid-fast stain, fungal culture
Nasopharyngeal swab – respiratory viral/multiplex PCR
Induced sputum (if CD4+ T cell count < 200/μL) – <i>P. jirovecii</i> immunofluorescence and PCR
Chest radiograph
Arterial blood gases
Blood cultures – bacterial, mycobacterial (if CD4+ T cell count < 50/μL)
Supplemental investigations
Computed tomography of chest – high resolution
Bronchoscopy with bronchoalveolar lavage
Electrocardiography
Echocardiography – pericardial effusion, cardiomyopathy, pulmonary hypertension
Ventilation perfusion lung scan
Pulmonary diffusing capacity/spirometry
Serum cryptococcal antigen titre
Examination of other organs if involved (e.g. bone marrow biopsy if pancytopenic)
Lung biopsy

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Sinusitis

Sinusitis is a common problem in people with HIV infection. In one retrospective review, 11% of hospitalised patients were affected by this disorder.⁽¹⁸⁾ Sinusitis is more common with immunodeficiency (CD4+ T cell count < 200/μL), and it is more likely to be extensive and chronic in very immunodeficient patients. Up to one-third of cases may be asymptomatic, although most have fever, headache and nasal discharge. A minority have facial pain and tenderness. Sinusitis should be considered in the differential diagnosis of headache and fever.

Most cases of sinusitis in people with HIV infection are caused by bacterial respiratory pathogens such as *Streptococcus pneumoniae* and *Haemophilus influenzae*, although *Pseudomonas aeruginosa* and *Staphylococcus aureus* may also be causative agents. Mycobacteria spp., cytomegalovirus (CMV), Encephalitozoon spp., Cryptococcus spp., Aspergillus spp., Acanthamoeba spp. Cryptosporidia spp. and *Pneumocystis jirovecii* have all been reported as pathogens in people with HIV infection (Table 4).^(19,20,21,22) Non-Hodgkin's lymphoma also may affect the sinuses.⁽²³⁾

Table 4. Infectious causes of sinusitis in HIV patients

Bacterial	Fungal	Protozoan	Viral
<i>Streptococcus pneumoniae</i> <i>Haemophilus influenzae</i> <i>Staphylococcus aureus</i> <i>Pseudomonas aeruginosa</i> <i>Mycobacteria</i> .	<i>Aspergillus spp.</i> <i>Cryptococcus spp.</i> <i>Pneumocystis jirovecii</i>	<i>Encephalitozoon spp.</i> <i>Acanthamoeba spp.</i> <i>Cryptosporidium parvum</i>	<i>Cytomegalovirus</i>

The presence of bony erosions on MRI or CT scan or ophthalmoplegia suggest possible infection with *Aspergillus spp* and mandates the need for biopsy.⁽²⁴⁾ Erosions may also be associated with *Pseudomonas* infection or lymphoma. Opportunistic pathogens need to be considered in the differential diagnosis, and a diagnostic aspirate should be performed in immunodeficient patients and in patients who have a poor response to therapy or severe disease. Samples should be examined for bacteria, fungi, mycobacteria and microsporidia and other microbes depending upon the level of immunosuppression of the patient.

Standard therapy with antibacterial agents (e.g. amoxicillin with clavulanic acid), decongestant and expectorant agents is appropriate in most cases. In severe cases where parenteral therapy is required, a third-generation cephalosporin (e.g. ceftriaxone) is recommended. In non-responsive disease, broadening of the antimicrobial spectrum to cover *Ps. aeruginosa* and *S. aureus* should be considered, pending results of sinus sampling. Surgery should be considered in the presence of ocular complications, systemic disease not responding to empirical antimicrobial therapy, and in conjunction with antifungal agents in fungal sinusitis. Surgical intervention for infective sinusitis is as effective in people with HIV as in those without HIV.⁽²⁵⁾

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Bacterial pneumonia

Bacterial pneumonia is a significant cause of morbidity and mortality in people with HIV infection. It is predominantly caused by *S. pneumoniae*. People with HIV are at much higher risk of invasive pneumococcal infection than the general population, with the incidence of pneumococcal bacteraemia 100 times that of age-matched populations, and pneumococcal pneumonia rates five to 17 times those of the general population.(26) Children with HIV infection appear to be at even greater risk of invasive pneumococcal disease. Recurrent pneumococcal infection is more common in patients with HIV infection than in the general population.(27)

Risk factors for pneumococcal infection in patients with HIV infection include cigarette smoking (both active and passive forms), injecting drug use, recent hospital admission, blood transfusion as the mode of HIV transmission, alcoholism, a previous acquired immune deficiency syndrome (AIDS)-defining illness and previous pneumococcal infection.(26,27,28,29) The risk of pneumococcal infection is greater in individuals with CD4+ T+ cell counts < 500/μL compared with > 500/μL, and is greatest with CD4+ T cell counts < 200/μL.(29) Infection with *S. pneumoniae* with reduced sensitivity to penicillin occurs at a similar frequency in people with HIV infection and the general population.(30)

Clinical presentation

People with HIV infection who present with *S. pneumoniae* disease most commonly present with pneumonia. The major symptoms are fever (96%), cough (90%) and dyspnoea (72%).(31) Bacterial pneumonia due to *H. influenzae* may be indistinguishable from that due to *S. pneumoniae*. In advanced immunosuppression, pneumonia secondary to *P. aeruginosa* and to *S. aureus* increases in frequency and may present with cavitary infiltrates. Rare presentations of pneumococcal infection include mediastinitis, multiple brain abscesses, meningitis(32) pericarditis and endocarditis(33) cervical cellulitis,(34) and testicular abscess.(35)

Diagnosis

The diagnosis of bacterial pneumonia is usually clinical. Nevertheless, blood should be sent for culture. Blood cultures are a sensitive diagnostic tool, with isolation of *S. pneumoniae* in 85% of patients.(26) Additional testing to be considered should include urine tests for pneumococcus and legionella antigen as well as atypical pneumonia serology. Leukocytosis may not occur, but a left shift with band forms may be observed. Chest X-ray findings include segmental, lobar or multilobar consolidation, although interstitial infiltrates are found in some patients.(26) Thoracentesis should be considered for patients with pleural effusions if there is clinical concern of empyema.

Management

Decisions on treatment are based on the severity of the pneumonia. Treatment for bacterial pneumonia is the same for patients with HIV infection as for the general population. For cases of mild-to-moderate pneumonia, amoxicillin 1 g three times daily may be used, with or without a macrolide or doxycycline if atypical pneumonia is suspected. However, if parenteral therapy is required, intravenous benzyl penicillin (penicillin G) 1.2 g every 6 hours is recommended with doxycycline 100mg orally 12 hourly for one week. In patients with penicillin allergy, doxycycline or clarithromycin may be used, or for parenteral therapy, moxifloxacin. In severe pneumonia, intravenous ceftriaxone 1 g daily (or benzyl penicillin 1.2 g every 4 hours with gentamicin) plus azithromycin 500 mg daily is recommended. Specific recommendations exist for tropical areas of northern Australia.(36)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Prevention

Historically, the role of vaccination with the 23-valent pneumococcal unconjugated polysaccharide vaccine had been controversial. Its use has been recommended by authorities in the USA, Europe, Brazil and Australia.(37,38) However, a randomised, placebo-controlled study in African adults showed no decrease in pneumococcal disease in the vaccinated group compared with the placebo group.(39) Importantly, this study also showed an increased risk for all types of pneumonia in the vaccine arm. However, other studies have shown an overall benefit from vaccination,(40) and both combination antiretroviral therapy (cART) and vaccination with pneumococcal vaccine had independent protective effects against pneumococcal infection regardless of CD4+ T cell count. A study of the 7-valent pneumococcal conjugate vaccine in Malawi showed adults with HIV-infection were protected from recurrent pneumococcal infection caused by vaccine serotypes or serotype 6A. (41) Since 2010, a 13-valent conjugate vaccine (PCV13) has been registered, which may offer additional protection. There is good evidence of immunogenicity and safety of this vaccine in patients with HIV infection (42, 43, 44) Most authorities would now therefore favour vaccination.(42, 45) Current guidelines generally suggest the use of the conjugated polysaccharide vaccine first followed by the unconjugated polysaccharide vaccine 8 weeks or more later.(42)

Pneumocystis jiroveci pneumonia

Pneumocystis jiroveci (previously *Pneumocystis carinii*)(46) is a fungus(47) that is ubiquitous. It is unclear whether infection occurs as a primary event(48) or as a result of colonisation with reactivation(49 50), although antibodies against the organism are present in more than 85% of children under 3 years of age, suggesting that reactivation occurs following immunosuppression. *P. jiroveci* pneumonia is still the most common AIDS-defining condition and is usually seen in people presenting late in the course of HIV infection(51) or in people with poor adherence to PJP prophylaxis or cART. *P. jirovecii* pneumonia occurs uncommonly in persons with a CD4+ T cell count > 200 cells/μL, or a proportion of CD4+ T cells that is > 14% of total lymphocytes, although cases have occasionally been reported in people with more preserved immune function.(52)

Clinical presentation

The major manifestation of *P. jiroveci* infection is PJP. The presentation of PJP is subacute with fever, a non-productive cough, chest tightness and dyspnoea. Symptoms may be present for 2 to 6 weeks or more before the diagnosis is made. Extrapulmonary manifestations are rare and require tissue biopsy for diagnosis. (53) The typical clinical scenario of a patient with PJP is an immunodeficient person (CD4+ T cell count < 200/μL), who has not achieved suppression of HIV replication, is not taking cotrimoxazole prophylaxis, and presents with fatigue and fevers. The patient may not necessarily have noticed cough or dyspnoea, yet a non-productive cough is commonly apparent during the clinical assessment. Respiratory examination may reveal no signs aside from tachypnoea and oxygen desaturation on exertion, although crackles may be present on auscultation of the chest. Pneumothoraces may complicate severe PJP.

Pneumocystosis-associated immune reconstitution inflammatory syndrome

Pneumonitis and organising pneumonia may be seen as manifestations of an immune reconstitution inflammatory syndrome (IRIS) after cART is commenced and occur in approximately 4% of cases. Distinguishing a pneumonitis secondary to an IRIS after commencement of cART from undiagnosed PJP may be difficult.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Diagnosis

The initial diagnostic approach to PJP includes consideration of the clinical likelihood of disease. People with advanced immunodeficiency who present with fever, fatigue and a dry cough have a high likelihood of PJP if they are not taking PJP prophylaxis, although other infections may present in such a manner. Other pathogens may cause respiratory disease (e.g. *Mycobacterium tuberculosis*, *Mycobacterium avium* complex, *Streptococcus pneumoniae*, *Rhodococcus spp.*, *Nocardia spp.* and *Cryptococcus neoformans*) and these need to be considered in the differential diagnosis of any pulmonary presentation. It is especially important to consider the possibility of tuberculosis, as infection control and public health issues need to be considered.

The initial recommended investigation is a chest radiograph, which may reveal peri-hilar interstitial infiltrates or diffuse alveolar shadowing (Figure 1). The chest radiograph may be normal in more than 10% of cases.

(54) Additional focal pathology is suggestive of an alternative diagnosis. PJP may be complicated by pneumothoraces and pleural effusions are very rare. If pleural effusions are detected, other diagnoses should be considered. Even in cases with a normal chest radiograph, high resolution computed tomography (CT) of the chest (Figure 2) may reveal the typical 'ground glass' changes seen in the alveolitis due to PJP.(55) Changes other than ground glass may occur but are less common.(56)



An expectorated sputum sample may be examined for *P. jirovecii* cysts by immunofluorescence (see below) but only has a sensitivity of approximately 55%.(57) A more sensitive approach is the examination of an induced sputum specimen which is obtained by the induction of a deep cough after the inhalation of hypertonic saline.(58,59) Pneumothorax should be excluded before sputum induction is undertaken. The procedure should be performed in an appropriately ventilated room, in case other pathogens are present. Induced sputum enables lower respiratory tract sampling, which is suitable for analysis for the presence of *P. jirovecii* cysts. An alternative to obtaining an induced sputum is bronchoscopy and bronchoalveolar lavage.

Figure 1. Chest radiograph showing bilateral infiltrates in an HIV patient with PJP

Source: Jeffrey J. Post, University of NSW, Sydney NSW. Used with permission:

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

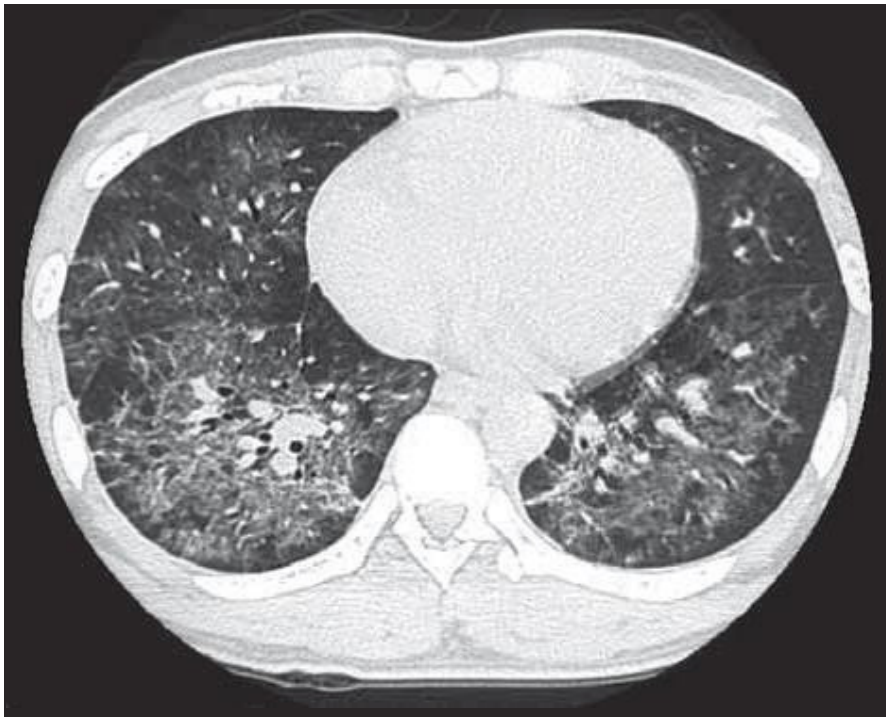


Figure 2. CT scan showing ground glass appearance suggestive of *Pneumocystis jirovecii* pneumonia

Source: Jeffrey J. Post, University of NSW, Sydney NSW. Used with permission

The diagnosis of *P. jirovecii* infection may be made by immunofluorescence (IF) staining of the sample using monoclonal antibodies, (60) which typically takes two hours to process. Other stains, including silver stains, have a lower sensitivity but may be the primary means of diagnosis in some laboratories. Investigation

of induced sputum is not warranted in asymptomatic immunodeficient people. (61) One older meta-analysis suggested that induced sputum with immunostaining is the preferred diagnostic approach. (62-68) A more recent meta-analysis which included studies with HIV and non-HIV associated PJP identified a sensitivity of 98.3% and a specificity of 91% for PCR testing of BAL fluid specimens. (69)

Despite the availability of direct and indirect identification methods, the diagnosis of PJ may be difficult. Some authors use the cycle threshold (C_T) values obtained by quantitative PCR (qPCR) to estimate the fungal burden: the higher that the fungal burden, the lower the C_T value. Testing of BAL fluid samples from HIV-positive patients demonstrated that a C_T value below 27 excluded colonization and a C_T value above 30 excluded PCP with a specificity of 100% and a sensitivity of 80%, respectively. (70)

In people with a high clinical likelihood of PJP, presumptive therapy is sometimes undertaken if the induced-sputum specimen is not diagnostic and other features are consistent with PJP, but bronchoscopy with BAL is generally indicated, as the differential diagnosis is broad. (71) Bronchoscopy with BAL is also indicated in cases of presumptive PJP that do not respond to therapy. Bronchoscopy may be preferred where there is a high likelihood of other infectious agents such as *M. tuberculosis*. (72) Open-lung biopsy is usually unnecessary as induced-sputum examination and bronchoscopy with bronchoalveolar lavage have a high sensitivity (approximately 97%). The pathology of PJP consists of an eosinophilic alveolar exudate with *Pneumocystis* organisms present. (73) Blood gas analysis should be undertaken to assess disease severity. Arterial blood hypoxaemia (while breathing room air), with a $PaO_2 < 70$ mmHg, an alveolar-arterial (A-a) oxygen gradient of > 30 mmHg or oxygen saturation of $< 94\%$ indicates moderately severe or severe disease. Lesser impairment of gas exchange indicates mild disease. Therapeutic studies of mild-to-moderate disease have included those with a $PaO_2 > 50$ mmHg.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Bronchoscopy and CT scan are now the key investigations following clinical suspicion or suspect CXR. Other investigations infrequently used in the diagnosis of PJP (these are now mainly of historical interest), include the following:

- Rapid clearance of technetium in lung scans indicates altered alveolar permeability that is consistent with PJP (74, 75)
- Pulmonary diffusing capacity for carbon monoxide is also typically impaired in persons with PJP (76, 77)
- Although serum lactate dehydrogenase level is often elevated in PJP, it is insufficiently specific to exclude other pathology or determine disease severity (78)
- More recently, there had been significant interest in serum markers of PJP, with low S-adenosylmethionine levels (a molecule that *jirovecii* must scavenge) seen in cases with PJP that recover in association with effective treatment (79, 80)
- Other non-invasive markers such as serum beta-D-glucan were of interest and have a reasonable sensitivity and specificity. (81,82)

Management

The management of PJP depends on the degree of disease severity.

Severe disease

People with severe disease should be managed in hospital, as ventilatory support may be required. Those who are not allergic to sulpha-containing drugs or hypersensitive to cotrimoxazole should receive high-dose intravenous cotrimoxazole (for adults trimethoprim + sulphamethoxazole 5+25 mg/kg intravenously every 6-8 hours) and should receive therapy for a total of 21 days (once improvement has occurred a switch to oral therapy may occur). People who are allergic to sulpha compounds, or unresponsive to cotrimoxazole, or who develop hypersensitivity during therapy should be treated with intravenous pentamidine (3-4 mg/kg/day for 21 days) (83), or clindamycin (900 mg intravenously every 8 hours) with primaquine (30 mg orally daily; after assessing risk of glucose-6-phosphate dehydrogenase deficiency). (84) Supplemental oxygen, non-invasive ventilation (e.g. continuous positive airways pressure or bilevel positive airways pressure (85) or intubation and ventilation may be required. It is not uncommon for patients to deteriorate during the first 48 hours after commencement of therapy. Patients with significant hypoxaemia ($\text{PaO}_2 < 70$ mmHg) should receive corticosteroids prior to the commencement of antimicrobial therapy to reduce the risk of this complication and improve prognosis (prednisone 40 mg orally twice a day for 5 days, then 40 mg daily for 5 days, then 20 mg/day until completion of treatment). (86-90) If oral corticosteroid therapy is not possible then hydrocortisone (100 mg intravenously every 6 hours) may be used. Corticosteroid therapy may be complicated by central nervous system toxicity (e.g. psychosis, mania), oral candidiasis and other opportunistic infections. Patients who respond well to initial intravenous therapy may complete the 21-day course with oral therapy (see below).

Moderate disease

If disease severity is moderate (i.e. dyspnoea on minimal exertion, PaO_2 50-70 mmHg) or adherence to, or tolerance of, an oral regimen is not likely, then initial inpatient management is recommended. Otherwise, oral regimens may be considered (see below). Patients with moderately severe PJP should also receive corticosteroids if $\text{PaO}_2 < 70$ mmHg.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Mild disease

People with mild disease may be treated with oral cotrimoxazole, two double-strength tablets three times daily (one double-strength tablet contains trimethoprim 160 mg and sulphamethoxazole 800 mg) for 21 days. Oral therapy should only be considered where adherence is likely. Adjunctive antiemetic therapy is commonly prescribed. Alternative regimens in cases of non-severe disease include clindamycin (450 mg orally four times daily) with primaquine (15 mg orally daily; after assessing risk of glucose-6-phosphate dehydrogenase deficiency); dapson (100 mg orally daily) with trimethoprim (300 mg orally every 8 hours; 15 mg/kg/day),⁽⁹¹⁾ or atovaquone (750 mg orally twice daily).⁽⁹²⁾

Salvage therapy

Salvage therapy for PJP with caspofungin has been reported in the non-HIV setting although the role of this agent in the initial treatment of PJP has not been studied and there are case reports of failure of this agent in the HIV setting in people thought to have multiple infective pathologies.^(93,94) Further data are needed before caspofungin can be recommended.

Cotrimoxazole hypersensitivity

The most common toxicity of cotrimoxazole is a hypersensitivity reaction. This typically manifests as a maculopapular rash with recrudescence of fever after initial resolution of fever due to PJP. There may be associated haematological and liver function test abnormalities. The hypersensitivity reaction may progress to a life-threatening systemic reaction if the drug is not ceased. Secondary PJP prophylaxis with cotrimoxazole following a hypersensitivity reaction may be considered if cotrimoxazole desensitisation is successful. PJP therapy should be completed and the hypersensitivity reaction fully resolved before cotrimoxazole desensitisation is undertaken.^(95, 96, 97) A rapid oral desensitisation protocol can be found in the most recent version of the Australian Therapeutic Guidelines: Antibiotics.⁽⁹⁸⁾ If immune reconstitution is unlikely to occur with cART, or is likely to be delayed (e.g. very low nadir CD4+ T cell count or adherence to cART is unlikely), then desensitisation should be undertaken, as PJP prophylaxis will be needed for this period.

Prognosis

Early in the HIV epidemic, patients with PJP had a poor prognosis. With better management of respiratory failure and the introduction of cART, prognosis has improved, with recent data suggesting a 10% mortality rate overall.⁽⁹⁹⁾ The prognosis of people with severe PJP requiring ventilation has improved, with one study reporting a 47% overall survival rate.⁽¹⁰⁰⁾ Factors associated with a poor prognosis include the degree of hypoxaemia, neutrophilia, high numbers of organisms in BAL fluid and severe radiological abnormalities. Mutations in the dihydropteroate synthase gene of *P. jiroveci*, which confers resistance against sulpha drugs, have been suggested to worsen the prognosis.^(101, 102)

Prophylactic Pneumocystis therapy

Primary prophylaxis

Prophylaxis against PJP is recommended in patients with a CD4+ T cell count < 200/μL or CD4+ T cell proportion < 14% of lymphocytes, or oral candidiasis or unexplained fever of more than 2 weeks duration. The institution of prophylaxis (without cART) reduces the risk of PJP in susceptible populations by nine-fold.⁽¹⁰³⁾ Mutations in dihydrofolate reductase may be associated with failure of prophylaxis.⁽¹⁰⁴⁾

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

The optimal regimen is cotrimoxazole: one double-strength tablet orally once per day, although half a tablet daily is efficacious and may have a lower rate of toxicity. The risk of acquiring PJP while taking cotrimoxazole prophylaxis is extremely low. Cotrimoxazole is also active against toxoplasmosis and some bacterial pathogens. The most common toxicity is a cotrimoxazole hypersensitivity reaction (see above). Alternative regimens include double-strength cotrimoxazole (orally twice daily on 2 or 3 days per week), nebulised pentamidine (300 mg once per month, with salbutamol retreatment to reduce bronchospasm), dapsone (100 mg orally daily) or atovaquone (750 mg orally twice daily).[\(105, 106\)](#) Hypersensitivity reactions may develop with several drugs used for prophylaxis (Table 5).

Table 5. Common toxicities of agents used in treatment or prophylaxis of *Pneumocystis jiroveci* pneumonia

Agent	Common toxicities
Atovaquone	Hypersensitivity, Gastrointestinal, Biochemical hepatitis
Clindamycin	Hypersensitivity, Diarrhoea, Pseudomembranous colitis, Haematological
Cotrimoxazole	Hypersensitivity – typically fever and maculopapular rash; dose related; may develop into Stevens-Johnson syndrome Nausea, vomiting Bone marrow toxicity – neutropenia, thrombocytopenia Biochemical hepatitis
Dapsone	Hypersensitivity Haemolysis in G6PDH-deficient people
Pentamidine	Renal tubule dysfunction – renal impairment, hyperkalaemia Pancreatic toxicity – hypoglycaemia, hyperglycaemia, Arrhythmias Hypotension

G6PDH = glucose 6-phosphate dehydrogenase

Secondary prophylaxis

Secondary prophylaxis after an episode of PJP is recommended to prevent relapse or recurrence until immune reconstitution has occurred.

Discontinuing prophylaxis

Cohort studies have demonstrated the safety of discontinuing both primary and secondary PJP prophylaxis after the CD4+ T cell count has risen above 200/ μ L or the proportion of CD4+ T cells is > 14% of total lymphocytes for longer than 3 months, in the setting of HIV suppression with cART.[\(107-112\)](#) More recent data suggest that the risk of PJP is as low with even earlier discontinuation of prophylaxis when the CD4+ T cell count is > 100 / μ L, in the setting of suppressed HIV replication.[\(113-115\)](#)

Respiratory tract infections caused by uncommon organisms

Many different organisms have been demonstrated as causing infectious syndromes involving the respiratory tract in persons with HIV/AIDS. A list of common and important infections can be found in other sections. Tuberculosis, which is a very important infection globally in relation to HIV, is covered elsewhere. Three infections not covered elsewhere in this monograph are covered here.

Penicilliosis (or talaromycosis)

Penicilliosis (or talaromycosis) is a systemic mycotic infection, caused by *Penicillium marneffei* (now called *Talaromyces marneffei*), a dimorphic fungus endemic in South-East Asia, Hong Kong and parts of southern China. *Talaromyces marneffei* was first isolated from a species of bamboo rat; however, the environmental source of infection remains unclear.[\(116\)](#) Infection is thought to occur by the respiratory route.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

An increased risk is seen with recent occupational exposure to soil.(116) Symptomatic infection occurs only rarely in the immunocompetent host. Clinical presentation may occur many years after exposure.(117) The rapid explosion of HIV infection in the areas endemic for this fungus has led to a significant increase in cases of *Talaromyces marneffei* infection with more than 1000 cases reported in a 7-year period at one hospital in Thailand.(118) Increased incidence occurs during the wet season (May to October).

Clinical presentations

Talaromyces marneffei infection is usually reported in late-stage HIV disease when the CD4+ cell count is < 100/μL.(116, 118) The presentation is subacute with constitutional signs and symptoms. Fever and weight loss occur in 95% of patients. Cough and pulmonary symptoms occur in up to one-third of patients. On examination, lymphadenopathy and hepatomegaly are seen in 70% of patients, and concomitant oral candidiasis in 50%. Characteristic skin lesions, cutaneous papules with central necrotic umbilication resembling molluscum contagiosum are present in 70% of patients (Figure 3).

Figure 3. *Talaromyces marneffei* infection



Source: Stewart GJ, Kunanusont C, Phanuphak P, Hanvanich M, Wabitsch R. Managing HIV with limited medical resources. Med J Aust 1996; 165:499-503. Used with permission.

These lesions of penicilliosis (talaromycosis) are similar to those seen in histoplasmosis and cryptococcosis, but are distributed predominantly on the upper parts of the body (scalp, face, upper extremities and trunk). (116) Disseminated disease is common at presentation, with possible lung, liver, spleen and bone involvement. In contradistinction to both histoplasmosis and cryptococcosis, dissemination to the central nervous system

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

is said not to occur with *Talaromyces marneffe* infection.(116) The reason for this lack of neurotropism is not clear. Anaemia and abnormal liver function tests are also frequently present. In patients with lung involvement, X-ray findings include nodules, interstitial infiltrates and pleural effusion. There has been a series of patients with hepatic disease who lacked skin manifestations, but whether this indicates a different form of the disease is not clear.(119)

Diagnosis

Diagnosis is made by fungal culture or histopathology examination of a specimen obtained from a normally sterile site (i.e. blood, skin lesions, bone marrow, lymph node, liver). Isolation occurs most frequently from bone-marrow aspirates and lymph-node samples (100%), followed by skin biopsy (90%) and blood cultures (76%).(116) Full identification of the organism may take up to 7 days. Galactomannan (GM) is a heteropolysaccharide in the cell walls of most *Aspergillus* and *Talaromyces* species. The use of the GM antigen assay may facilitate earlier diagnosis of *Talaromyces marneffe* infection for patients with HIV infection in areas of endemicity, as 73% of patients have positive tests, particularly those with fungaemia.(120) Research continues on a serological assay and polymerase chain reaction (PCR) assay to assist in diagnosis, but these tests are not generally currently available for clinical use.

Management

Therapy for penicilliosis (talaromycosis) depends on severity of disease. Mild-to-moderate disease can be treated with itraconazole 200 mg per day. Severe disease requires treatment with amphotericin B (0.5-1.0 mg per kg per day) for induction therapy followed by itraconazole (400 mg per day) as maintenance therapy. Measurement of itraconazole levels is recommended. Relapse rates without maintenance therapy approach 50%.(121) Maintenance therapy with itraconazole (200 mg daily) had been recommended to be continued lifelong.(118) Relapse occurs infrequently in the presence of maintenance therapy, although it is more likely in patients who remain in endemic areas.(116) However, there have been more recent reports of successful discontinuation of maintenance therapy in patients who have achieved immune reconstitution with antiretroviral therapy (CD4+ T cell count > 100/μL for 6 months).(122, 123) In patients with HIV infection and a CD4+ T cell count < 200/μL who live in an endemic area, primary prophylaxis with itraconazole at a dose of 200 mg per day is recommended. (124)

Nocardiosis

Originally considered fungi, *Nocardia spp.* are a group of ubiquitous actinomycetes. *Nocardia* taxonomy is complex and, of the nine species described, only seven have been associated with human disease, with *N. asteroides* the most commonly identified, though this may change with the use of MALDI and other modern microbiological techniques.(125) Although distributed worldwide, disease is most common in men, and mainly occurs in severely immunocompromised people. A preponderance of cases occur in rural areas, probably reflecting exposure via contact with soil.(126) *Nocardia spp.* may cause cutaneous, pulmonary or disseminated disease. Dissemination is thought to occur primarily from the lung, but in the case of injecting drug users with HIV infection the occurrence of mediastinal disease exclusive to this population suggests direct intravenous contamination as the portal of entry.(127) Pulmonary and disseminated disease occur almost exclusively in association with defects in cell-mediated immunity, immunoglobulin production or leukocyte function.(128) Prevalence in people with HIV infection is low, varying from 0.3-1.8%.(129, 130) although one West African autopsy study showed 4% of patients with pulmonary nocardial infection.(131) Infection in people with HIV infection is strongly associated with injecting drug use (127, 130) and advanced immunodeficiency (CD4+ T cell count <200 /μL).(132)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Clinical presentation

Cutaneous disease may present as one of four types: mycetoma; lymphocutaneous (sporotrichoid) infection; acute cutaneous infection; or systemic disease with cutaneous involvement. Multiple types may occur in the same person. Mycetoma is a chronic, indurated, granulomatous, subcutaneous infection consisting of nodules and draining sinus tracts, often localised to the site of inoculation.⁽¹³³⁾ The discharge from these sinus tracts often contains small white granules consisting of masses of mycelia. Dissemination from mycetoma is rare, but local invasion from head and neck lesions may result in severe disability or death. Lymphocutaneous disease also develops as a nodule at the site of inoculation; however, central ulceration rather than draining sinus formation occurs, and as ulceration spreads to the lymph nodes, multiple subcutaneous nodules develop along the draining lymphatics.⁽¹³⁴⁾ Acute cutaneous infection may manifest as a superficial skin infection with pustules, abscesses, cellulitis, granulomas and ulcers (Figure 4).⁽¹³⁴⁾

Figure 4. Localised nocardial infection



Source: Allworth AL, Bowden FJ. Managing HIV. Part 5: Treating secondary outcomes. 5.16 HIV and bacterial infections. Med J Aust 1996; 164:546-8.

Pulmonary disease is the most common manifestation of nocardial infection in the immunocompromised patient, typically presenting as a subacute illness. Fever and cough with thick purulent sputum are usually present; other constitutional signs are variable.⁽¹³⁵⁾ Chest X-ray findings are variable and may consist of a necrotising pneumonia with cavitation formation, infiltrates of varying size, single or multiple nodules which are highly suggestive of malignant tumours,⁽¹³⁶⁾ and pneumonia-associated empyema.⁽¹³⁷⁾ Pulmonary infections have a propensity for haematogenous spread with extrapulmonary dissemination occurring in half of all patients and seeding of the central nervous system (CNS) occurring in one third.⁽¹³⁵⁾ Brain abscesses, usually supratentorial, are the most common CNS presentation; meningitis is rarely reported.⁽¹³⁸⁾ Clinically silent CNS involvement is sufficiently common that cerebral-imaging studies are recommended, preferably magnetic resonance imaging (MRI), in all patients.⁽¹³⁸⁾

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Diagnosis

A high index of suspicion for *Nocardia spp.* infection may be the most useful aid in diagnosis. In all suspected cases, early notification to the microbiology laboratory is essential. Sputum or pus should be examined for weakly acid-fast, gram-positive filamentous bacteria. Sputum smears are often negative, and bronchoscopy or lung aspiration is usually necessary. *Nocardia* grow quite slowly, and colonies may take up to 4 weeks to develop.(139) Thirty per cent of patients with *Nocardia spp.* infection detected in blood cultures also have concomitant bacteraemia with other pathogens.(137) If cerebrospinal fluid or urine is used for culture, specimens should first be concentrated to optimise yield.

Management

The treatment of nocardial infections may include both surgical and medical interventions; however, prospective, controlled, clinical trial data are lacking. Antibiotics should not be delayed as early administration has been shown to improve outcomes.(140) Sulfonamides are the best studied drugs,141 with trimethoprim-sulphamethoxazole (cotrimoxazole) the most frequently used formulation, despite limited efficacy data and poor in vitro results. Minocycline generally has excellent in vitro activity and has been successfully used at doses of 100-200 mg twice daily as an alternative agent in pulmonary and even cerebral infection.(126) Other useful drugs in the management of nocardial infection include imipenem, meropenem, cefotaxime, ceftriaxone, amikacin, and amoxicillin/clavulanic acid.(139, 142, 143) Therapy should be continued in the immunosuppressed person for at least 12 months, as shorter durations of therapy have been associated with relapse and increased mortality.(140, 144) In cases of disseminated infection, therapy should include at least two active agents. In CNS infections, cotrimoxazole is generally used in combination with imipenem, meropenem, amikacin or a third-generation cephalosporin. Different *Nocardia* species may differ in their in vitro susceptibility to antibiotics, and species or complex identification is critical to guiding the selection of therapeutic agents.(126)

Prophylaxis

Although it is often stated that cotrimoxazole reduces the risk of nocardiosis in people with HIV infection, there is no compelling clinical evidence to support this claim, especially at the doses used for PJP prophylaxis.(127, 129, 130) Indeed, there are numerous case reports of patients who develop nocardiosis despite receiving cotrimoxazole prophylaxis.

Prognosis

The mortality rate in pulmonary disease and extrapulmonary dissemination is high, with rates of 60% to 85% reported.(130, 139)

Rhodococcus equi infection

Rhodococcus equi (formerly *Corynebacterium equi*) is an aerobic, gram-positive, weakly acid-fast, non-spore forming coccobacillus. *R. equi* was first isolated from horses and has been widely reported as a pathogen in domestic animals. However, contact with either farm environments or animals is rarely documented in people with HIV and *R. equi* infections.(140, 141, 142) *R. equi* is usually acquired through the respiratory route in both animals and humans, although person-to-person and nosocomial transmissions have been described.(140, 143)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Clinical presentation

equi infection in people with HIV infection presents with pulmonary involvement, usually accompanied by bacteraemia and frequent dissemination to extrapulmonary sites. (143, 144) It usually presents subacutely with fever and cough. Weight loss, pleuritic chest pain and haemoptysis are also frequently reported. (145, 150, 151, 152) *R. equi* infection in people with HIV infection usually occurs at CD4+ T cell counts < 200/μL, and concomitant infections with other opportunistic pathogens occur frequently. (145, 147, 151) Radiological features consist of cavitating lesions with a strong predilection for involvement of the upper lobe (50-75% of cases). Consolidation is also frequently seen. However, in one case series normal chest X-ray findings were reported in one-quarter of patients. (145) Both the clinical picture and X-ray findings may suggest infection with *Mycobacterium tuberculosis* or *Nocardia spp.* (147, 152) Histological examination demonstrates multiple microabscesses with dense infiltration by histiocytes and intracellular gram-positive coccobacilli. (149)

Diagnosis

equi can be cultured from blood, sputum, BAL fluid and biopsy material using standard media. (153) *R. equi* resembles oropharyngeal commensal diphtheroids and is frequently regarded as a contaminant, leading to late diagnosis in many cases. (150, 151, 152)

Management

The optimal choice and duration of antibiotic therapy for *R. equi* infection remains to be determined. (150, 154) Based on *in vitro* susceptibility, *R. equi* is sensitive to erythromycin, rifampicin, vancomycin, gentamicin and ciprofloxacin. Initial therapy with erythromycin or imipenem plus rifampicin for at least 2 weeks is recommended. Ciprofloxacin is an alternative agent, but ciprofloxacin-resistant strains from South-East Asia have been reported. Surgical intervention is sometimes needed and lifelong, suppressive, oral therapy with a macrolide and rifampicin has been recommended in the past. (146, 151) Mortality in patients with HIV and *R. equi* infections is historically high, often with death resulting from other concomitant infections. (146)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Mycobacterium tuberculosis infection in people with HIV infection

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Last reviewed: October 2019

Introduction

Tuberculosis (TB) is an airborne infectious disease caused by *Mycobacterium tuberculosis* and is an acquired immune deficiency syndrome (AIDS)-defining illness in Australia and other high-income countries. TB remains a global health crisis with an estimated 10 million new cases and 1.6 million deaths occurring each year. The intersection of the TB and human immunodeficiency virus (HIV) epidemics has contributed to an increase in the global TB burden, with 9% of all new TB cases occurring in people with HIV infection in 2017.⁽¹⁾ Globally, TB is the most common presenting illness and leading cause of mortality in people with HIV infection, accounting for 1 in 3 of deaths. The emergence and transmission of multidrug-resistant (MDR, resistance to at least isoniazid and rifampicin) *M. tuberculosis* is a growing challenge, particularly for the Asia-Pacific region.

Australia has one of the lowest TB case notification rates in the world (5.7 cases per 100,000 population in 2014) with higher rates in indigenous Australians (6 times the rate of the non-indigenous population). Eighty-six per cent of TB cases occur in overseas-born persons, making this the most significant risk factor.⁽⁴⁾ Accordingly, HIV-associated TB in Australia is mainly found in overseas-born people. In 2014, HIV testing occurred in 82% of reported TB cases, among them 55% had a result reported and among them, 2% were (17 cases) were identified as being HIV positive.⁽⁴⁾

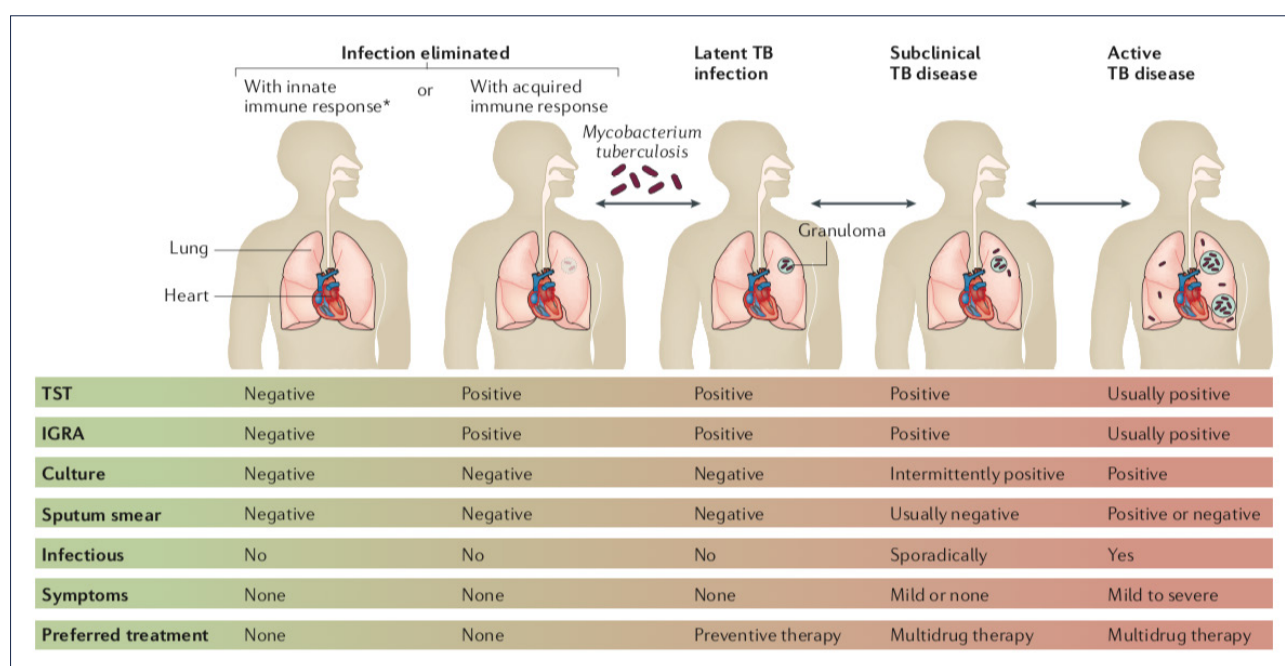
Tuberculosis infection ensues when airborne droplets containing *M. tuberculosis* from an infectious host are inhaled, taken up by alveolar macrophages at the terminal airways and encounter the immune system. The conventional model considered TB to be a binary state between latent TB infection (LTBI), an inactive, non-infectious state, and active disease, the infectious form where clinical signs and symptoms are present. Transitions between the binary states result in one of three clinical outcomes – primary disease, TB infection and reactivation or post-primary disease. There is no gold standard test for direct identification of *M. tuberculosis* infection in humans. (LTBI is defined as the absence of active TB disease and evidence of an antigen-specific T cell response to mycobacterial proteins measured by reactivity in the tuberculin skin test (TST, also known as a Mantoux test) or an interferon-gamma release assay (IGRA). Active disease is classified as either primary TB (involving progression 1-2 years following infection due to loss of immune containment) or reactivation TB (also known as post primary) with disease following infection resulting from LTBI previously seeded at the time of primary infection. Approximately one-quarter of the world's population is estimated to have *M. tuberculosis* infection and 90-95% of these people (HIV negative, no other risk factors) will not develop active disease, indicating that the human immune system can control *M. tuberculosis* infection. It is estimated that 5.1% of the Australian population had LTBI in 2016.

A conceptual scientific shift has occurred to view *M. tuberculosis* infection as a continuous spectrum spanning eliminated infection (early clearance by innate immune responses or delayed clearance by adaptive immune responses), LTBI (quiescent infection with immune containment), subclinical active disease and fulminant active disease (see figure 1). However, significant biomedical knowledge gaps exist in the understanding of the

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

factors that govern infection, pathogenesis and progression to active disease (the host-pathogen interaction). This has resulted in a lack of adequate biomarkers to measure states of infection and disease and therapeutic targets for preventive, diagnostic and therapeutic tools for TB and TB-HIV co-infection. Many prefer to use the term TB infection, rather than LTBI as latent may imply that management or treatment is not needed. Further, not all who are considered to clinically have LTBI (e.g. household contacts) and receive treatment, are tested or have a positive result. However, for simplicity in clinical and public health settings, patients are usually categorized as having either LTBI or active TB disease.

Figure 1. The spectrum of TB, from *Mycobacterium tuberculosis* infection to active (pulmonary) TB disease.



Source: Pai M, Behr M, Dowdy D, et al. Tuberculosis. Nat Rev Dis Primers 2016; 2: 16076. Used with permission.

HIV/TB co-infection

HIV co-infection is the most powerful known risk factor for progression of LTBI to active disease. The risk of progression from LTBI to active TB in people with HIV infection is approximately 5 to 8% per year, in contrast to a 10% lifetime risk in HIV-negative people.⁽¹⁾ HIV has an impact on the host-pathogen (*M. tuberculosis*) relationship with a shift towards poor immune control, high bacillary numbers, and subsequent development of active infection and symptomatic disease.⁽⁹⁾ The risk of developing active TB increases 2-3 fold after HIV seroconversion due to an initial rapid depletion of CD4+ T cells⁽²⁾ and continues to increase thereafter with ongoing decline in CD4+ T cell counts.⁽³⁾ Re-infection with *M. tuberculosis* in endemic high prevalence settings is likely to contribute to the risk by further increasing bacillary numbers and increasing the likelihood of progression to disease.⁽⁹⁾ The development of TB in a person with HIV infection may accelerate HIV disease progression, probably related to prolonged immune activation.⁽⁴⁾ Combination antiretroviral therapy (cART) and treatment of LTBI have been shown to have a significant impact in decreasing the incidence of TB in HIV-infected populations.^{(5),(6)}

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Clinical presentation of TB

TB may present with pulmonary disease, extrapulmonary disease (can involve almost any organ in the body including lymph nodes, central nervous system and blood/bone marrow) or disseminated disease. The typical presentation of TB (fever, weight loss, night sweats, constitutional symptoms with or without cough) has a wide differential diagnosis in patients with HIV infection. TB can occur at any CD4+ T cell count. Unlike most other opportunistic infections, the TB risk is increased irrespective of CD4+ T cell count, however is greater with increasing immunodeficiency, with a systematic review estimating a 1.4 fold increase in TB incidence for every 100 cells/mL decrease in CD4+ T cell counts. Pulmonary disease is present in most patients with both HIV and TB, as evidenced by autopsy studies and subclinical disease found during prevalence surveys or active case finding. Extra pulmonary and disseminated disease are more common in the setting of HIV infection, especially with advanced immunodeficiency. As a result, the World Health Organization (WHO) current staging system considers extrapulmonary TB as stage 4 (AIDS-defining) whereas pulmonary TB is stage (3).

The clinical manifestations of HIV-associated TB are influenced by the degree of immunodeficiency. When the CD4+ T cell count is greater than 350/ μ L, clinical manifestations are similar to persons without HIV infection. Advanced immunodeficiency impairs the host inflammatory response, resulting in lower rates of granuloma formation and pulmonary cavitation. This result accounts for more frequent sputum-smear negative disease and increased time to positivity of automated liquid mycobacterial cultures in HIV patients with TB.(24) A second factor influencing clinical presentation in people with HIV infection, versus those without infection, is that TB progresses more rapidly in HIV patients, reflecting a subacute rather than chronic clinical course.

Diagnosis

Active tuberculosis

The optimal diagnosis of active TB involves early and accurate bacteriological confirmation in order to confirm *M. tuberculosis* infection and to detect potential anti-mycobacterial drug-resistance at baseline. Early diagnosis of HIV-associated TB can be difficult due to the non-specific clinical symptoms, inadequate diagnostic tools available and failure to consider it in the differential diagnosis. A history of past treatment for TB, contact history with a known case of TB, and residence or travel in settings with high endemicity for drug-resistant TB (DR-TB) all suggest an increased risk for resistance and should be ascertained in the clinical history in addition to testing on microbiological specimens.

The diagnosis of *M. tuberculosis* infection can be established by microscopy, mycobacterial culture or nucleic acid amplification techniques (NAAT), in combination with histological examination of tissue biopsy samples and radiography. Sputum smear microscopy allows diagnosis when there are more than 5000 bacilli/mL of sputum and only detects 40-70% of all TB cases. The sensitivity of sputum microscopy depends on the quality of sputum collection and the preparation and interpretation of microscopy slides. Techniques to improve the yield of sputum samples include sputum induction and broncho-alveolar lavage. HIV-associated TB is more often pauci-bacillary and therefore smear-negative, accounting for 24 to 61% of all pulmonary cases in people with HIV infection. Light microscopy has been more recently replaced in some settings with the more sensitive fluorescence microscopy.

Gold standard bacteriological confirmation requires mycobacterial culture on automated liquid or solid media or both and is highly sensitive, being able to detect 10 bacilli/mL. The limitations of culture are that it requires highly specialised laboratory infrastructure, trained technicians, quality assurance procedures and takes up to 4 to 6 weeks for the result to be reported. Drug-susceptibility testing (DST) should be performed on all culture-positive TB isolates to diagnose DR-TB. This 'phenotypic test' evaluates the growth (or metabolic) activity of

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

the *M. tuberculosis* isolate in the presence of the drug. Drug-resistant isolates of *M. tuberculosis* are common in many parts of the world and should be considered in people who are likely to have acquired the infection outside of Australia, and in people who have been previously treated for *M. tuberculosis* infection and have experienced a relapse. Globally, transmission is now considered to be the main route of acquisition, rather than amplification of resistance within an individual.

Molecular or 'genotypic tests' undertaken by NAAT can be used to detect drug resistance by identifying mutations in genes of the *M. tuberculosis* isolate. NAAT has enabled a more rapid and accurate diagnosis of *M. tuberculosis* infection in biological specimens (increasing the yield in smear-negative pulmonary cases). The Xpert MTB/RIF test is a cartridge-based fully automated platform that detects *M. tuberculosis* and rifampicin resistance by automated real time polymerase chain reaction (PCR), providing results in less than 2 hours. Rifampicin resistance is a reliable predictor of MDR-TB in high burden settings (MDR-TB prevalence > 10%), however a 'phenotypic' DST should be performed if possible. The Xpert MTB/RIF test was endorsed by the WHO in 2010 for use in high-burden countries and is the recommended initial test for TB in people with HIV infection. It increases the detection of smear-negative TB by 67%. The performance is not significantly affected by HIV infection, with a sensitivity of 81% and specificity of 98%. In possible extrapulmonary TB, every effort should be made to obtain samples for microscopy, NAAT, culture and histology. Sensitivity for NAATs is lower in extra-pulmonary samples when compared to sputum. The Xpert MTB/RIF test has good sensitivity (80%) and excellent specificity (> 98%) when performed on cerebrospinal fluid, lymph node aspirates and gastric aspirates, where it can replace smear microscopy. Xpert MTB/rif Ultra (Xpert Ultra), has been introduced. Xpert Ultra has greater sensitivity for detecting TB than Xpert but at the cost of a slight reduction in specificity. False positive Xpert Ultra results are more common in persons previously treated for TB. Other commercially available molecular techniques are available such as line probe assays (Hain MTBDR, for detection of isoniazid and rifampicin resistance mutations, and Hain Genotype MTBDRsl, for detection of fluoroquinolone and injectable resistance) and many diagnostic laboratories also offer an in-house PCR assay.

Detection of *M. tuberculosis* liparabinomannan (a component of the cell wall) in urine by lateral flow assay (Alere Determine TB LAM Ag) is a low-cost, point-of-care test that has a high specificity but variable sensitivity depending on the CD4+ T cell count (sensitivity of 66.7% when CD4+ T cell count is <50/μL). It is recommended by WHO for use as a diagnostic test for TB in people with HIV infection who have a CD4+ T cell count <100/μL or those who are seriously ill, as a randomised trial showed a mortality reduction in this group compared with routine care. A newer version (Fujifilm SILVAMP TB LAM) assay has been developed and is under further evaluation, with the initial studies demonstrating a superior sensitivity of 70.4%.

Whole genome sequencing (WGS) and targeted next generation sequencing of *M. tuberculosis* DNA have great potential for rapid diagnosis of DR-TB through the detection of drug resistance mutations, in addition to providing information for surveillance and public health responses (clustering of strains). DNA sequencing is the most accurate of the molecular tests and is increasingly cheaper and quicker than phenotypic testing. It is possible that DNA sequencing will be able to replace phenotypic testing in the future if automated, affordable platforms and improved understanding of the clinical implication of drug resistance mutations is developed. Some laboratories in Australia provide WGS routinely for culture positive *M. tuberculosis* isolates. Drug resistance mutations can be classified by how strongly they are associated with phenotypic resistance tests. However, mutations for some drugs are not yet fully known, especially for some of the newer drugs used for DR-TB, and there is still limited understanding of causes of discordance between phenotypic tests and sequencing. Interpretation of results is recommended to be done in consultation with an expert. New diagnostic tests and biomarkers for TB are in development, with several tests in the process of having evidence submitted to the WHO for review prior to a recommendation being made on their use.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

The radiological features of TB in people with HIV infection and CD4+ T cell counts >200 / μ L are similar to the general population, with a predominance of upper lobe abnormalities, cavitary disease and the presence of pleural effusions. In immunodeficient persons (CD4+ T cell count <200/ μ L), mediastinal lymphadenopathy, middle and lower zone infiltrates, non-cavitary disease and extrapulmonary disease are more common. Up to 10% of patients will have a normal chest X-ray. Radiography, including computerised tomography and ultrasound, may be a useful adjunct test in localising and defining the site of extrapulmonary disease.

Screening tests for TB

People with HIV infection in Australia who are from high-burden TB countries, or have travelled to them, should be systematically screened for active TB and LTBI, given their increased risk of having these problems. Screening strategies based on cough only have a low sensitivity for HIV-associated TB. Chest X-ray used in combination with symptom screening has the highest sensitivity for detecting TB and, thus, should be used to exclude active TB before initiating treatment for LTBI. Software for artificial intelligence-based computer aided detection of TB from chest X-rays has been developed and clinical evaluation is ongoing.

Latent tuberculosis infection

The diagnosis of LTBI can be established with the TST or an IGRA, commercially available as QuantiFERON-TB assay and T-SPOT TB assay. Neither assay can differentiate accurately between latent and active TB. The TST is an intradermal injection of tuberculin that stimulates a delayed-type hypersensitivity immune response, mediated by T lymphocytes and macrophages, that results in skin induration, measured by a clinician. False-positive TSTs can be caused by T cell responses to antigens of non-tuberculous mycobacteria (NTM) or Bacillus Calmette-Guerin (BCG), resulting from previous BCG vaccination. The IGRAs measure T-cell responses to *M. tuberculosis*-specific proteins in whole blood (QuantiFERON-TB Gold In-Tube assay) or by enzyme-linked immunospot assay (T-SPOT TB assay) and do not detect T cells reactive to NTM or BCG. They therefore offer greater specificity than the TST.

As both IGRAs and TSTs measure T-cell responses, they are more likely to be positive in people with HIV infection who have relatively high CD4+ T cell counts than in those with severe immunodeficiency. A lower cut-off for a positive TST is used in the HIV-infected population (5 mm induration rather than 10 mm used in those without HIV infection). As there is no gold standard for mycobacterial detection in LTBI, sensitivity is determined among culture-confirmed active TB cases. The sensitivity of the QFN-TB test is 67% in people with HIV infection and there is no current evidence to suggest superiority of IGRA over TST in the diagnosis of LTBI in people with HIV infection.⁽⁴⁹⁾

Given the high risk of progression to active TB in individuals with HIV infection, all patients from countries where *M. tuberculosis* infection is endemic, or who have been exposed to someone with TB, should be tested for LTBI. National guidelines vary in their recommendation of testing algorithm to include one, both or sequential TST and IGRA. The Australian National TB Advisory Committee (NTAC) recommends a TST or IGRA or both, with a diagnosis of LTBI to be made if either test is positive. Patients with a negative TST or IGRA and advanced HIV disease (i.e. CD4+ T cell counts < 200/ μ L) should have a repeat TST or IGRA after initiation of cART and increase in the CD4+ T cell count to > 200/ μ L.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Management of active tuberculosis

The management of active TB-HIV co-infection involves prompt initiation of an appropriate multidrug TB regimen that is guided by DST, commencing cART and treatment monitoring. The ASHM Antiretroviral Guidelines, an Australian handbook and several international guidelines include a more complete discussion of the diagnosis and treatment of TB in patients with HIV infection. TB can be a rapidly progressive illness in advanced immunodeficiency. After collection of appropriate specimens for NAAT, culture and DST, empiric treatment for TB may be warranted while awaiting results in persons with clinical and radiographic features suggestive of HIV-TB co-infection. It is recommended that all patients initiated on TB treatment are screened at baseline for viral hepatitis and diabetes mellitus.⁽⁵³⁾ There are several specific issues related to the treatment of TB-HIV co-infection: when to start cART; shared toxicity and drug-drug interactions with cART (especially between the rifamycins); and the development of TB-associated immune reconstitution inflammatory syndrome (TB-IRIS).

Drug-susceptible tuberculosis

In TB-HIV co-infection, the same standard regimen for drug-susceptible TB is used as in people without HIV infection. A four-drug regimen of isoniazid, a rifamycin (rifampicin or rifabutin), pyrazinamide and ethambutol for 2 months (intensive phase), followed by isoniazid and a rifamycin for 4 months (continuation phase) is recommended. Some guidelines recommend that ethambutol can be ceased sooner than 2 months if drug susceptibility to isoniazid and rifampicin is confirmed.⁽⁵⁴⁾ The optimal duration of therapy depends on the site of disease and response to treatment. In patients with pulmonary disease, short-course therapy for 6 months is adequate, unless there is persistent culture-positive sputum after 2 months of therapy without drug-resistance, when therapy should be extended to 9 months. Concerns about relapse rates after short-course therapy have come from trials in countries with a high prevalence of TB and re-infection may be the explanation for this phenomenon. Irrespective of HIV status, patients with miliary, meningeal or skeletal disease should be treated for a total of 9 to 12 months. Three randomised controlled trials have evaluated 4-month regimens for drug sensitive TB, but all have had higher relapse rates and are not recommended. A meta-analysis demonstrated that increasing rifamycin duration to 8 months or more was associated with reduced relapse in patients with HIV infection with active TB.⁽⁵⁵⁾ However, the majority of patients were not on cART and it cannot be determined if relapse was due to re-infection or recurrence.

Treatment should be administered daily, as intermittent therapy (three times a week) in the intensive phase increases relapse rates. The choice of which rifamycin is guided by avoidance of drug-drug interactions and cost as their efficacy is considered equivalent. Pyridoxine supplementation is administered to reduce the risk of peripheral neuropathy caused by isoniazid and exacerbated by HIV infection and/or certain antiretroviral drugs. See Table 2 for the common side-effects of anti-tuberculosis agents.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Table 2. Side-Effects of commonly used anti-tuberculosis agents(54)

Drug	Potential Side-Effects
Amikacin	Nephrotoxicity, ototoxicity, electrolyte abnormalities
Bedaquiline	Nausea, arthralgia, headache, elevated transaminases, hepatitis, QTc prolongation
Clofazimine	Skin pigmentation, anorexia, nausea, skin dryness, pruritis, abdominal pain, conjunctival irritation, QTc prolongation
Cycloserine	Depression, mania, tiredness, peripheral neuropathy, convulsions
Delamanid	Nausea, vomiting, dizziness, QTc prolongation, paraesthesia, anxiety, tremor
Ethambutol	Optic neuritis (usually at higher doses eg. 25mg/kg/day), reduced visual acuity, restricted visual fields, peripheral neuropathy, headache, rash,
Isoniazid	Peripheral neuropathy (prevent with administration of pyridoxine), hepatitis, neurologic manifestations (convulsions, encephalopathy, optic neuritis), fever
Levofloxacin / moxifloxacin	Nausea, vomiting, abdominal pain, diarrhoea, C. difficile-associated diarrhea, headache, dizziness, sleep disturbances, tendonitis and tendon rupture (associated with >60 years of age and concomitant steroid use), photosensitivity, hypoglycaemia, hepatotoxicity, QTc prolongation, neurotoxicity (especially with high doses, use in elderly patients, or use in patients with renal dysfunction), seizures (rare), peripheral neuropathy
Linezolid	Peripheral neuropathy, optic neuritis, anaemia, thrombocytopenia, neutropenia, serotonergic syndrome, lactic acidosis (rare), diarrhea, headache, nausea, vomiting
Prothionamide/ Ethionamide	Dose-dependent gastrointestinal side effects (nausea, vomiting, diarrhoea, abdominal pain, metallic taste, anorexia), dizziness, drowsiness, depression, postural hypotension, hepatotoxicity, hypothyroidism (with or without goiter), gynecomastia, impotence, hypoglycaemia
Pyrazinamide	Arthralgia, hepatitis, hyperuricemia, gastric irritation, photosensitivity, rash, pruritis,
Rifabutin	Leukopenia, nausea, vomiting, diarrhoea, discolouration of urine, tears, saliva, stool and skin, neutropenia, hepatitis, febrile illness, haemolysis, myositis
Rifampicin	Anorexia, nausea, vomiting, diarrhoea, rash, febrile reaction, hepatitis, discolouration of urine, tears, saliva, stool and skin, Haemolysis, febrile illness

In cases of marked immunodeficiency (CD4+ T cell count < 50/μL) where *Mycobacterium avium complex* (MAC) infection is in the differential diagnosis of a diagnosis of TB, and in the absence of the result of a NAAT or culture, empirical therapy should cover both MAC and *M. tuberculosis* infections. This regimen involves the addition of clarithromycin or azithromycin to the standard four-drug TB therapy (See section on non-tuberculous mycobacterial infections).

Drug-resistant tuberculosis

The management of DR-TB poses a major challenge to treatment due to the requirement for a longer duration of therapy, complex clinical management issues (including drug toxicity, monitoring and drug-drug interactions), and a paucity of evidence to guide decisions. Drug-resistant TB includes mono-resistant (e.g. isoniazid-resistant, rifampicin-resistant TB, RR-TB) and poly-drug resistant TB; multidrug-resistant TB and resistance beyond MDR-TB. Currently, extensively drug-resistant TB (XDR-TB) is defined as MDR-TB with additional resistance to any quinolone and any second-line injectable agent. If the DST reveals resistance to any of the drugs in the standard initial TB regimen, expert consultation is essential.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

The WHO treatment guidelines for DR-TB underwent a major revision in 2019 and are likely to change significantly each year, as new evidence emerges for shorter and more effective regimens and novel and repurposed drugs. Of note were recent studies showing that, in comparison with the previous WHO standard of care, a reduction in mortality in patients treated with bedaquiline in South Africa, and the results of a randomised trial of a shorter MDR-TB treatment regimen. The current WHO recommended treatment regimen for MDR-TB is at least four 'effective' second-line TB drugs administered over at least 18 months. The second line drugs have been re-classified into 3 groups on the basis of meta-analyses of evidence of efficacy and adverse events. Four or five drugs should be selected first from Group A (later generation fluoroquinolone, linezolid, bedaquiline) and then from group B (clofazimine, cycloserine) unless there is resistance or intolerance to 1 or more of the drugs in which case group C drugs are added (see table 3). Bedaquiline is well tolerated, safe, and efficacious in patients with HIV infection and TB. However, patients must be monitored for QT prolongation. A shorter 9-11 month regimen is conditionally recommended by WHO based on a randomised controlled trial showing non-inferiority to standard longer regimens.⁽⁶¹⁾ However, this regimen has not been compared to updated regimens including bedaquiline and linezolid, and includes drugs with a high adverse event profile including injectable agents with risk of ototoxicity. Both the randomised trial and an observational study in African countries had higher mortality rates in patients with HIV infection than in patients without.⁽⁶³⁾ This regimen is not recommended in the Australian context. For isoniazid-mono-resistant tuberculosis, a four-drug regimen of a later generation fluoroquinolone (levofloxacin or moxifloxacin) together with rifampicin, pyrazinamide, and ethambutol is recommended for a duration of at least 6 months.⁽⁵⁹⁾ Several trials of new all oral regimens are underway, and treatment guidelines are likely to change frequently in the next few years.

Table 3. WHO grouping of medicines recommended for use in longer MDR-TB regimens⁽⁵⁹⁾

Groups & steps	Medicine	
Group A: Include all three medicines	levofloxacin <i>OR</i>	Lfx
	moxifloxacin	Mfx
	bedaquiline	Bdq
	linezolid	Lzd
Group B: Add one or both medicines	clofazimine	Cfz
	cycloserine <i>OR</i>	Cs
	terizidone	Trd
Group C: Add to complete the regimen and when medicines from Groups A and B cannot be used	ethambutol	E
	delamanid	Dlm
	pyrazinamide	Z
	imipenem-cilastatin <i>OR</i>	lpm-Cln
	meropenem	Mpm
	amikacin	Am
	(<i>OR</i> streptomycin)	(S)
	ethionamide <i>OR</i>	Eto
	prothionamide	Pto
	p-aminosalicylic acid	PAS

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Antiretroviral therapy in patients with HIV infection and TB

All patients with HIV-associated TB should be treated with cART, regardless of CD4+ T cell count and ideally within 8 weeks.

When to start cART

The decision to commence cART is a balance between the risk of high mortality and morbidity in patients with a very low CD4+ T cell counts (especially counts < 50 / μ L) and the potential for drug toxicity and interactions and TB-IRIS. Several large randomised controlled trials have now been conducted and full recommendations are expanded in the ASHM guidelines.(52)

- In patients with CD4+ T cell counts <50/ μ L, cART should be initiated as soon as possible but within 2 weeks of starting TB treatment, as this has improved survival, despite an increase in the risk of TB-IRIS by 2-3-fold.
- In patients with CD4+ T cell counts $\geq$ 50 cells/ μ L, cART should be initiated within 8 weeks of starting TB treatment.
- In patients with TB meningitis, optimal timing is less certain, but should be commenced between 2 and 8 weeks after starting TB treatment, regardless of CD4+ T cell count due to the higher rates of morbidity and mortality associated with TB-IRIS of the central nervous system (CNS).(55)
- In all pregnant women with HIV infection and active TB, cART should be started as early as feasible, both for maternal health and for prevention of mother-to-child transmission of HIV infection.
- In patients with HIV infection and documented MDR-TB, cART should be initiated within 2 to 4 weeks of confirmation of TB drug resistance and initiation of second-line TB therapy.

Drug toxicity and interactions

Anti-tuberculosis treatment and cART have overlapping and additive toxicity profiles that include drug-induced liver injury (DILI), cutaneous reactions, renal impairment, neuropathy and neuropsychiatric adverse effects. A comprehensive review can be found in the DHHS and ASHM guidelines.(52,54) All drugs can cause DILI but it is more common from isoniazid, rifamycins, pyrazinamide, bedaquiline, nevirapine, efavirenz and protease inhibitors. HIV-TB co-infection has been associated with a five-fold increased risk of rash or drug fever. Renal impairment can be caused by different mechanisms; tenofovir disoproxil fumarate (tubular), injectable agents (tubular), rifampicin (interstitial). Peripheral neuropathy can occur with administration of isoniazid or may be a manifestation of HIV infection. All patients receiving isoniazid, and potentially linezolid, should also receive supplemental pyridoxine to reduce peripheral neuropathy.

When cART is used with anti-tuberculosis treatment, consideration of potential drug interactions is of paramount importance and a database such as <http://www.hiv-druginteractions.org> should be consulted. After determining the drugs and doses to use, clinicians should monitor patients closely to assure good control of both TB and HIV infections. Suboptimal HIV suppression or suboptimal response to TB treatment should prompt assessment of drug adherence, subtherapeutic drug levels (consider therapeutic drug monitoring, TDM), and acquired drug resistance.

Rifamycins are potent inducers of the hepatic cytochrome P (CYP) 450 and uridine diphosphate gluconyltransferase (UGT) 1A1 enzymes and are associated with significant interactions with most antiretroviral drugs including all protease inhibitors, non-nucleoside reverse transcriptase inhibitors (NNRTIs; to a moderate extent), maraviroc and raltegravir. Rilpivirine, etravirine, and elvitegravir co-formulated with

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

cobicistat should not be used with rifampicin. The nucleoside reverse transcriptase inhibitors (NRTIs) can be used with rifampicin without dose adjustments. The exception is Tenofovir alafenamide (TAF) which is more likely to have drug-drug interactions than TDF and caution is urged.

The cART regimen for which there is most experience of use in combination with first-line anti-tuberculosis treatment is: tenofovir disoproxil fumarate + emtricitabine + efavirenz. Alternatives include dolutegravir 50mg twice daily with rifampicin. Raltegravir levels are reduced by rifampicin, however it is unclear whether to adjust the dose as a phase II trial showed equivalent virologic response with raltegravir 400mg BD or 800mg in people taking rifampicin.

Other options for using cART in combination with anti-tuberculosis therapy are more problematic because rifampicin reduces the concentration of ritonavir-boosted protease inhibitors by 75-90%. Rifampicin is not recommended in combination with all protease inhibitors and the NNRTIs, etravirine, and rilpivirine. When rifampin is used with maraviroc or raltegravir, increased dosage of the antiretroviral drug is generally recommended. Rifabutin, a weaker enzyme inducer, is an alternative to rifampicin. Rifabutin has little effect on ritonavir boosted atazanavir or lopinavir, but moderately increases darunavir levels. However, all protease inhibitors increase serum concentrations of rifabutin and its metabolites. The dose of rifabutin should be decreased to avoid potential toxicity (uveitis, neutropenia).

Bedaquiline should not be used with efavirenz and use with lopinavir-ritonavir requires careful monitoring. Dolutegravir, has no known interactions with bedaquiline and might be better tolerated. Delamanid has no known interactions with antiretroviral therapy.⁽⁵⁴⁾

TB-associated immune reconstitution inflammatory syndrome

TB-associated immune reconstitution inflammatory syndrome (TB-IRIS) occurs in two forms, unmasking and paradoxical. Case definitions have been published for resource-limited settings. Disease pathogenesis mechanisms are similar for both forms of TB-IRIS and reflect restoration of an immune response against *M. tuberculosis* after administration of cART that results in an exaggerated inflammatory response to live or dead bacilli. Unmasking TB-IRIS refers to the clinical manifestations of active TB that occur soon after cART is started in patients with undiagnosed TB. Paradoxical TB-IRIS refers to the worsening of TB after cART is started in patients who are receiving TB treatment. Both forms of TB-IRIS have a wide range of clinical features such as fever, worsening respiratory symptoms, lymphadenopathy (often with suppuration), TB abscesses and serous effusions. Central nervous system TB-IRIS is particularly severe. TB-IRIS can involve multiple sites, reflecting dissemination of TB in patients with profound immunodeficiency. A meta-analysis revealed a summary risk estimate of 18% for paradoxical TB-IRIS with 2% mortality.

Predictors for the occurrence of TB-IRIS include a CD4+ T cell count < 50 cells/μL pre-cART; high pre-cART and lower on-cART HIV viral loads; severity of TB disease (high pathogen burden); and less than 30-day interval between initiation of TB and HIV treatments. Most TB-IRIS occurs within 3 months of the start of TB treatment. There is no diagnostic test for TB-IRIS and alternative diagnoses such as the failure of anti-tuberculosis treatment (drug interactions, non-adherence, drug resistance) and other opportunistic infections must be considered.

Patients with mild or moderately severe TB-IRIS can be managed symptomatically or treated with non-steroidal anti-inflammatory agents (although no clinical data exist to support their use). Patients with more severe TB-IRIS can be treated successfully with corticosteroids. A randomised, placebo-controlled trial demonstrated the benefit of corticosteroids in the management of TB-IRIS symptoms (as measured by decreasing days of

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

hospitalisation and Karnofsky performance score) without adverse consequences. In the presence of TB-IRIS, neither TB therapy nor cART should be stopped because both therapies are necessary for the long-term health of the patient. In patients at high risk of TB-IRIS (CD4+ T cell count <100/mL and commencing cART within 30 days of TB treatment), a randomised trial showed that steroids reduced TB-IRIS without a significant increase in other opportunistic events or mortality. The dosing strategy for prednisolone was 40 mg daily for two weeks, followed by 20 mg daily for two weeks during the first four weeks after initiation of cART. Steroids should be used in cerebral TB as they reduce mortality. In the setting of pericarditis, it is less clear as a randomised controlled trial did not show a reduction in mortality, with a reduction in constrictive pericarditis offset by an increase in some cancers including Kaposi's sarcoma.

Treatment delivery and monitoring

Close collaboration among clinicians, health-care institutions and public health programs involved in the diagnosis and treatment of patients with HIV infection and TB is necessary in order to integrate care and improve patient outcomes. A specialist or specialists with appropriate expertise should supervise the management of all patients with HIV-TB co-infection in Australia. Hospital admission is not mandatory and depends on clinical indications. The treatment delivery model varies between jurisdictions in Australia but is either a community-based or ambulatory model of care. A patient-centred approach with treatment support that mitigates barriers to adherence such as patient education, social support, provision of transport and addressing any comorbidities (e.g. substance dependence, mental illness) is recommended by WHO. This approach can include directly observed therapy (DOT), or video observed therapy (VOT), although a meta-analysis demonstrated that DOT is not significantly better than self-administered therapy (SAT) in preventing failure, relapse or acquired drug resistance.

Patients should be monitored closely, in order to ensure they are making the appropriate response to treatment with minimal drug-related toxicity. Patients should have monthly clinical review, biochemical (liver and kidney function tests) and microbiological investigations. Patients with pulmonary TB should have monthly sputum smears and cultures performed (especially in patients with MDR-TB) to document culture conversion on therapy (defined as two consecutive negative cultures). Sputum cultures typically convert to negative between 2 and 4 months, although may be delayed in extensive or cavitary disease. Failure of conversion or clinical improvement should prompt evaluation (adherence, drug-drug interactions, alternative diagnoses) and drug-resistance testing. Therapeutic drug monitoring in patients being treated for HIV infection and TB has a potential role because of the individual pharmacokinetic variability and risk of drug-drug interactions in this patient population. It is available in some Australian laboratories and is having an increasing role, although not recommended as standard of care in guidelines. (55)

Adequate infection control measures (personal, administrative, environmental) should be implemented in health facilities where patients with TB are admitted and ambulatory points where treatment is received. Nosocomial outbreaks of TB have been documented in Australia. It is unknown when patients are non-infectious after the initiation of anti-tuberculosis treatment; however, evidence suggests that a marked reduction in infectiousness occurs rapidly after the onset of effective therapy. There is a statutory requirement to notify all cases of TB (including patients started on empirical anti-tuberculosis therapy) to public health authorities. Investigation and management of contacts of the index case is carried out by the state TB services.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Prognosis

If active TB and HIV infection are untreated in a patient with co-infection, the outcome is almost universally fatal. Patients with HIV-TB co-infection respond well to anti-tuberculosis treatment and have similar culture conversion and treatment completion rates compared to HIV-negative TB patients. However, the case fatality rate is higher despite cART. The degree of immunodeficiency is the most important predictor of survival in HIV patients with TB. In high TB burden settings, cART reduces the mortality risk by 64-95% in patients with HIV-TB co-infection.

Treatment of latent tuberculosis infection (preventive treatment)

Treatment of LTBI to prevent the development of active TB is called preventive treatment (PT; previously prophylaxis) and is often commenced irrespective of confirmed LTBI diagnosis and based on risk of LTBI. Preventive treatment can reduce the progression of LTBI to active TB in people with HIV infection by 32-62% and reduces the risk of death by one-third, irrespective of concurrent cART. Before commencing PT, it is important to exclude active TB by clinical and radiological or bacteriological assessment.

The 2018 WHO LTBI guidelines recommend that adults and adolescents with HIV infection, with unknown or a positive TST or IGRA and are unlikely to have active TB, should receive PT as part of a comprehensive package of HIV care. Treatment should be given to these individuals irrespective of the degree of immunodeficiency and also to those on cART, those who have previously been treated for TB and pregnant women. Additionally, adults and children with HIV infection who are in close contact with anyone with active TB should receive PT, regardless of their LTBI test results. In high TB burden settings, PT decreases TB risk and mortality regardless of TST or IGRA result. (88)

In Australia and other low incidence TB settings, people with HIV infection who have a negative TST or IGRA and no recent exposure to, or contact with, a person with active TB are unlikely to benefit from PT and it is therefore not recommended. (54) All people with HIV infection who have a positive test for LTBI, recent exposure to or close contact with someone who has TB, and without a history of previous treatment for LTBI or active TB, should receive PT.

Several new regimens are currently recommended by WHO and international guidelines for PT. (5,54,55)

The previous standard of care was isoniazid for 6 to 9 months. The following options are recommended for treatment of LTBI in countries with a low TB incidence in people with HIV infection: 6-9 months of isoniazid (6H or 9H), or a 3-month regimen of weekly rifapentine plus isoniazid (3HP), or 3 months of isoniazid plus rifampicin (3RH), or 4 months of rifampicin alone (4R). In addition, a recent randomised multicentre trial has demonstrated the non-inferiority of 1 month of daily rifapentine plus isoniazid (1HP) to 9 months of isoniazid for the outcome of active TB and death, and more patients completed treatment. (5)

There are no clear data to guide duration of PT in people with HIV infection. British and WHO guidelines recommend 6 months of isoniazid, whereas US guidelines prefer 9 months. Isoniazid should be supplemented with pyridoxine at a dose of 25 to 50 mg/day to prevent peripheral neuropathy. In high TB burden and transmission settings, the recommendation is to treat with isoniazid for 6 months, with a consideration of up to 36 months (continuous PT) as clinical trials show benefit with longer duration, presumably by preventing re-infection. Two large randomised trials conducted in South Africa and North America have demonstrated the equivalence of once-weekly isoniazid plus rifapentine, given under DOT for 12 weeks, compared with 6 months of isoniazid preventive therapy. In the case of isoniazid intolerance, an alternative regimen is 4R, however, the drug interactions with cART may be problematic. The 4R regimen was shown to be non-inferior to 9H with

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

better treatment completion and lower adverse events, although the number of participants with HIV was low. There are no data demonstrating the efficacy of rifabutin as PT. The 1HP regimen had better completion rates and lower adverse events than 9H.(91) Rifapentine is currently not available in Australia.

Selection of PT regimen should be based on the individual's ART regimen(52):

- Any ART regimen can be used when isoniazid alone is used for LTBI treatment
- Only efavirenz (EFV)- or raltegravir (RAL)-based regimens (in combination with either abacavir/lamivudine [ABC/3TC] or tenofovir disoproxil fumarate/emtricitabine [TDF/FTC]) can be used with once-weekly isoniazid plus rifapentine
- If rifampin or rifabutin is used to treat LTBI, clinicians should assess the potential for interactions with antiretroviral drugs.

Patients on PT should have baseline assessments including liver function tests monitored monthly for adverse effects. There is no value in repeating TST or IGRA on completion of PT.

For MDR-TB contacts, WHO recommends a risk versus benefit assessment and an individualised drug regimen on a case-by-case basis due to the assumption that isoniazid and rifamycins are not effective and there is limited evidence base for alternatives.(5) There are ongoing randomised trials of PT for MDR-TB contacts, 2 with levofloxacin vs placebo (V-QUIN [ACTRN12616000215426], TB CHAMP [NCT02365623], and 1 with delamanid vs isoniazid (PHOENIX [NCT03568383]). The results are expected after 2022. There is observational evidence of the safety and efficacy of PT in over 600 MDR-TB contacts with regimens that include a fluoroquinolone. The benefit of PT is likely to outweigh the risks in most situations.

Co-trimoxazole preventive therapy is recommended by the WHO for all patients with active TB irrespective of CD4+ T cell count, as it has been shown to have a mortality benefit in Sub-Saharan Africa.(72) The generalisability of this treatment recommendation to settings such as Australia can be questioned, as the mechanism may involve an effect on malaria and other bacterial infections.

Preventing exposure to and infection with *M. tuberculosis*

People with HIV infection who live or work internationally in settings with a high prevalence of TB should be counselled about the risk of TB acquisition, infection prevention measures (particularly if working in a health care setting) and the advisability of getting tested for LTBI upon returning to Australia.

The Bacillus Calmette-Guérin (BCG) vaccine is contraindicated in people with HIV infection, although universal BCG vaccine at birth is recommended in high burden TB settings. Several potential new vaccines are under development and being assessed in clinical trials

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Non-tuberculous mycobacterial infections in people with HIV infection

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Last reviewed: November 2019

Introduction

The most common non-tuberculous mycobacteria (NTM) that infect and cause disease in people with HIV infection are members of the *Mycobacterium avium* complex, typically in severely immunodeficient people. Other NTM infections have been reported less frequently and the level of evidence for treatment is less in HIV infection than in other clinical situations.

Mycobacterium avium complex disease

Mycobacterium avium and *Mycobacterium intracellulare* are the most common NTM in the group of organisms known as the *Mycobacterium avium* complex (MAC), which cause disease in HIV-infected people with advanced immunodeficiency. MAC is ubiquitous in the environment. There is a strong relationship between the severity of CD4+ T cell depletion and the presence of disseminated MAC infection, with nearly all cases occurring at a CD4+ T cell count of <50/μL. (1) A MAC-associated immune reconstitution inflammatory syndrome (MAC-IRIS) may occur at higher CD4+ T cell counts in the setting of combination antiretroviral therapy (cART), with an incidence rate of 3.5% in people commencing cART with a CD4+ T cell count of <100/μL. (2) Disseminated MAC infection has become rare since the introduction of cART. (3)

Clinical presentation

The most common manifestations of MAC disease in people with HIV infection who are not taking cART are the result of disseminated infection. The typical clinical scenario is a markedly immunodeficient person (CD4+ T cell count <50/μL) with fevers, drenching night sweats, weight loss, anaemia (or pancytopenia), diarrhoea, lymphadenopathy and hepatosplenomegaly with abnormal liver function tests (particularly an elevation of alkaline phosphatase). Intra-abdominal lymphadenopathy may occur and cause significant abdominal pain. Although uncommon, pulmonary involvement can present with a persistent dry cough, fever and loss of weight.

MAC-associated immune reconstitution inflammatory syndrome

Disease resulting from the restoration of cell-mediated immunity to MAC was recognised after zidovudine monotherapy for HIV infection (4), although clinical reports of MAC-IRIS have been more frequent following the introduction of cART. (5-9) There are three main clinical presentations of MAC-IRIS: peripheral lymphadenitis and fever; intra-abdominal disease (abdominal lymphadenopathy, chylous ascites, peritonitis, abscess and lesions or masses in the bowel); and lung disease (mediastinal lymphadenopathy, infiltrates, cavitary lesions and pulmonary nodules). (2) The lymphadenopathy may be peripherally located, with sinus formation and

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

chronic percutaneous drainage of purulent material, or intra-abdominal (para-aortic and mesenteric), which is often associated with abdominal pain. A peripheral blood leukocytosis may be present. Biopsy specimens of lymph nodes typically reveal granulomata and acid-fast bacilli may be detected. However, mycobacteria may not be cultured, especially if the MAC infection was treated prior to commencing cART, indicating that non-viable mycobacteria can elicit an immune response. Osteomyelitis, bursitis, pericarditis, parotitis, cerebral abscess, peritonitis and skin nodules have also been reported. In one study in a resource limited setting, 9 out of 793 (1%) patients developed MAC disease after commencing cART.(10)

In the event of lymphadenitis caused by MAC-IRIS, treatment should consist of standard therapy for MAC infection. Up to 20% of patients with MAC-IRIS fail to respond to up to 2 years of MAC therapy and experience persistent or relapsing disease. These patients are more likely to have abdominal lymphadenopathy and are less likely to have a significant rise in CD4+ T cell counts in response to cART.(11) In severe cases, a short course of prednisone may be used,(2) but some patients relapse on tapering the dose. In rare cases, surgical drainage, lymphadenectomy or the temporary interruption of cART may be required.(12)

The presence of MAC infection at the time of cART commencement is associated with a poorer recovery of CD4+ T cell counts than matched subjects without MAC infection, possibly reflecting the occurrence of inflammation from a mild form of MAC-IRIS that impairs recovery of CD4+ T cell counts.(13)

Diagnosis

The diagnosis of disseminated MAC disease can be made by culture of blood or histological examination and culture of bone marrow, enlarged lymph nodes or liver. Although the presence of MAC in stool culture has a 60% predictive value for the subsequent development of disseminated MAC disease in people not taking cART,(14) it is not diagnostic of disseminated disease. A presumptive diagnosis, pending the results of appropriate investigations, may be made in the typical clinical context (CD4+ T cell count <50/μL, not taking MAC prophylaxis, with fevers, night sweats, weight loss and anaemia). Such a presumptive diagnosis may only be confirmed by culture of MAC from blood (MAC bacteraemia) or bone marrow in approximately 20% of cases.(15) It is important to consider other causes of the symptom complex as multiple pathological processes can coexist and mimic one another in HIV-infected people with severe immunodeficiency.

Management

The usual regimen for the treatment of MAC infection is clarithromycin 500 mg twice a day and ethambutol 15 mg/kg/day with or without rifabutin 300 mg daily. Treatment with a three drug regimen was associated with reduced mortality compared with two drugs in one study.(16,17) If clarithromycin is not tolerated, then azithromycin 500 mg daily may be substituted. If clarithromycin is not used, then the dose of rifabutin should be increased to 450 mg daily. The dose of clarithromycin should not exceed 500 mg twice daily, as excess mortality has been observed at doses of 1000 mg twice daily.(18) Alternative agents, including amikacin, ciprofloxacin or clofazimine, should only be used if there is no clinical response to initial therapy after 6 weeks. Antimicrobial-sensitivity testing is not routinely undertaken but should be performed if a macrolide antibiotic (azithromycin or clarithromycin) has been used for prophylaxis, and breakthrough MAC infection has occurred. Some authors have recommended that macrolide resistance be routinely assessed as two of nine (22%) isolates in one small US study were found to be macrolide resistant despite little or no previous macrolide exposure.(19)

When cART is used in combination with MAC treatment, consideration of drug interactions between antiretroviral and antimycobacterial drugs is required. In all cases where HIV and mycobacterial infections are

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

treated simultaneously, a careful review of potential multi-directional drug interactions should be undertaken, with reference to a pharmacist or reliable drug-interaction website (such as www.hiv-druginteractions.org). The degree of interaction varies, with some combinations being contraindicated and others requiring a dose modification of one or both agents.

In general, cART should be commenced within 2 weeks of commencing MAC therapy.(20) This may be associated with an immune reconstitution inflammatory syndrome, but most data suggest a reduced risk of mortality.

MAC therapy needs to be lifelong unless cART-associated immune reconstitution occurs. Maintenance therapy may be ceased when the HIV viral load has been suppressed and the CD4+ T cell count is >100/μL after treatment for 12 months.(21)

If a histological diagnosis of mycobacterial infection is made and the results of cultures are unavailable, empirical therapy should cover both MAC and *M. tuberculosis* infections. In the circumstance of probable MAC infection, isoniazid 300 mg daily and pyridoxine 50 mg daily (to prevent peripheral neuropathy) should be added to the standard MAC regimen of rifabutin, ethambutol and clarithromycin until identification of the mycobacterial species is available. Isoniazid and pyridoxine should be ceased as soon as MAC has been identified. If *M. tuberculosis* is the most likely diagnosis, then therapy should be targeted at this infection, although clarithromycin should be added to increase the spectrum of activity to include MAC until identification of the organism is available. If *M. tuberculosis* may be the aetiological agent and samples of sputum are positive on acid-fast bacilli smear(22) or there is respiratory involvement, then respiratory isolation of the patient is required until organism identification is complete, or the sputa are negative on the acid-fast bacilli smear, or 2 weeks of effective therapy has been completed.

The side effects of commonly used antimycobacterial agents are listed in Table 1. Regular clinical review should be undertaken while on therapy with at least monthly clinical visits initially. Liver function tests and haematological parameters should be monitored. Ophthalmological complications are extremely rare with a lower dose of ethambutol (15 mg/kg/day) so regular ophthalmological review is not warranted. However, patients should be warned of potential ophthalmological side effects from ethambutol and to report these as soon as they occur.

Table 1. Side effects of commonly used antimycobacterial agents

Drug	Side effects
Amikacin	Nephrotoxicity, ototoxicity, neuromuscular blockade
Azithromycin	Diarrhoea, nausea, abdominal pain, vomiting, ototoxicity, abnormal liver function tests, central nervous system toxicity, leukopenia, erythema multiforme
Ciprofloxacin	Anorexia, nausea, diarrhoea, vomiting, abdominal pain, headache, restlessness, insomnia, psychosis, seizures, rash, arthralgia, intestinal nephritis, tendon rupture.
Clarithromycin	Diarrhoea, nausea, taste change, abdominal pain, headache, taste perversion, abnormal liver function tests, rash
Clofazimine	Skin pigmentation, anorexia, nausea, skin dryness, pruritus, abdominal pain, conjunctival irritation, retinal crystal deposition
Ethambutol	Optic neuritis (usually at higher dose i.e. 25 mg/kg/day), reduced visual acuity, restricted visual fields, scotomata, loss of colour discrimination, peripheral neuropathy, headache, rash, arthralgia, hyperuricaemia, gastrointestinal side effects

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Isoniazid	Peripheral neuropathy (prevent with co-administration of pyridoxine), allergy, lymphadenopathy and vasculitis, hepatitis (greater risk with increasing age, alcohol consumption and chronic liver disease), antinuclear antibody, blood dyscrasia, liver failure, other neurological manifestations (optic neuritis, encephalopathy, convulsions, psychosis) fever
Pyrazinamide	Arthralgia, hyperuricaemia, hepatitis, gastric irritation, photosensitivity, rash, fever, pruritus, thrombocytopenia, skin discolouration, sideroblastic anaemia
Rifabutin	Leukopenia, nausea, vomiting, diarrhoea, polyarthralgia, uveitis, rash, discolouration of urine, tears, sweat, saliva, stool and skin, neutropenia, febrile illness, hepatitis, haemolysis, myositis
Rifampicin	Anorexia, nausea, vomiting, diarrhoea, rash, febrile reaction, hepatitis, abnormal liver function tests, discolouration of urine, tears, sweat, saliva, stool and skin, haemolysis, febrile illness

Prognosis

The prognosis of untreated MAC infection therapy is poor. Combination antimicrobial therapy against MAC improves survival and cART provides an additional survival benefit.(23,24)

Prophylactic therapy for MAC infection

Primary prophylaxis

Primary prophylaxis against MAC infection has been shown to reduce the incidence of MAC disease in patients with advanced immunodeficiency (CD4+ T cell count <50/μL) and probably improves survival.(25-28) Three agents have been studied. Azithromycin (1200 mg orally once weekly) is the best tolerated agent with the fewest drug interactions. Clarithromycin (500 mg orally twice daily) or rifabutin (300 mg orally daily) are alternatives. Both of these medications interact with antiretroviral drugs and other agents and dose adjustment or alteration of the cART regimen may be required. Combination therapy with these agents is more efficacious but is associated with greater toxicity.(26)

Before instituting prophylaxis for MAC infection, it is important to exclude active MAC or *M. tuberculosis* infection. Blood specifically cultured for MAC, chest radiograph and full investigation of fevers, weight loss, night sweats, anaemia, abnormal liver function tests, hepatosplenomegaly, respiratory symptoms or unexplained lymphadenopathy are required. A stool culture for MAC should be undertaken in people with diarrhoea to exclude MAC enteritis before commencing prophylaxis. Prophylaxis with a single agent during active MAC or *M. tuberculosis* infection will lead to antimicrobial resistance.

Some authors have suggested that primary prophylaxis to prevent MAC infection is not required for those who commence cART with CD4+ T cell counts of <50 /μL, because the risk of disseminated MAC infection is low after the commencement of cART and patients can be followed closely for the signs of disseminated MAC infection(29-32)

In the event that MAC infection develops despite macrolide prophylaxis, antimicrobial sensitivity testing of MAC to macrolides is warranted, as macrolide resistance is detected in up to 30% of breakthrough isolates after clarithromycin prophylaxis(31) and 11% after azithromycin prophylaxis.(26)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Secondary prophylaxis

Secondary prophylaxis involves the life-long continuation of therapy for MAC infection unless cART-induced immune reconstitution occurs. As with other mycobacterial infections, a maintenance phase of treatment with two drugs is recommended. Rifabutin is most commonly eliminated, as it is associated with significant drug interactions and uveitis. A strategy of 12 months of MAC treatment followed by cessation of treatment if the CD4+ T cell count is >100/μL while on fully suppressive cART appears to be safe for people that achieve this degree of immune reconstitution.(21)

Discontinuing prophylaxis

Primary prophylaxis against MAC infection may be ceased when the CD4+ T cell count is >100/μL for 3 months in the setting of adequate viral suppression(33-35) and after 12 months of MAC treatment in those receiving maintenance treatment (secondary prophylaxis).(21)

Other non-tuberculous mycobacteria

The frequency of other NTM infections in people with HIV infection is lower than infections with MAC. In one retrospective series from Germany over 10 years (2006-2016), there were 87 patients with HIV infection out of a total of 297 (29%) patients with NTM infection.(36) Thirty eight per cent of the people with HIV infection had disseminated mycobacterial infection and 50% had pulmonary disease or colonisation. MAC was the most common organism (56%) with *M. xenopi*, *M. kansasii*, *M. fortuitum* being the next most common, representing 16 (18%), 5 (6%) and 4 (5%) cases, respectively. A similar frequency distribution was found in a study from Shanghai, China, where MAC was the most common NTM isolated from people with HIV infection (42% of isolates), followed by *M. gordonae* (28%) and *M. kansasii* (25%).(37) Another study from Guangxi, China confirmed a similar distribution in sputum samples, where 54% were MAC, 9% were *M. gordonae* and 8% were *M. kansasii*.(38) Other NTM species may also infect people with HIV infection.

Infections by NTM other than MAC may present as disseminated disease, pulmonary disease, lymphadenitis, arthritis, vertebral osteomyelitis, pleural and pericardial disease and other manifestations.(39) As described for MAC, other NTM may colonise the respiratory tract as well as cause invasive pulmonary disease. Severe CD4+ T cell deficiency is also a risk factor for invasive disease.(40)

Due to the relative rarity of infection with other NTM, the evidence base for treatment of non-MAC NTM disease in HIV infection is limited to case reports and is generally conducted in line with the treatment of NTM infections in the HIV-uninfected population. Clinicians should check for drug-drug interactions before prescribing therapy for NTM infection in people treated for HIV infection. An IRIS syndrome has been reported with non-MAC NTM infections.(41-44)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Gastrointestinal disease in people with HIV infection

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Last reviewed: November 2019

General approach to the assessment of gastrointestinal symptoms in HIV patients

Gastrointestinal symptoms and illnesses are extremely common in the general population and also in patients with human immunodeficiency virus (HIV) infection. When assessing them it is important to assess:-

1. Detailed history of presenting symptoms including: onset, severity, site/location, frequency and progression, triggering and relieving factors and associated features such as fevers and weight loss.
2. Degree of immunodeficiency: CD4+ T cell count – opportunistic infections such as cytomegalovirus (CMV) colitis occur in advanced immunodeficiency. Duration of CD4+ T cell depletion, as a long duration is likely to be associated with multiple immune defects. Additional immunosuppressive factors (e.g. corticosteroids, immunosuppressant therapy).
3. Use of primary and secondary prophylactic therapy for gastrointestinal tract pathogens: azithromycin for *Mycobacterium avium* complex (MAC), valganciclovir for CMV (including dose and adherence).
4. Risk behaviour and activities:
5. i) Injecting drug use – increased risk of hepatitis B virus (HBV) and hepatitis C virus (HCV) infection and bacterial sepsis.
6. ii) Sexual history, particularly for men who have sex with men (MSM) – risk of enteric pathogens and proctitis caused by sexually-transmitted pathogens.
6. iii) Recent travel – risk of parasitic infections, hepatitis A virus infection and enteric pathogens such as salmonella and campylobacter.
7. Past medical history and family history – previous endoscopy/colonoscopy, family history of inflammatory bowel disease and colorectal cancer.
8. Medications: prescribed (including antibiotics) and over-the-counter.
9. Previous abdominal surgeries – cholecystectomy, appendicectomy or other surgery.
10. Gynaecological history in women.

Common symptoms and signs of gastro-intestinal tract disease reported in people with HIV infection and the more common causes are presented in Table 1, along with a number of associated features and differential diagnoses that are particularly important to consider in patients with HIV infection.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Table 1. Common gastrointestinal symptoms and signs and causes to consider in people with HIV infection

Symptoms	Concerning associated features	Common causes	HIV-associated causes	Investigations to consider
Dysphagia/odynophagia	Weight loss Rapidly progressive; solids initially and liquids later Iron deficiency anaemia, gastrointestinal bleeding	Peptic stricture Eosinophilic oesophagitis Oesophageal webs and rings Achalasia and other oesophageal motility disorders Oesophageal cancer Food bolus	Oesophageal candidiasis Viral oesophagitis – CMV, HSV Oesophageal SCC (HPV-related)	Upper gastrointestinal endoscopy Barium swallow Mouth swab or gargle for fungal culture Swab of any oral ulcers for HSV and CMV
Diarrhoea	Blood or mucus in the stool Recent travel Recent antibiotics Large volume, watery diarrhoea Weight loss Prolonged symptoms Significant abdominal pain Fevers/rigors	Viral gastroenteritis Bacterial enterocolitis including campylobacter, salmonella and shigella <i>Clostridium difficile</i> colitis Parasite infections Coeliac disease Inflammatory bowel disease Irritable bowel syndrome	CMV colitis MAC enterocolitis Crypto-sporidiosis Micro-sporidiosis HIV protease inhibitors Lymphoma Kaposi's sarcoma HIV enteropathy	FBC, U+E, LFT, CRP Stool culture microscopy and multiplex PCR <i>Clostridium difficile</i> toxin Blood cultures – for MAC Colonoscopy and colonic biopsy CT scan of the abdomen-pelvis
Rectal bleeding	Weight loss Recent change in bowel habits Tenesmus Family history of colorectal cancer	Haemorrhoids Anal fissures Proctitis Colorectal tumours STIs, including chlamydia and gonorrhoea	Anal SCC (HPV-related)	Digital rectal examination Rectal swab for STI screen (including LGV) Anoscopy Sigmoidoscopy Colonoscopy
Abdominal pain	Weight loss Persistent diarrhoea Rectal bleeding Ascites	Gastroenteritis Inflammatory bowel disease Irritable bowel syndrome Appendicitis Diverticulitis Cholecystitis Pancreatitis Bowel obstruction	Opportunistic infections – CMV, MAC Neoplasms – lymphoma, Kaposi's sarcoma	CT scan of abdomen Upper abdominal ultrasound Endoscopy and colonoscopy
Jaundice	Fevers Weight loss Substance abuse Ascites Encephalopathy	Alcoholic hepatitis Viral hepatitis Choledocholithiasis Pancreatic cancer Haemolysis Medications Gilbert's syndrome Cirrhosis	Atazanavir therapy Lymphoma HIV-related cholangiopathy	LFTs, INR, LDH Conjugated and unconjugated bilirubin Ultrasound of biliary tree CT scan of abdomen MRCP ERCP

CMV: cytomegalovirus; CRP: C-reactive protein; CT: computerised tomographic; ERCP: endoscopic retrograde cholangiopancreatography; FBC: full blood count; HSV: herpes simplex virus; INR: international normalised ratio for prothrombin time; LFT: liver function test; LDH: lactate dehydrogenase; LGV: lymphogranuloma venereum; MAC: *Mycobacterium avium* complex; MRCP: magnetic retrograde cholangiopancreatography; U+E: urea and electrolytes

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Specific gastrointestinal disorders associated with HIV infection

The following section will discuss the diagnosis and management of a number of common bacterial, viral and parasitic gastrointestinal infections that may be seen in people with HIV infection, and also non-infectious diarrhoea. A number of important HIV-associated conditions are covered elsewhere in the website – Kaposi's sarcoma and HBV and HCV infections. Readers are referred to other texts for the management of common illnesses such as gastroesophageal reflux disease and the Australian Therapeutic Guidelines (1) and Sanford Guides (2) for specific treatment advice.

Dysphagia/ odynophagia

When assessing patients with dysphagia (difficulty swallowing with a sensation of food sticking), it is important to determine if their symptoms are due to an oropharyngeal or oesophageal cause. Patients with oropharyngeal dysphagia often have difficulty initiating a swallow, reporting a sensation that food gets stuck immediately on swallowing (usually localising/pointing to their neck) and may experience coughing, choking or nasal regurgitation during swallowing. Patients with oesophageal dysphagia usually report a sensation of food getting stuck soon after swallowing (they may localise/point to their neck or behind their sternum). Oesophageal dysphagia may be due to structural or motility disorders. A detailed history can give clues to the likely cause. The types of food that produce symptoms (solids, liquids or both), the changes over time (types of food at onset, intermittent or progressive nature) and associated symptoms (pain, heartburn, regurgitation, weight loss) should be ascertained. Previous interventions (surgery, radiotherapy), other diseases, such as atopy, asthma or eczema which are associated with eosinophilic oesophagitis, and other medications (tetracycline, bisphosphonates) may be relevant.

Oesophageal candidiasis is the most common cause of dysphagia in patients with HIV infection. Patients may also report odynophagia (pain on swallowing) and retrosternal discomfort. Most patients will have oropharyngeal candidiasis (oral thrush); however, its absence does not exclude the diagnosis. (3) An upper gastrointestinal endoscopy is generally not required for patients with HIV infection and oral candidiasis with oesophageal symptoms. Treatment consists of a loading dose of 200mg, then 100mg of oral fluconazole for 14 days. (4) Intravenous fluconazole can be administered to patients who are unable to tolerate oral therapy. For patients with a poor clinical response to oral fluconazole, an upper gastrointestinal endoscopy is necessary to exclude other diagnoses, such as CMV or HSV disease or oesophageal malignancy, and to obtain specimens to culture for fungal speciation and antifungal susceptibility testing. (5)

HSV and CMV disease should be considered in patients presenting with odynophagia as this is the predominant complaint in patients with this type of oesophagitis. HSV oesophagitis usually has a severe and abrupt onset of intense pain (reviewed in Lavery *et al.* (6)). CMV oesophagitis is more subacute and generally associated with weight loss. The absence of oral lesions (herpes labialis) does not exclude the diagnosis of HSV oesophagitis. An endoscopy and biopsy is required to confidently distinguish these two conditions. HSV oesophagitis responds to aciclovir 5 mg/kg intravenously every 8 hours followed by famciclovir 500mg twice a day or valaciclovir 1g twice a day, when oral therapy is possible, to complete a 10-day course. (7) Maintenance therapy is usually reserved for frequent recurrences.

Diarrhoea

Diarrhoea is common amongst people with HIV infection. The differential diagnosis is strongly influenced by the risk factors, duration of symptoms (acute versus chronic) and the degree of immunodeficiency. A detailed clinical history and physical examination is essential. Investigations should include stool culture

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

and microscopy and/or multiplex PCR. Additional investigations that may be required include mycobacterial blood cultures, endoscopy with biopsies and abdominal imaging with CT scan. Causes of acute and chronic diarrhoea that occur in patients without HIV infection should also be considered.

Enteric pathogens causing diarrhoea

Acute, infective diarrhoea is common in patients with HIV infection. Transmission may be food borne, waterborne, institutional or person-to-person via faecal-oral or sexual transmission. The patterns of infecting enteric pathogens vary based on patient and geographical epidemiology. In Australia, bacterial pathogens such as salmonella, shigella and campylobacter are common. *Shigella sonnei* is frequently sexually transmitted via the oro-faecal route with no history of overseas travel. Common viral infections such as norovirus and adenovirus are mostly self-limiting. A history of unprotected, receptive anal intercourse may suggest sexual transmission of organisms such as *Neisseria gonorrhoeae* or *Chlamydia trachomatis*. These organisms may cause anal discomfort and discharge. *Clostridium difficile* is most common after antibiotic usage. Parasitic infections are more common in returned travellers, although some parasites e.g. *Giardia lamblia* and *Strongyloides stercoralis* can be acquired in Australia (see Table 2).

Table 2. Common causes of infectious diarrhoea in patients with HIV infection in Australia – clinical presentation, diagnosis and management (8,9)

Infection	Clinical presentation	Diagnosis	Management	Comments
<i>Salmonella spp.</i>	Abrupt onset of watery diarrhoea, nausea, abdominal pain and fevers occurring 6-48 hours post-contact	Stool culture, microscopy and multiplex PCR Blood culture	IV ceftriaxone if bacteraemic, then oral azithromycin or ciprofloxacin for 5 to 7 days as guided by susceptibility testing	Patients may be bacteraemic without diarrhoea
<i>Shigella spp.</i>	Fever and watery diarrhoea (dysentery), with or without blood, usually, 1-7 days post-contact Tenesmus	Stool culture, microscopy and multiplex PCR Blood culture	Oral ciprofloxacin for 5 days if susceptible May need IV ceftriaxone for resistant isolates (10)	Strict rules for food handlers
<i>Campylobacter spp.</i>	Voluminous watery diarrhoea followed by proctocolitis with blood, mucous and tenesmus (usually 2-6 days post-contact)	Stool culture, microscopy and multiplex PCR Blood culture	Uncomplicated diarrhoea – oral azithromycin or ciprofloxacin for 3 days if symptoms persist. Resistant strains are emerging (11)	Patients may be bacteraemic without diarrhoea
<i>Clostridium difficile</i>	Diarrhoea, fever, abdominal pain Antibiotic exposure	<i>Clostridium difficile</i> toxin	Metronidazole 400 mg three times a day OR Oral vancomycin 125 mg four times a day for 10-14 days	Contact isolation in health services
<i>Norovirus</i>	Acute watery diarrhoea	Faecal multiplex PCR	Is usually self-limiting. No antiviral therapy available.	Contact isolation in health services

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

<i>Giardia lamblia</i>	Non-bloody, chronic diarrhoea occurring 1-3 weeks post-exposure associated with nausea, vomiting, abdominal pain, belching, bloating and flatus. Fevers are rare	Faeces microscopy to demonstrate cysts and trophozoites; erythrocytes are rare. Multiplex PCR	Tinidazole 2g as a single dose or oral metronidazole 2g daily for 3 days	
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Chronic infective diarrhoea caused by unusual organisms such as *Cryptosporidium parvum*, microsporidia, *Cyclospora cayetanensis* and *Cystoisospora belli* are now uncommon in resource-rich settings, although occupational exposure may occur. These are often associated with advanced immunodeficiency and patients present with profuse prolonged diarrhoea associated with anorexia, fatigue, weight loss and occasional fevers. Travel, animal exposure and occupational histories are helpful. Careful stool examination for ova, cysts and parasites should be undertaken and may require the addition of special stains such as modified acid-fast and auramine-rhodamine fluorescent stains. Some multiplex PCR assays will detect unusual organisms such as microsporidia and cryptosporidium. Although rare in Australia, *Mycobacterium avium* complex (MAC) infection should be considered in patients with advanced immunodeficiency and appropriate blood cultures obtained. Endoscopy with biopsies may be required, particularly for the diagnosis of CMV colitis.

Non-infectious diarrhoea

While antiretroviral therapy ART has clearly reduced the incidence of diarrhoea due to opportunistic infections in people with HIV infection, up to a quarter of patients receiving ART are estimated to experience four or more loose motions a day.⁽¹²⁾ Non-infectious diarrhoea may be associated with ART, or HIV-infection itself (HIV enteropathy). Protease inhibitors have the highest rates of diarrhoea (13.3%) when compared with nucleoside reverse transcriptase inhibitors (NRTIs) (10%, and 2% in non-nucleoside reverse transcriptase inhibitors (NNRTIs)).⁽¹³⁾ ART-associated diarrhoea has been postulated to be due to damage to the intestinal epithelial barrier and altered secretion of calcium-dependent chloride ions. HIV enteropathy is caused by viral infection of enterocytes leading to a loss of epithelial barrier and permeability, immune activation and autonomic dysfunction. ⁽¹²⁾

Dietary, non-pharmacological and pharmacological approaches should be attempted before switching ART from a successful regimen. Clinical trials in this area are limited. Proposed modifications include: reduction in caffeine, fat and lactose intake and an increase in fibre consumption. Psyllium husk and oat bran, as bulking agent, and probiotics or bovine serum-derived immunoglobulin to modulate and normalise enteric flora have been investigated. Pharmacological treatment includes adsorbents (e.g. bismuth), anti-motility agents (e.g. loperamide) and anti-secretory agents such as octreotide.^(12,13,14) Crofelemer, a novel dual inhibitor of cAMP-stimulated CFTR (cystic fibrosis transmembrane conductance regulator) chloride channel and CaCC (calcium-activated chloride channel) has shown promising results.⁽¹⁵⁾ While the only current indication for faecal microbiome transfer (FMT) is *Clostridium difficile* infection, ⁽¹⁶⁾ FMT may become a novel therapy for other indications in the future.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Ocular disease in patients with HIV infection

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Last reviewed: August 2019

Introduction

HIV infection and particularly HIV-induced immunodeficiency and its treatment may be complicated by a large number of ocular complications, especially opportunistic infections and cancers (Table 1). While ocular disease is encountered infrequently in HIV patients receiving antiretroviral therapy (ART), it is still an important consideration in HIV-infected patients who are not receiving ART or remain immunodeficient on ART. The occurrence and type of ocular disease can be predicted to a large degree by the CD4+ T cell count (Table 2). A fundal examination should be a routine part of the examination of HIV patients presenting with severe immunodeficiency. The management of eye disease should always be coordinated between an Ophthalmologist with experience in the ocular complications of HIV infection and a physician experienced in managing HIV-infected patients.

Table 1. Ophthalmic complications of HIV infection (1)

	Red flags	Infective	Neoplastic	Other	Investigations
Adnexae²	Blisters; Pain; Decrease in vision	Herpes zoster ophthalmicus Molluscum contagiosum Preseptal cellulitis	Kaposi's sarcoma Squamous cell carcinoma	Conjunctival microvasculopathy	Viral swab: HSV PCR Bacterial swab: MCS
Orbit	Pain; Redness; Swelling	Orbital cellulitis	Non-Hodgkin's lymphoma		Bacterial swab: MCS
Anterior segment	Pain; Decrease in vision	Viral keratitis (VZV, HSV) Bacterial keratitis (<i>S. aureus</i> ; <i>S. epidermis</i> , <i>P. aeruginosa</i>) Protozoan keratitis (microsporidia) Syphilis		Conjunctival microvasculopathy Allergic eye disease Vortex keratopathy Dry eye Disease Meibomian gland dysfunction Uveitis (HLA B27-related)	Viral swab: HSV, VZV PCR Bacterial swab: MCSSmear: wet prep for free living amoeba Tissue or fluid ³ : Amoeba PCR, Serum T. <i>pallidum</i> antibodies

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Posterior segment	Decrease in vision; Floaters	CMV retinitis VZV retinitis (PORN/ARN) HSV retinitis Toxoplasma retinitis Syphilis uveitis Pneumocystis choroiditis Cryptococcal choroiditis TB-related uveitis	Ocular CNS Non-Hodgkin's lymphoma	Retinal microvasculopathy Ischaemic maculopathy Immune recovery uveitis Drug induced uveitis (Rifabutin)	Detection of DNA in blood, vitreous fluid or tissue by PCR: CMV, VZV, HSV, Pneumocystis, Toxoplasma, <i>M. tuberculosis</i> Serology: Toxoplasma, <i>T. pallidum</i> , CMV antibodies; Cryptococcal antigen
Neuro-ophthalmic	Decrease in vision; Pain	Cerebral toxoplasmosis Cryptococcal meningitis Neuro-syphilis PML VZV encephalitis/radiculitis TB related neurological disorders	Ocular CNS Non-Hodgkin's lymphoma	Optic neuritis Optic atrophy Ocular motility disorders	Brain imaging: CT, MRI CSF examination: – Opening pressure, protein, glucose, culture (bacterial, fungal, mycobacterial) – DNA by PCR: HSV, VZV, CMV, JC virus, Mtb, <i>T. pallidum</i> , Toxoplasma – Serology: <i>T. pallidum</i> , CrAg

2) Eyebrow, eyelids and lacrimal apparatus

3) Investigations include an anterior chamber tap (in young patients) and /or vitreous tap with PCR to identify underlying pathogen.

Abbreviations:

MCS – microscopy, culture, sensitivity;

PCR – polymerase chain reaction;

PORN – progressive outer retinal necrosis;

ARN – acute retinal necrosis;

PML – Progressive multifocal leukoencephalopathy;

HSV – herpes simplex virus;

VZV – varicella zoster virus;

CMV – cytomegalovirus

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Table 2. Typical occurrence of ocular disease at different CD4+ T cell counts

CD4+ T cell count (cells/mm ³)	Ocular disease
250-500	Herpes Zoster Ophthalmicus TB
120-250	Lymphoma Kaposi's sarcoma
50-150	Pneumocystis Toxoplasmosis Microsporidiosis Varicella Zoster Virus retinitis
<50	Cytomegalovirus retinitis

HIV-associated disease of the anterior segment

HLA-B27 associated disease

HIV positive individuals can get severe anterior uveitis as part of a systemic HLA-B27 related illness or as isolated HLA-B27 related ocular disease. HLA-B27 related anterior uveitis can occur as part of a HLA-B27 related reactive disease triggered by gram negative bacterial gut infection or chlamydial genito-urinary infection.



Keratouveitis

Varicella Zoster Virus keratouveitis

Varicella Zoster Virus (VZV) keratouveitis is common in HIV-infected patients, with or without the typical dermatomal rash of Herpes Zoster Ophthalmicus (HZO). VZV is a dsDNA virus of the herpes group. Primary infection of VZV results in chickenpox (varicella). Reactivation of virus dormant in the sensory ganglion results in shingles (herpes zoster) of the innervated dermatome. Involvement of the ophthalmic branch of the trigeminal nerve (Cranial nerve Va) occurs in 25% of shingles cases and results in HZO (Figure 1). VZV infection may be more severe in the immunosuppressed. (2)

Figure 1. Right nasociliary nerve involvement in Herpes Zoster Ophthalmicus.

Source: Uveitis Department, Sydney Eye Hospital, with permission.

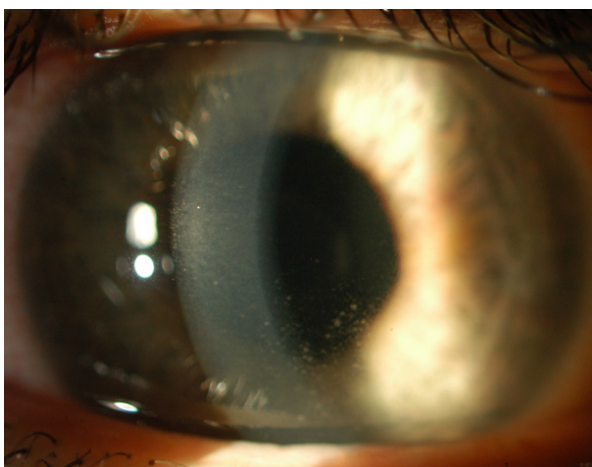
CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Clinical features of HZO include a viral prodrome, preherpetic neuralgia (mild intermittent tingling to severe constant electric pain), rash (papules, vesicles, pustules, scabs) predominantly within the one dermatome (Cranial nerve Va); Hutchinson's sign (cutaneous involvement of the tip of the nose, indicating nasociliary nerve involvement and increased likelihood of ocular involvement); it may be disseminated (involving multiple dermatomes) in immunocompromised patients. (3)

Once the cornea becomes involved there can be epithelial involvement, stromal nummular keratitis with anterior stromal granular deposits, necrotizing keratitis with stromal infiltrates, thinning, and even perforation. Disciform endotheliitis, Descemet's folds, anterior uveitis and Keratic Precipitates (KPs – an inflammatory cellular deposit seen on the corneal endothelium) can also occur (Figure 2). Neurotrophic changes can occur with corneal nerve damage causing persistent epithelial defects, thinning, and even perforation. Mucus plaques with linear grey elevations, loosely adherent to underlying diseased epithelium/ stroma can occur later on and be chronic. Laboratory investigations include obtaining a sample of vesicle fluid in viral transport media for VZV nucleic acid testing by PCR. Initial systemic treatment includes antivirals, which should be commenced as soon as the rash appears (Table 3).

Table 3. Directed treatment for anterior segment opportunistic infections

Condition	Treatment	Duration
VZV keratouveitis	Valaciclovir 1g orally q8h OR Famciclovir 500mg orally q8h OR Aciclovir 800mg orally 5 times daily OR Aciclovir 10mg/kg/day intravenously	7 to 14 days
HSV keratouveitis	Valaciclovir 1g orally q12h OR Famciclovir 500mg orally q12h OR Aciclovir 800mg orally 3 times daily OR Aciclovir 10mg/kg/day intravenously	7 to 10 days

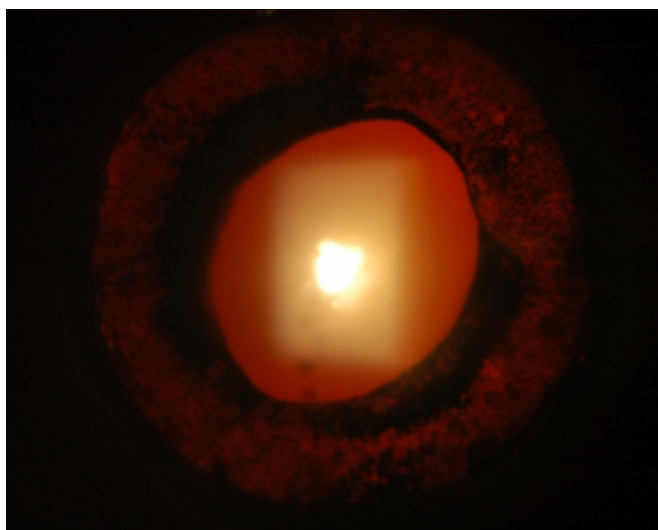


Post-herpetic neuralgia may cause depression (sometimes resulting in suicide). Treatments include amitriptyline and gabapentin. Viral reactivation, replication, and retrograde migration to the cornea results in recurrent keratitis, which may be epithelial, stromal, endothelial (discoid), or neurotrophic. Potential intraocular involvement includes anterior uveitis and retinitis. Additionally, the resultant neurotrophic cornea is vulnerable to bacterial and fungal keratitis. Depending on which layer of the eye is affected will dictate further localized treatment. Treatment options can include topical lubricants, topical acyclovir gel 5x per day and systemic antiviral +/- topical steroids, as indicated for anterior chamber inflammation. People with HIV infection often require ongoing suppressive antiviral therapy.

Figure 2. Anterior uveitis with keratic precipitates on the endothelium of the right eye.

Source: Uveitis Department Sydney Eye Hospital, with permission.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		



Herpes simplex virus keratouveitis

Herpes simplex virus (HSV) keratouveitis has equal prevalence to the general population in people with HIV infection. HSV is a dsDNA virus with two serotypes. The most common ocular manifestation of HSV infection is a self-limiting blepharoconjunctivitis, characterized by periorbital vesicular rash, follicular conjunctivitis, and preauricular lymphadenopathy. Following this, the virus ascends the sensory nerve axon and, similar to VZV, resides in the trigeminal ganglion from where viral reactivation, replication, and retrograde migration may occur. In the setting of HIV infection, HSV disease of the eye tends to be limbal, more

severe, with more recurrences, and dendrites may be larger and less defined compared with HIV seronegative subjects (Figure 3). HIV-infected individuals often require ongoing suppressive antiviral therapy.

Figure 3. Iris transillumination defects and irregular pupil secondary to HSV infection.

Source: Uveitis Department Sydney Eye Hospital, with permission.

Microsporidiosis

Microsporidia are protozoan obligate intracellular parasites, of which four genera may cause the human disease microsporidiosis. This is usually seen in the immunosuppressed patients (notably in AIDS) where it may present as chronic diarrhoea, respiratory infection, or keratoconjunctivitis. Microsporidial keratouveitis presents with bilateral irritation and photophobia, punctate keratopathy, often with a follicular conjunctivitis and/or an anterior uveitis. Microsporidia are protozoan obligate intracellular parasites, of which four genera may cause the human disease microsporidiosis. It may present as chronic diarrhea or respiratory infection as well as keratoconjunctivitis.

Anterior uveitis

Uveitis may also be caused by concurrent therapy for non-ocular infections, such as Rifabutin for *Mycobacterium avium* complex infection and Cidofovir for ganciclovir-resistant non-ocular CMV infection, as well as by tuberculosis (TB) and syphilis. Ocular syphilis may present during all stages of disease (primary, secondary and tertiary stages). (4) Anterior uveitis is the commonest ocular feature of both secondary and tertiary syphilis. It can be granulomatous or non-granulomatous with variable severity and occasionally roseolae (vascular fronds on the iris) are seen. Iris atrophy and nodules on the iris / iridocorneal angle can occur in tertiary syphilitic uveitis. It is treated (in conjunction with an infectious diseases physician) with systemic antibiotics and topical steroids for the ocular disease. (5)

Ocular TB can be difficult to diagnose due to its myriad manifestations and the frequent absence of any systemic or radiological evidence of respiratory disease. Clinical features may include lid abscess, conjunctival infiltration/nodules, phlyctenulosis, scleritis (usually anterior necrotizing), interstitial keratitis, granulomatous anterior uveitis with mutton fat Keratic Precipitates (KPs), iris granulomata, Posterior Synechiae (PS) and non-granulomatous anterior uveitis. Ocular TB occurs as a manifestation of disseminated TB in patients with advanced HIV infection and is seen mostly in sub Saharan Africa.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

HIV-associated disease of the posterior segment

CMV retinitis

In the 'pre-HAART era', CMV retinitis affected up to 40% of people with AIDS, but usually only when CD4+ T cell counts were <50/mL (Figure 4a). Since the advent of combination antiretroviral therapy (ART), there has been a dramatic reduction in the incidence of CMV retinitis. Clinical features include floaters and decreased visual acuity and/or field loss. Vitritis is usually mild or absent. CMV retinitis may be either 1) haemorrhagic (associated with necrosis), with loss of fundal details ('pizza pie' appearance – Figure 4b), 2) granular, which is relatively indolent with minimal haemorrhage and vascular sheathing, 3) perivascular, seen as 'frosted branch angiitis' which spreads along the course of the retinal vessels. It may be asymptomatic and consequently, regular screening should be performed in patients at risk of CMV infection. Complications include retinal detachment (up to 30% of patients), retinal atrophy, and optic nerve disease (5%).⁽²⁾

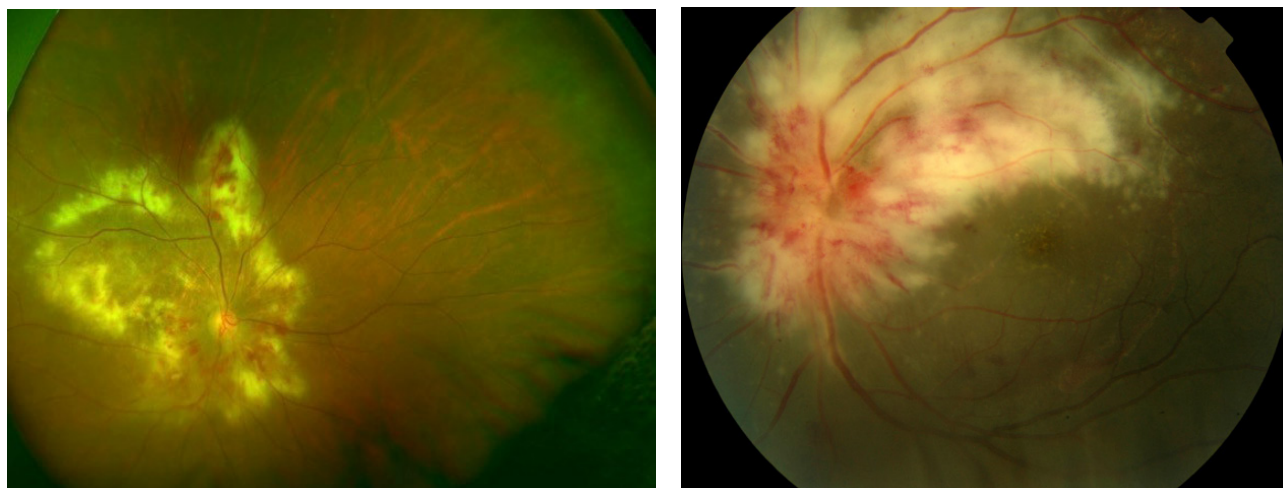
CMV retinitis is usually treated with systemic antivirals (Table 4). Intravitreal foscarnet or ganciclovir is often used, particularly when the macula and optic disc are involved. ART is an essential component of overall management; however timing of ART should be discussed between an HIV physician and ophthalmologist. Anti-CMV secondary prophylaxis is continued until the CD4+ T cell count is >100/mL for three to six months. If stopped prior to this time, the patient is at increased risk of immune reconstitution uveitis. Lifelong maintenance treatment is recommended for all patients without immune recovery.

Table 4. Systemic antiviral therapy for CMV and HSV ocular disease (6)

Condition	Treatment	Duration
CMV infection – systemic therapy	Valganciclovir 900mg orally q12h loading then 450mg BD OR Ganciclovir 5mg/kg q12h intravenous OR Foscarnet 90mg/kg q12h intravenous OR Cidofovir 5mg/kg weekly	14 to 21 days until required 14-21 days 14-21 days 14 days
CMV retinitis	In addition to above: <i>Management by an ophthalmologist:</i> <i>Ganciclovir 4mg/0.1ml per injection, 1-4 doses</i>	Initial, then as needed
Herpetic retinitis	<i>Management by an ophthalmologist:</i> Intravitreal foscarnet 2.4mg/0.1mL WITH aciclovir IV dose 5-10mg/kg/d WITH systemic steroid 1mg/kg then acyclovir orally PO 400–800mg 5x/day OR valaciclovir 2g q8h then valaciclovir 1g q8h then valaciclovir 500mg q8h	Initial 2 weeks tapering steroid dose 6 weeks 10 days 14 days until required

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Figure 4a. Optos colour fundus image of the right eye of a patient with CMV retinitis with newly diagnosed HIV infection and a CD4+ T cell count of 30/mL.



Source: Uveitis Department Sydney Eye Hospital, used with permission.

Herpetic viral uveitis acute retinal necrosis

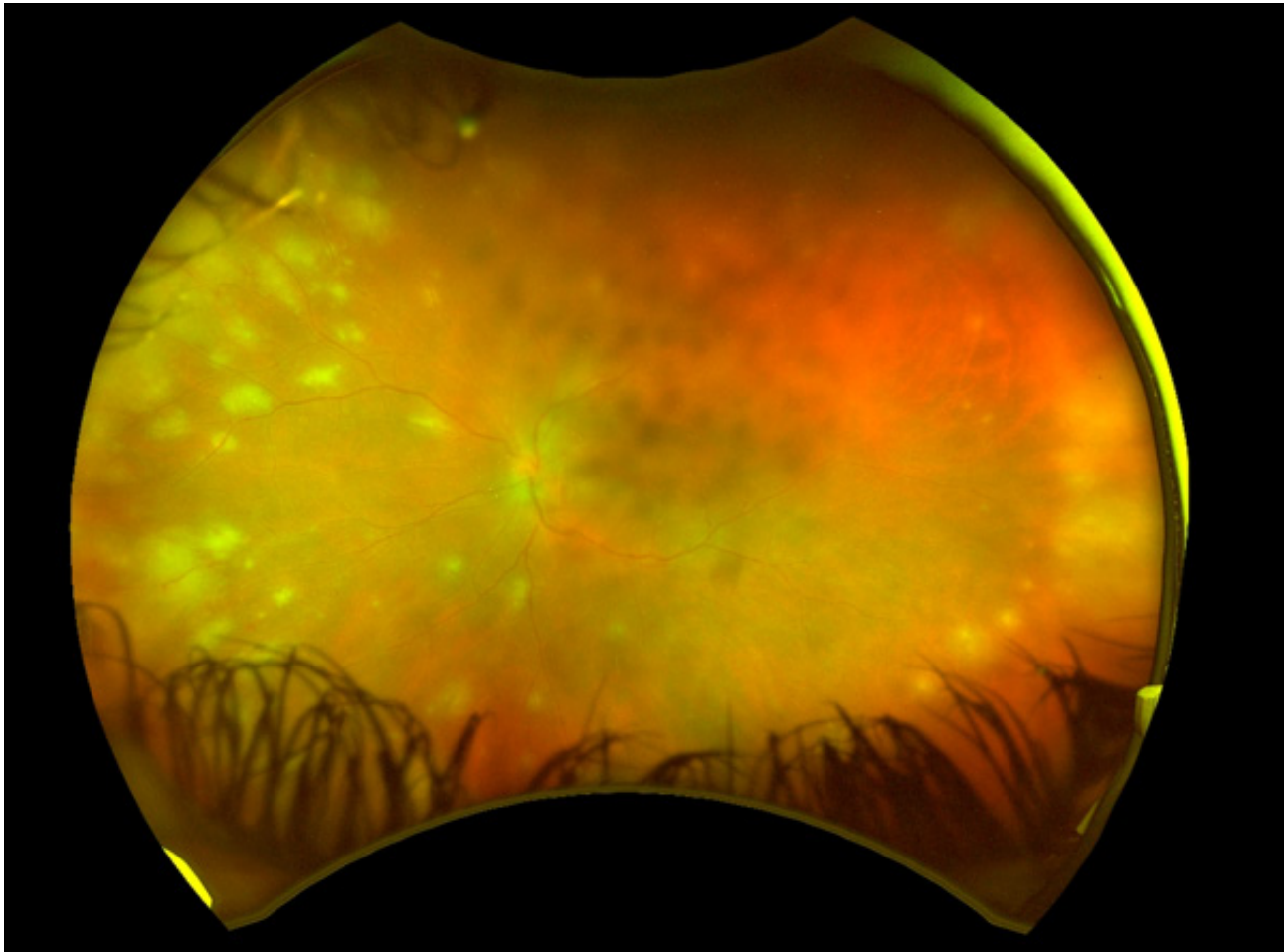
This rare syndrome of acute retinal necrosis is caused by VZV, HSV-1 or HSV-2 infection (Table 5). It may occur in the both the immunocompromised as well as healthy individuals of any age (Figure 5 and 6). Clinical findings include either unilateral or bilateral decrease in visual acuity, floaters and discomfort. (7) It is predominantly a peripheral disease comprising occlusive arteritis, full-thickness peripheral necrotizing retinitis (well demarcated, spread circumferentially), marked vitritis and anterior chamber activity. Complications include retinal detachment (in up to 75%; rhegmatogenous or tractional) and ischaemic optic neuropathy. Second eye involvement occurs in around 30% and may occur simultaneously or up to several years later.

Figure 5. Optos widefield colour fundus image of the left eye of a patient with HSV retinitis

Source: Uveitis Department Sydney Eye Hospital, used with permission.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Figure 6. Optos widefield colour fundus image of the left eye of a patient with VZV retinitis highlighting a large amount of vitritis



Source: Uveitis Department, Sydney Eye Hospital, with permission.

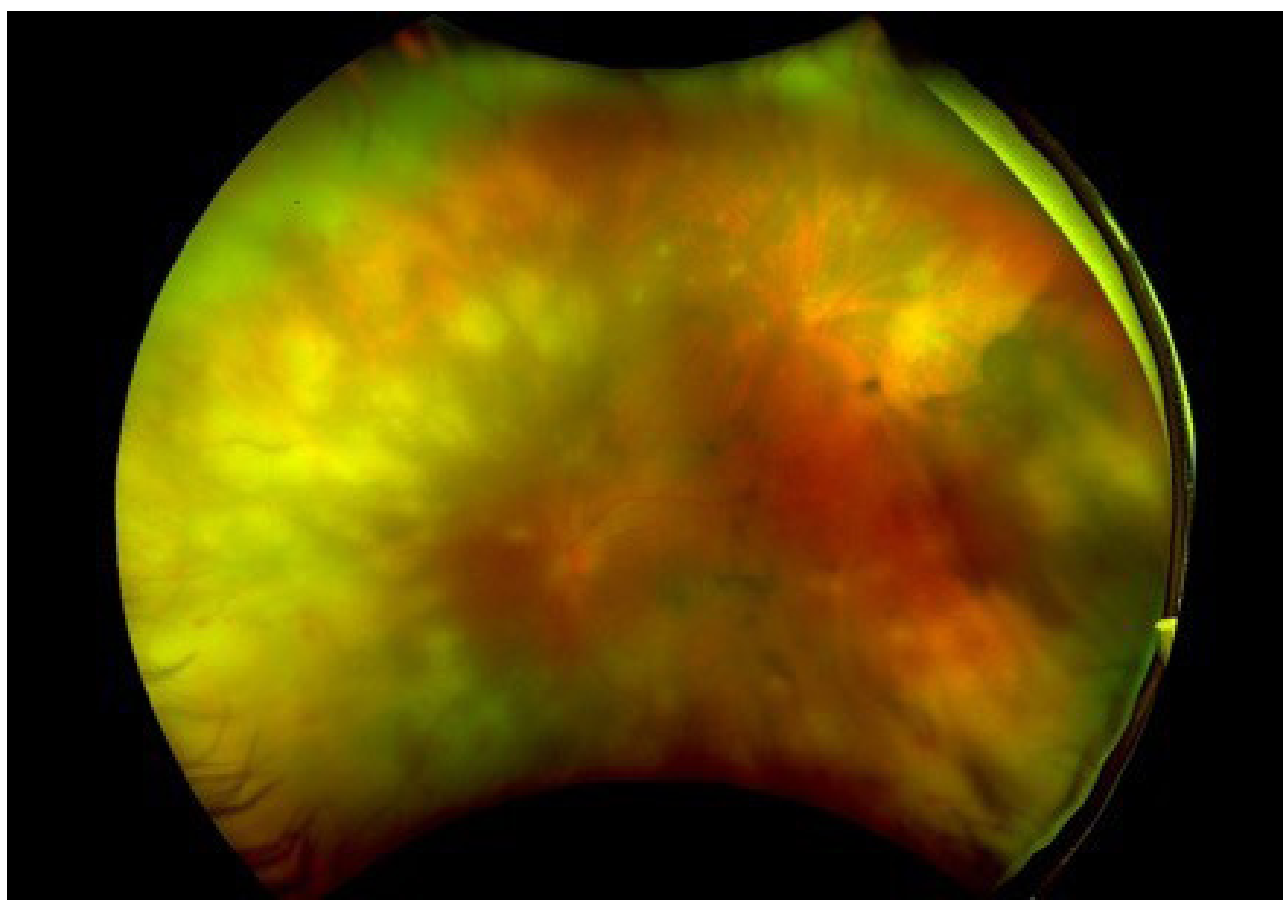
All patients with clinically suspected herpetic retinitis are treated with intravitreal foscarnet 2.4mg/0.1mL as initial treatment, then a combination of antivirals and systemic corticosteroids to treat the inflammation (Table 4). Retinal detachment repair is challenging due to the necrotic retina and number of breaks; vitrectomy with silicone oil injection is usually needed.

Progressive outer retinal necrosis

Progressive outer retinal necrosis (PORN) is a very rare devastating necrotizing retinitis caused by VZV infection in advanced HIV infection (usually with CD4+ T-cell counts <50/mL) (Table 5). Clinical findings include bilateral, painless, rapid decrease in visual acuity. Retinal examination reveals rapidly coalescing white areas of outer retinal necrosis (often central as well as peripheral) but with minimal vasculitis, retinitis, or vitritis (Figure 7). Treatment is similar to above.⁽⁸⁾

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Figure 7. Colour fundus photo of the left eye showing progressive outer retinal necrosis



Source: Uveitis Department Sydney Eye Hospital, with permission.

Table 5. Diagnostic criteria for ARN, PORN and CMV retinitis (1)

	ARN	PORN	CMV retinitis
Appearance	One or more foci of full thickness retinal necrosis	Multiple foci of deep retinal opacification which may be confluent	Creamy 'brush-fire' (along vessels) retinitis + haemorrhage and hard exudate ('Pizza fundus') +/- Papillitis
Location	Peripheral retina (usually adjacent outside arcades)	Peripheral retina Macula involvement	Begins anywhere in the retina
Progression	Rapid but usually responds to treatment	Extremely rapid	Slow; 1 Disc Diameter every 3 weeks, painless
Direction	Circumferential	No consistent direction	No consistent direction
Vessels	Occlusive vasculopathy (arterial)	No vascular inflammation	Occlusive periphlebitis à sheathing (frosted branch angiitis)
Inflammation	Prominent anterior chamber and vitreous inflammation	Minimal or none	Minimal
Suggestive features	Optic neuropathy / atrophy Scleritis Pain	Perivenular clearing of retinal opacification	Haemorrhage, which leaves behind thin fibroglial scar

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Syphilis

Syphilis affecting the eye may be unilateral or bilateral, unifocal or multifocal and cause numerous types of ocular inflammation (Table 6), including retinitis, chorioretinitis, yellow plaque-like lesions at the level of the Retinal Pigment Epithelium (RPE) (Figure 8a,8b,8c) with overlying vitritis and serous retinal detachment and optic peri-neuritis (Figure 9). Resolution of the lesions results in a pigmentary retinopathy. Serum should be tested for antibodies to *Treponema pallidum* as evidence of current or previous *T. pallidum* infection and for 'non-treponemal antibodies' (RPR, VDRL) to assess disease stage or treatment response. Management of syphilitic eye disease should be undertaken in conjunction with an infectious disease or sexual health physician as treatment requires high-dose penicillin, with an extended regimen for late latent and tertiary syphilis. Spirochete death may transiently worsen inflammation (Jarisch-Herxheimer or J-H reaction). Systemic steroids may also be used to treat the paradoxical J-H reaction and the intraocular and/or optic nerve inflammatory response.(9)

Table 6. Ophthalmic complications of syphilis (1)

Anterior segment	Conjunctival chancre Pupillary conjunctivitis Episcleritis scleritis Interstitial Keratitis Anterior uveitis
Posterior segment	Multi-/ unifocal choroiditis/ chorioretinitis Neuroretinitis Retinal vasculitis
Neuro-ophthalmic	Argyll Robertson Pupils Papilloedema Retrobulbar neuritis optic peri-neuritis Ocular motility disorders Visual Field defects

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		



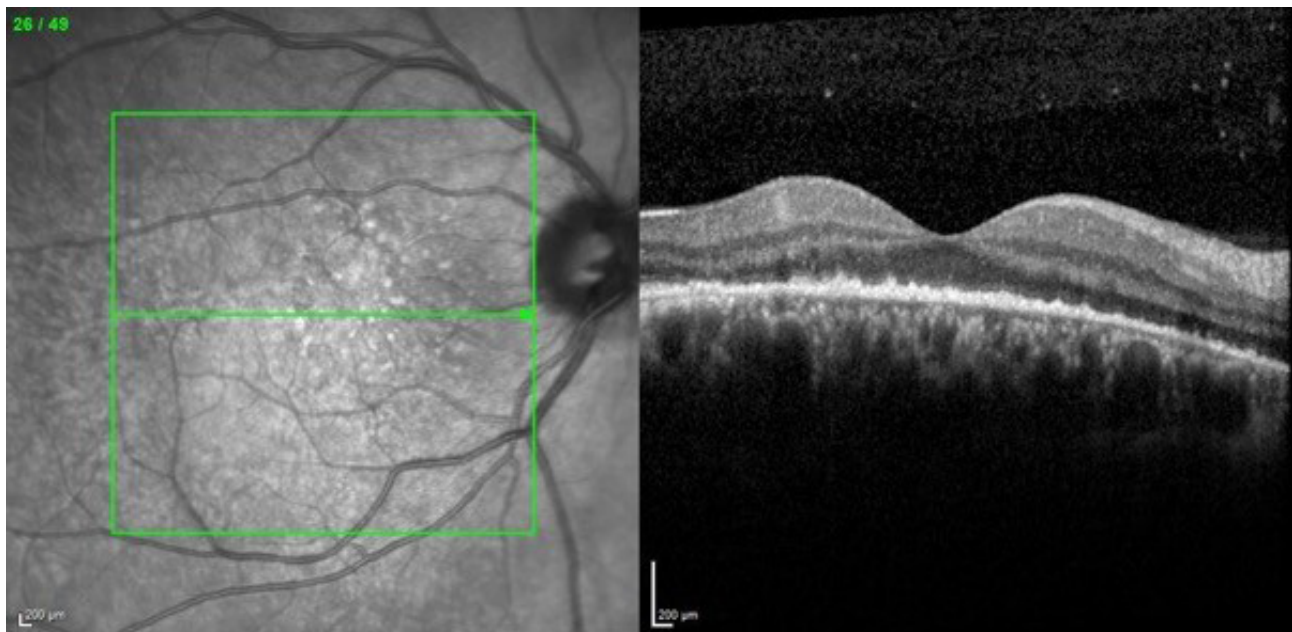
Figure 8a. Acute syphilitic posterior placoid chorioretinitis (ASPPC) of the right eye in a newly diagnosed patient with HIV infection



Figure 8b. ASPPC in the same patient in the right eye on fundal autofluorescence

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Figure 8c. OCT image in the same patient highlighting the hyperreflective nodularity of the choroid-retinal pigment epithelium (RPE) complex with focal disruption of the overlying photoreceptor inner-outer segment junction in the areas seen on the colour and autofluorescence image. Changes along the RPE improved after antibiotic treatment.



Source: Uveitis Department Sydney Eye Hospital, with permission.

Figure 9. Colour fundus photo of the left eye highlighting perioptic neuritis secondary to syphilis infection.



Source: Uveitis Department Sydney Eye Hospital, with permission.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Tuberculosis

Tuberculosis and HIV infection are common co-infections in sub-Saharan Africa and other parts of the developing world but are uncommon in the developed world unless there are additional risk factors for TB. The ocular manifestations of TB can be protean and depend on the exact pattern of systemic *Mycobacterium tuberculosis* infection. Posterior segment involvement by TB can include vitritis, occlusive retinal vasculitis (periphlebitis, ischaemia, neovascularization and haemorrhage), macula oedema, choroidal granulomata (usually multifocal around the posterior pole), serpiginous choroidopathy and optic neuropathy. Investigations for systemic TB should be performed, although ocular TB may occur without evidence of active, infectious extra-ocular disease (ie sputum cultures, chest X-ray and whole blood interferon gamma release assay or tuberculin skin test). While PCR testing and culture of aqueous or vitreous fluid may be attempted, they are of low yield and the diagnosis is usually made on clinical grounds. Treatment is with a standard four drug regimen +/- localised treatment of disease complications. Visual acuity should be checked before starting treatment with ethambutol and the patient advised to report any disturbance of visual acuity, colour vision or visual fields.

Toxoplasma retinochoroiditis

Ocular infections by *Toxoplasma gondii* are decreasing in frequency due to the use of ART and the anti-toxoplasma efficacy of pneumocystis pneumonia prophylaxis. However, when it does occur, ocular toxoplasmosis in patients with HIV infection is more severe than in HIV seronegative subjects and often multifocal (even bilateral), associated with moderate/severe anterior uveitis and vitritis, and commonly associated with neuro-toxoplasmosis. In contrast to immunocompetent individuals, it always requires treatment. Corticosteroids, if used, should be used extremely cautiously.



Ocular toxoplasmosis may include anterior uveitis (often with high intraocular pressure and Keratic Precipitates), vitritis (may have 'vitreous precipitates' on the posterior surface of a posterior vitreous detachment), retinitis and retinal vasculitis (periphlebitis). Other presentations include: scleritis, punctate outer retinitis (with quiet vitreous), large lesions, endophthalmitis-like, neuroretinitis, serous retinal detachments, pigmentary retinopathy. HIV-positive individuals may have life-

threatening disease, including encephalitis, intracerebral cysts, hepatitis and myocarditis. (10) Toxoplasma retinitis appears as a white, fluffy circumscribed area of retinitis when active (Figure 10) and becomes pigmented as it heals to form an atrophic scar. Active satellite lesions often develop adjacent to old scars.

Figure 10. Fundal image showing focus of toxoplasmic retinitis and associated retinal vasculitis in the right eye.

Source: Uveitis Department Sydney Eye Hospital, with permission.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Toxoplasma retinochoroiditis is essentially a clinical diagnosis. Positive serological tests must be interpreted with caution as the majority of the adult population has anti-Toxoplasma IgG antibodies from previous exposure. Although IgM antibodies are suggestive of recently acquired infection, there may be IgM cross reactivity and persistence. Negative serology in undiluted serum makes the diagnosis unlikely. Detection of Toxoplasma DNA by PCR in intraocular fluids can be very useful diagnostically. Systemic treatment varies depending on severity of HIV associated immunosuppression. The mainstay of treatment is pyrimethamine with sulfadiazine, clindamycin or atovaquone. Trimethoprim/sulfamethoxazole is an alternate agent. Steroids should be used very cautiously in HIV / immunosuppressed individuals.

Other infections and tumours

Pneumocystis jirovecii choroiditis

This is now uncommon, as a result of the use of ART or systemic prophylactic therapy to prevent Toxoplasma infection. The choroiditis is typically bilateral, comprising yellow choroidal patches of 1/4 to 2-disc diameters in size around the posterior pole, with minimal vitritis. It is often asymptomatic. Treatment is with trimethoprim/sulfamethoxazole, clindamycin/primaquine or pentamidine.

Cryptococcus choroiditis

This rare condition is usually associated with cryptococcal meningitis and may be associated with an optic neuropathy or papilloedema. It is characterized by multifocal off-white choroidal lesions, occasionally with a retinitis or endophthalmitis. Treatment is as for cryptococcal meningitis with induction therapy using an antifungal agent, such as amphotericin, followed by consolidation with fluconazole.

HIV retinopathy

HIV microvasculopathy is seen most frequently in HIV patients who are ART-naïve and with high HIV viral loads. HIV targets retinal vascular endothelium resulting in microvascular abnormalities such as microaneurysms, intraretinal microvascular abnormalities and most characteristically cotton wool spots. These are infarcts within the superficial retinal capillary plexus that result in stasis of axoplasmic flow in axons in the retinal nerve fibre layer that swell and become opaque and visible. They resolve over 6-8 weeks with return of normal axon function. Rarely, patients affected by HIV microvasculopathy can develop significant retinal ischaemia, which can result in vision loss.

Sometimes it can be difficult clinically to differentiate early CMV retinitis from cotton wool spots. Serial observation over an interval of 4-6 weeks will resolve this uncertainty. CMV lesions will enlarge, while cotton wool spots will either remain unchanged or begin to resolve. Imaging studies can be valuable at determining this.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Opportunistic infections acquired in localised geographical regions of the world

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Last reviewed: November 2019

Introduction

There are number of lesser-known opportunistic infections presenting in people with HIV infection that may be acquired in localised geographical regions of the world (Table 1). Disease caused by these infections may occur at different stages of HIV disease, ranging from early stages of HIV infection to more advanced stages of immunodeficiency. They may be recently acquired following travel or reactivated following long-term latency in immigrants or travellers. It is important for Australian clinicians to be aware of these conditions when treating patients from different regions of the world, or when providing pre-travel health advice for patients with HIV infection. Travel is increasingly common amongst HIV-infected people. (1-4)

Table 1: Opportunistic infections caused by organisms from different geographic regions of the world.

	Disease	Causative organism	Typical geographic region
Endemic fungal infections	Talaromycosis	<i>Talaromyces marneffe</i>	Southeast Asia, Hong Kong, north-east India and southern parts of China
	Histoplasmosis	<i>Histoplasma capsulatum</i>	Central eastern USA, and Latin America
	Coccidioidomycosis	<i>Coccidioides immitis</i>	Geographically restricted arid and semi-arid areas in the Americas
Endemic parasitic infections	Leishmaniasis	<i>Leishmania</i> spp. (numerous)	South and Central America, Africa, Asia and southern Europe
	Chagas disease	<i>Trypanosoma cruzi</i>	Rural areas of Mexico, Central America and South America
	Malaria	<i>Plasmodium falciparum</i> , <i>Plasmodium vivax</i> , <i>Plasmodium ovale</i> , <i>Plasmodium malaria</i> and <i>Plasmodium knowlesi</i>	Widespread in tropical and subtropical regions globally
Other opportunistic infections	Buruli ulcer	<i>Mycobacterium ulcerans</i>	West and central Africa, Asia, South America, the western Pacific and Australasia

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Endemic fungal infections

The incidence of systemic fungal infections in people with HIV infection in high-income countries has decreased over time with improved testing for HIV infection, earlier diagnosis and the availability of antiretroviral therapy (ART) (5). While systemic infections with *Cryptococcus neoformans* and *Pneumocystis jirovecii* are well-recognised opportunistic infections in people with HIV infection, other endemic fungi are also important pathogens in different geographic and epidemiological contexts.

Talaromycosis (formerly Penicilliosis)

Talaromycosis (formerly *Penicilliosis*), is a life-threatening mycosis caused by the fungus *Talaromyces marneffe* (formerly *Penicillium marneffe*). This systemic mycosis is endemic in Southeast Asia, Hong Kong, north-east India and the southern parts of China. (5, 6) While initially thought to be a rare human pathogen, (6) it has increasingly been recognised as a major cause of HIV-associated death in areas such as Thailand, Myanmar, Hong Kong and Vietnam. (6-9) Infection is thought to occur via inhalation (similar to other systemic opportunistic mycoses), (10) although delayed presentations (in keeping with latency and subsequent disease reactivation) have been described. (11) The bamboo rat is the only non-human host frequently found to have a high prevalence of infection. Isolates from bamboo rats have been found to be closely related by genotype to those that cause human disease, (12) although their role as a potential disease vector is not clear. A recent case-control study from Vietnam identified exposure to tropical plants and to farm animals as risk factors for infection. (13) Similarly, patients living in or travelling to highland regions in Southern Vietnam were at increased risk. The incubation period is estimated to be 1 to 3 weeks in acute disease, although disease reactivation can occur years after exposure. (5)

Clinical Presentation

Most episodes of *Talaromycosis* occur in patients with CD4+ T cell counts <100/μL (5, 10). The clinical presentation is typically subacute and may be nonspecific with fever, weight loss, cough, hepatosplenomegaly and lymphadenopathy. However, perhaps the most distinctive clinical feature that may hint at the diagnosis is the presence of characteristic papulonecrotic skin lesions, which are present in 60-70% of patients. (5) These lesions often have central necrotic umbilication and may resemble molluscum contagiosum. They are usually distributed on the upper parts of the body (face, upper extremities and trunk). Umbilicated papules may also be present on the oral mucosa in disseminated disease. (10) Diagnosis can be more challenging when skin lesions are not present.

Laboratory findings are non-specific and may include anaemia, thrombocytopenia, and elevated liver enzymes. (8, 9) Reported mortality rates vary from around 10-30% in treated patients, depending on the context, time of diagnosis, and access to ART. (6, 14-16) Immune reconstitution inflammatory syndrome (IRIS) reactions have been reported in patients starting ART (as 'unmasking' IRIS). (5)

Diagnosis

Diagnosis is made by fungal culture or histopathologic examination of body fluid or tissue from a normally sterile site. Microscopy may reveal yeast-like organisms in smears from skin lesions, biopsy specimens, blood cultures or bone marrow aspirates. Culture can be slow and polymerase chain reaction (PCR)-based assays are currently not sufficiently sensitive for clinical use. (5) The galactomannan assay may be a useful diagnostic tool in some settings, particularly in patients with fungemia. (17) Serological assays have shown some promise, (18) but are not widely used in clinical practice.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Management

Treatment of *Talaromycosis* is usually specialised and therapy depends on the severity of the disease. As HIV-infected patients with *Talaromycosis* usually have advanced immunodeficiency, initiation of ART is an important consideration. There are no data to guide the optimal timing of ART initiation (with regards to the risk of an IRIS). However, extrapolating from recommendations for other opportunistic infections such as tuberculosis, early initiation of ART is advisable for patients with very low CD4+ T cell counts ($\leq 50/\mu\text{L}$), while initiation may be delayed for 2 weeks where the CD4+ T cell count is $>50/\mu\text{L}$. (19) Amphotericin B and itraconazole are effective drug therapy for *Talaromycosis* but fluconazole is not. In a recent randomised controlled trial in Vietnam, Amphotericin B deoxycholate (0.7 to 1.0 mg per kg for 14 days) was found to be superior to itraconazole (600mg for 3 days followed by 400mg per day for 11 days) as initial induction therapy with regards to 6-month mortality and clinical response (20). Induction therapy is usually followed by maintenance therapy with itraconazole 400mg daily for 10 weeks, and then secondary prophylaxis with itraconazole 200mg daily until CD4+ T cell counts are $>100/\mu\text{L}$ for at least 6 months. (5, 19) Primary prophylaxis with itraconazole 200mg daily may be considered for patients with CD4+ T cell counts $<200/\mu\text{L}$ who reside in endemic areas (21); however, the strategy has not been widely adopted. Liposomal amphotericin B and Voriconazole are effective alternative drugs but are not widely available in many endemic settings.

Histoplasmosis

Histoplasmosis is caused by infection with the thermally dimorphic fungus *Histoplasma capsulatum*. Although rarely seen in Australia, it remains an important HIV-associated opportunistic infection in other parts of the world. The mould form has a wide distribution, especially in rich, moist soils containing bird droppings or bat guano. (22) While widely distributed, the majority of cases occur in central-eastern USA and Latin America. (5) The usual route of acquisition is inhalation from contaminated environments when soil disruption aerosolises microconidia or mycelial fragments.

Clinical presentation

In immunocompetent adults, infection is either asymptomatic or takes the form of a self-limiting flu-like illness. In advanced HIV infection, however (typically when CD4+ T cell counts are $<150/\mu\text{L}$), *histoplasmosis* presents as a disseminated disease with fever, fatigue and weight loss. (23) All organs can be involved, and symptoms can be nonspecific. Diffuse radiological infiltrates, often with a miliary reticulonodular pattern, may be seen on chest imaging. Abdominal symptoms of pain, diarrhoea and gastrointestinal bleeding, associated with colonic ulceration, may occur. Laboratory test findings may be nonspecific and include elevated lactate dehydrogenase, liver enzymes and ferritin. (5) As with *Talaromycosis*, skin lesions may occur and onset may vary from a septic shock-like syndrome to a subacute presentation occurring over months. A history of potential environmental exposure, such as exposure to bat guano in caves, can sometimes provide a diagnostic clue when taking a patient history. (24) IRIS-type presentations have also been described. (25)

Diagnosis

Diagnosis can be made on microscopy (with special staining when the diagnosis is suspected) and culture of normally sterile tissue or body fluids. These may include blood, biopsy specimens or bone marrow aspirates. Laboratory precautions should be taken, and the laboratory informed in advance when the diagnosis is suspected. Urine antigen testing is reportedly a sensitive test for histoplasmosis, (26) and may be accessible in Australia as a 'send-away' test to the USA. (24) Acute and convalescent serology may also be performed, but may not be as useful in the context of HIV infection due to impaired antibody responses. (27)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Management

Treatment involves an acute phase of induction therapy, followed by long-term maintenance therapy. In a randomised controlled trial, (28) liposomal amphotericin B (3mg/kg daily) was more effective than standard IV amphotericin B deoxycholate (0.7 mg/kg daily). For moderate to severe cases, treatment with intravenous liposomal amphotericin B is recommended for 2 weeks or until clinical improvement. This is followed by treatment with oral itraconazole 200mg tds, and then 200mg bd for ≥ 12 months. (19) Non-severe cases may be treated with itraconazole alone. Consideration should be given to potential drug interactions with antiretroviral drugs and therapeutic drug monitoring may be of value. (5) Long term suppressive therapy with itraconazole 200mg should be given to patients with severe disseminated infection, central nervous system (CNS) infection or following relapse. This may be safely discontinued when certain criteria are met, including completion of at least one year of maintenance therapy, ART for 6 months, antigen levels that are low or negative, blood cultures that are negative, and a CD4+ T cell count of $>150/\mu\text{L}$. (29)

Primary prophylaxis with itraconazole may be considered in certain endemic settings, (21) and additionally activities associated with increased risk, such as working with soil or environments which may be contaminated with bird droppings or bat guano, should be avoided. (19)

Coccidioidomycosis

Coccidioidomycosis, also known as 'San Joaquin Valley fever' or 'Valley fever', is caused by *Coccidioides immitis*, a soil-dwelling fungus. It is geographically restricted to certain arid and semi-arid areas of the Americas (30). Infection occurs via inhalation of soil or dust containing the fungus, and among immunocompetent individuals, the majority of those infected are asymptomatic. The remainder of cases may have a self-limiting pulmonary syndrome that resembles community-acquired pneumonia. (31) Immunocompromised individuals, including those with HIV infection, may develop a number of different clinical syndromes including focal pneumonia, diffuse 'reticulonodular' pneumonia (resembling *Pneumocystis jirovecii* pneumonia) or extra-thoracic involvement including meningitis. (19) Response to treatment can be poor, particularly in cases of severe disease, with high rates of mortality. Expert advice and specialised care should be sought in all cases.

Diagnosis is most often made on the basis of a positive serological test in the context of a compatible clinical syndrome. Culture of body fluids or tissues is also a useful diagnostic tool, and *Coccidioides* species may be detected on histological examination of biopsy samples, though this is less common. (31) Laboratory staff should be informed if the diagnosis is suspected so that additional precautions may be taken.

There is no proven benefit to primary prophylaxis, and no absolute ways to avoid risk of infection (most infections occur without any definable exposure). Most immunodeficient HIV patients warrant treatment, regardless of severity, although there are limited published data to guide choice of therapy. (31) In addition to ART, antifungal therapy with either fluconazole or itraconazole are typically used and treatment continued for at least 6 months. In more severe forms of disease, combination therapy with an amphotericin B formulation and a triazole antifungal is often preferred. (19)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Endemic parasitic infections

Although not at first considered typical HIV-related opportunistic infections, endemic protozoan parasitic infection such as leishmaniasis, trypanosomiasis and malaria have increasingly become recognised as important co-infections in people with HIV infection. (32)

Leishmaniasis

Leishmania spp. are protozoa that can cause a variety of clinical syndromes, including visceral, cutaneous and mucocutaneous forms of disease. Of particular importance is visceral leishmaniasis that been recognised as an important opportunistic infection in patients with HIV infection. (33) Although rarely seen in Australia, it is one of the most common protozoan infections seen in people with HIV infection worldwide. (34) It is found in almost a hundred countries across the tropics, subtropics and southern Europe. A number of different species exist in different geographic areas, which result in different clinical manifestations. (19)

In endemic areas, the usual route of transmission is from the bite of an infected female sand fly. In parts of southern Europe, however, transmission has been reported in association with injecting-drug use. (19, 35) The best way for travellers to protect themselves is by avoiding sand fly bites by using personal protective measures such as protective clothing and insect repellents.

Clinical presentation

Systemic visceral disease is the most common clinical presentation of leishmaniasis in people with HIV infection and is associated with advanced immunodeficiency (CD4+ T cell counts <200/μL). Onset may be in the context of primary infection or reactivation of latent infection. In contrast to immunocompetent individuals, isolated cutaneous disease is rare in HIV-infected individuals, although cutaneous involvement may accompany visceral disease. (36) Systemic symptoms, such as fever and malaise are often seen along with lymphadenopathy and hepatosplenomegaly. Pancytopenia is another notable characteristic feature. (19, 33) Commonly involved organs include bone marrow, liver, spleen, lymph nodes, the gastrointestinal tract, and occasionally atypical sites such as the myocardium and adrenals. (37, 38) While splenomegaly is often a defining feature in non-HIV infected individuals, it may be less pronounced in the setting of HIV infection. (39)

Diagnosis

The standard investigation for diagnosing leishmaniasis in HIV co-infected patients is direct demonstration of parasites in blood smears (up to 50% sensitivity reported), (40) or tissue samples (scrapings, biopsies, bone marrow or splenic aspirates). PCR is also of value in diagnosis. (41) Serological assays are commercially available, and while useful in immunocompetent individuals, the false positive rate is high in the context of HIV co-infection. (42)

Management

The management of HIV-associated visceral leishmaniasis is extremely challenging, with high rates of relapse and mortality. Treatment has traditionally been with either pentavalent antimonial salts or amphotericin B, both of which are associated with significant toxicity. Liposomal amphotericin B is better tolerated and has increasingly become the drug of choice in HIV co-infected patients, although the optimal dosage has not been determined. (19) Oral miltefosine and parenteral paromomycin are alternative agents, (43, 44) and programs in endemic regions are increasingly moving towards combination therapy. (45) Prompt initiation of ART should be standard practice in this setting, although there is no leishmaniasis-specific data on the optimal timing of initiation. IRIS-type reactions have also been described. (46)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

In cases of treatment failure or relapse, immunotherapy, including interferon-gamma and recombinant human granulocyte macrophage colony stimulating factor have been used experimentally as an adjunct to anti-leishmanial treatment (47, 48); however, supporting data are limited. Relapses are common and therefore secondary prophylaxis with an antileishmanial drug, administered at regular intervals, is recommended, particularly for patients with CD4+ T cell counts <200/ μ L. (19, 49) The only published randomized control trial of secondary prophylaxis compared amphotericin B lipid complex in 8 patients to no prophylaxis in 9 patients, and reported that relapse rates were 50% versus 78%, respectively, after 1 year of follow up. (50) There are limited data to guide the recommended duration of secondary prophylaxis but because of the high risk of disease relapse, some experts recommend indefinite prophylaxis. (19)

Chagas disease

Chagas disease (American trypanosomiasis) is caused by the protozoa *Trypanosoma cruzi*, and is transmitted to humans by infected triatomine bugs, small insects that live in crevices of dirt walls and roofs of rural dwellings. They defaecate during or after feeding, usually at night. The parasite is present in the faeces of the infected bugs, and enter through the bite wound, or through mucous membranes. The disease is endemic in the Americas, and historically transmission has occurred largely in rural areas of Latin America. Cases of transmission following blood or organ transplantation, or from mother to infant, have also been described. (51, 52) In the Australian context, exposure in a traveller is unlikely unless travel is planned to rural areas in endemic countries, or from receiving blood products in an area where blood screening is not universal. (53)

Clinical presentation

In the acute phase of infection, patients may present with the characteristic Romana's sign – unilateral periorbital oedema, sometimes with a non-specific febrile illness. At the end of this phase, as parasitemia levels fall, patients move into the chronic phase. (19) Most patients with chronic infection are asymptomatic, and over the course of their lives around a third may progress to clinically evident Chagas disease, typically cardiomyopathy. (52) In the setting of HIV infection and associated immunodeficiency, *Trypanosoma cruzi* infection can reactivate to cause disease. The most common manifestation of this is meningoencephalitis, with or without brain abscess (chagoma). This presentation may be very similar clinically, and on radiological imaging, to toxoplasmosis and may be difficult to distinguish. (54) The second most common manifestation in HIV-infected patients is acute myocarditis, although it is usually associated with concurrent CNS involvement. (55, 56)

Diagnosis

Most people infected with *Trypanosoma cruzi* globally are in the chronic phase of infection and asymptomatic. Hence screening for asymptomatic infection is important in HIV-infected patients who have potentially been exposed because of the risk of reactivation of the infection. Diagnosis of chronic *Trypanosoma cruzi* infection is made using serological assays; however, there is no gold standard assay and interpretation of results can be challenging. Often, more than one assay may need to be performed based on different antigens and techniques. PCR is generally not useful due to variable primers and methods used, and also because results may be positive in chronic infection, even in the absence of infection reactivation. (19)

In the setting of a HIV-infected patient presenting with a CNS mass lesion, meningoencephalitis, arrhythmia or heart failure, Chagas disease should be considered if there are epidemiological risk factors. A definitive diagnosis is made by direct identification of the parasite in tissue (such as brain biopsy), in CSF or in blood. (55)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Management

Treatment of Chagas disease is specialised. Chemotherapy is usually with benznidazole or nifurtimox, which are effective in reducing parasitemia, but have limited efficacy in achieving parasitological cure. The duration of therapy in HIV co-infection is unclear and mortality is high for symptomatic reactivated *Trypanosoma cruzi* infection. The role of secondary prophylaxis or long-term suppression is also unknown. Timing of ART initiation in opportunistic infections of the CNS in HIV patients is often an important consideration due to the risk of an IRIS; however, no cases of Chagas disease-associated IRIS have been described in the medical literature. (19)

Malaria

There is a significant interaction between malaria and HIV infection. An increased frequency (one to two times higher) of both parasitaemia and clinical malaria is observed in HIV-infected adults, with increasing risk associated with worsening immunodeficiency, particularly when CD4+ T cell counts are <200 cells/μL. (57-59) Data on the effect of malaria on maternal to child transmission of HIV in the pre-ART era are conflicting, (60-62) but there is an increased risk of pre-term deliveries, low birthweight infants, and post-natal mortality.

Pre-travel advice should be sought with a travel medicine specialist as risk can vary with different geographic locations and travel itineraries. Chemoprophylaxis and personal protective measures are recommended for those who may be exposed, and recommendations are the same as for HIV-negative individuals. Consideration should be given to potential drug interactions with antiretroviral drugs; for example, mefloquine is known to decrease plasma levels of nevirapine, ritonavir and possibly other protease inhibitors, while plasma levels of mefloquine may decrease when it is co-administered with efavirenz.

Other opportunistic infections

Buruli ulcer

Buruli ulcer (BU) is a necrotising infection of skin and soft tissue caused by the bacterium *Mycobacterium ulcerans* and is the third most common mycobacterial disease worldwide after tuberculosis and leprosy. It mainly affects children living in rural and remote regions of Africa but is endemic in 33 countries, including South and Central America, Asia and Australasia. The prevalence of BU is increased in people infected with HIV infection (63, 64) and it has been reported in travellers to endemic areas. (65) The mode of transmission to humans remains unknown but it may be via skin contact with contaminated soils or water, or the bite of a vector like a mosquito or water-bug. (66, 67)

Clinical presentation

The classic lesion is a painless ulcer, usually on the limbs, which slowly progresses. However non-ulcerative forms can occur that include papules, nodules, plaques and aggressive oedematous lesions that present as cellulitis. (68) Patients with HIV infection have more severe lesions with an increased incidence of multiple and non-ulcerative lesions. There also appears to be an increased mortality in HIV-infected patients with BU. (64, 69) The incubation period is estimated on average to be 4-5 months. (70)

Diagnosis

Diagnosis is best made by performing an IS2404 PCR of lesion fluid or tissue, although biopsy specimens can be examined for acid-fast bacilli and sent for mycobacterial cultures. (71)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Management

Combination antibiotic therapy for BU should be commenced before starting ART and given for 8 weeks duration. The recommended combination is rifampicin (10mg/kg daily up to 600mg) plus clarithromycin (7.5 mg/kg twice daily up to 600mg), although due to drug interactions this regimen should be used with caution when used with efavirenz. An alternative regimen is rifampicin plus moxifloxacin (400mg once daily). Rapid ART initiation (preferably within 2 weeks) for those not on ART is recommended to all BU–HIV coinfecting patients, regardless of clinical stage and CD4+ T cell count. (72)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Human papillomavirus infection and associated malignancies in HIV-infected people

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Last reviewed: November 2019

Introduction

The human papillomavirus (HPV) is a DNA virus from the papillomavirus family that infects cells at mucosal and cutaneous sites. There are over 170 types of HPV known, of which 40 are sexually transmitted. (1) They are generally classified as "low risk" or "high-risk" types depending on their association with malignant transformation of cells (oncogenicity). High risk types include type 16, 18, 31, 33, 35, 45, 51, 52, 56, 58, 59, and 68. (2) HPV-associated malignancies include squamous cell carcinomas (and some adenocarcinomas) of the cervix, anus, oropharynx, vulva, vagina and penis.

Infection with HPV may lead to the development of Squamous Intraepithelial Lesions (SIL). High-grade Squamous Intraepithelial Lesions (HSIL) are considered to be the precursors of squamous cell cancer (SCC). The natural history of HPV infection in the cervix has been extensively studied but further research is needed to understand the natural history of HPV infection in non-cervical sites, particularly the progression and regression rates of cancer precursor lesions. Likewise, treatments for cervical lesions are established but there is still no consensus regarding management of non-cervical lesions.

HPV vaccination is highly effective at preventing infection with HPV vaccine-types. (3) This has resulted in marked reductions of the prevalence of warts reported in settings with established HPV vaccination programs. (4) The potential of vaccination to reduce HPV-related malignancies will only be realized in the coming decades.

The following section discusses HPV-associated malignancies in general and in people with HIV infection and provides practical information regarding current screening recommendations, clinical presentation of the malignancy, diagnostic considerations and management options. The role of HPV vaccination in the prevention of HPV-associated malignancies in people with HIV infection is also discussed.

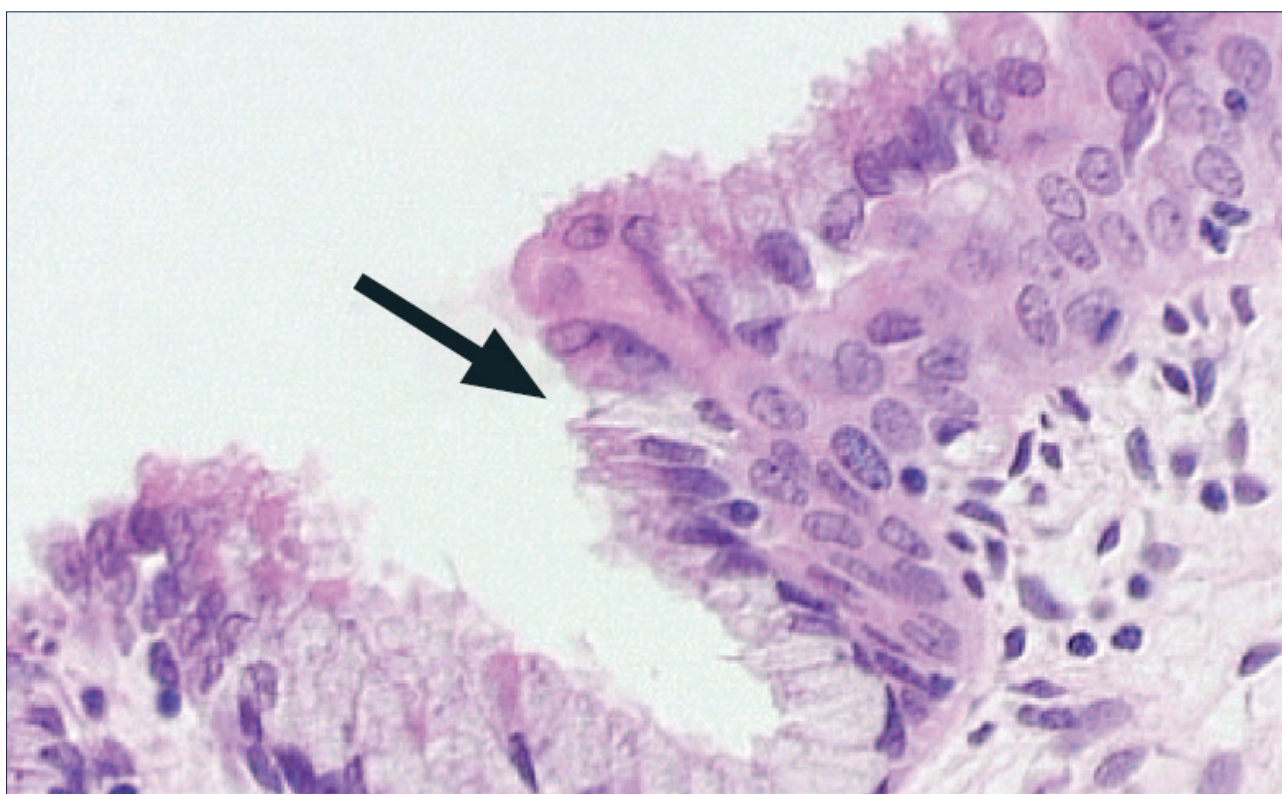
Cervical cancer

Cervical cancer is the 14th most commonly diagnosed cancer among women in Australia with an age standardised incidence rate of 6.8/100,000 in 2013. (5, 6) Almost all (99.7%) cervical cancers have HPV detected in biopsy specimens. (7) Cervical cancer incidence starts to rise in women in their late 20s with 30% of cases occurring in women under the age of 45 and the highest burden being in women over 45 years of age. (8) There is a second peak of disease in the age group of 60-65 years.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

The cervix is particularly vulnerable to the effects of HPV infection at the transformation zone (Figure 1), where the stratified squamous cells of the vagina change to become the columnar cells lining the endocervix and uterus, and most HPV-associated cervical lesions occur within this area. (9) Infection in the general population is extremely common with up to 60% of sexually active adults acquiring HPV infection within 36 months of commencing sexual activity and an annual incidence of 14%. (10) Other studies have demonstrated a cumulative incidence of up to 60% over 5 years. (11) The lifetime risk of acquiring an HPV infection is estimated to be 80%. (12-15) The majority of individuals infected with HPV clear the infection within 12-24 months. (16, 17) However, persistence of HPV may lead to the development of intraepithelial neoplasia (IN), which is the cancer precursor. (18, 19) HPV 16 is a particularly virulent genotype, (20, 21) with a lower clearance rate than other HPV types (22) and a higher likelihood of progression to precancerous disease.

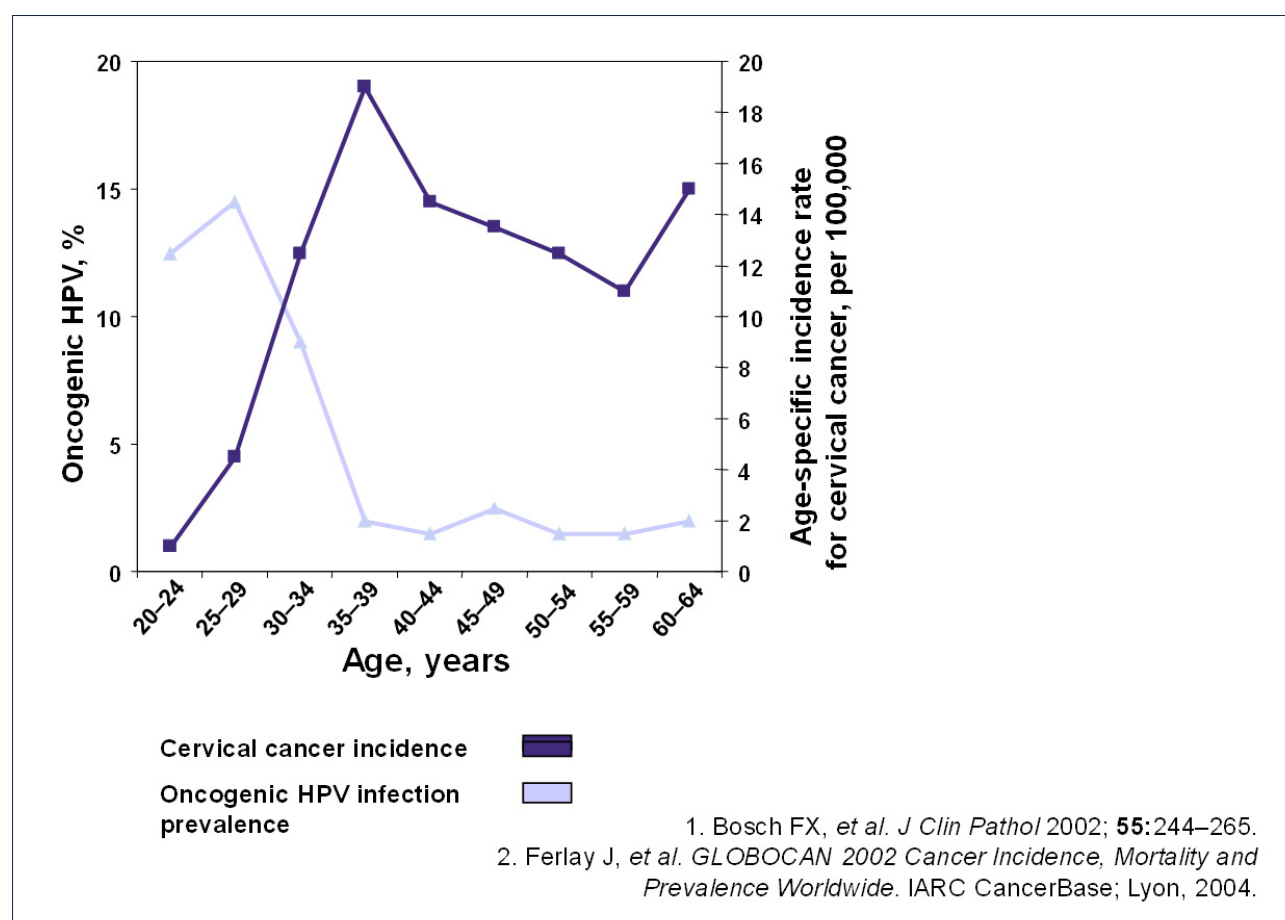
Figure 1. The cervical transformation zone. (23)



Cervical HSIL may develop within 1-10 years from the time of first infection with “high-risk” HPV types, but the modal time is about 7-10 years. (24) Only a small proportion of women with HSIL progress to cancer, and of the women who progress most take a long time to develop invasive disease, which allows for a long interval in which detection can occur and treatment can be given. It is estimated that the risk of invasion is about 20-30% over 5-10 years from HSIL. (25, 26) The prevalence of HPV infection is high in young women, but as the infection is cleared in the majority of women, the prevalence of HPV infection falls while the incidence of cervical cancer rises with increasing age (Figure 2).

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Figure 2. Age-specific incidence of cervical cancer and prevalence of oncogenic HPV infection (23)



Most cervical carcinomas are squamous in origin with a smaller proportion being glandular in origin (adenocarcinoma). (27, 28) The prognosis for adenocarcinoma is not as good as for squamous cell carcinoma, with a higher likelihood of recurrence. (29) The HPV types most commonly associated with cervical adenocarcinoma are HPV 16, 18 and 45, which account for 90%. (30-32) Adenocarcinomas in older women have a lesser association with HPV, being present in only 43% compared to 89% in women under the age of 40 years. (27)

Screening

Usually, the precursors of cervical squamous cell carcinoma occur on the ectocervix and are detected by screening for high-risk HPV genotypes followed by colposcopy with visualisation of the lesion, cytology and biopsies. (33, 34) In Australia, the Cervical Screening Test (an HPV test) has replaced the Pap test as of 1 December 2017. This test detects high-risk HPV. Screening commences at age 25 and women exit the program by the age of 75. For more details, see (35).

Clinical presentation

Precursor lesions of cervical cancer are usually asymptomatic. Symptoms of cervical cancer can be vaginal bleeding or discharge, weight loss, dyspareunia or unexplained, persistent pelvic and/or back pain.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Diagnosis

Diagnosis requires cytology, colposcopy and biopsy.

Treatment

Current treatment of cervical HSIL is by surgically removing the areas of the cervix that may possibly be involved by laser excision, loop excision or cold coagulation of the cervix. No treatment is currently provided for the HPV infection of the cervix in the absence of dysplasia, even though many of these women will go on to develop cervical dysplasia.

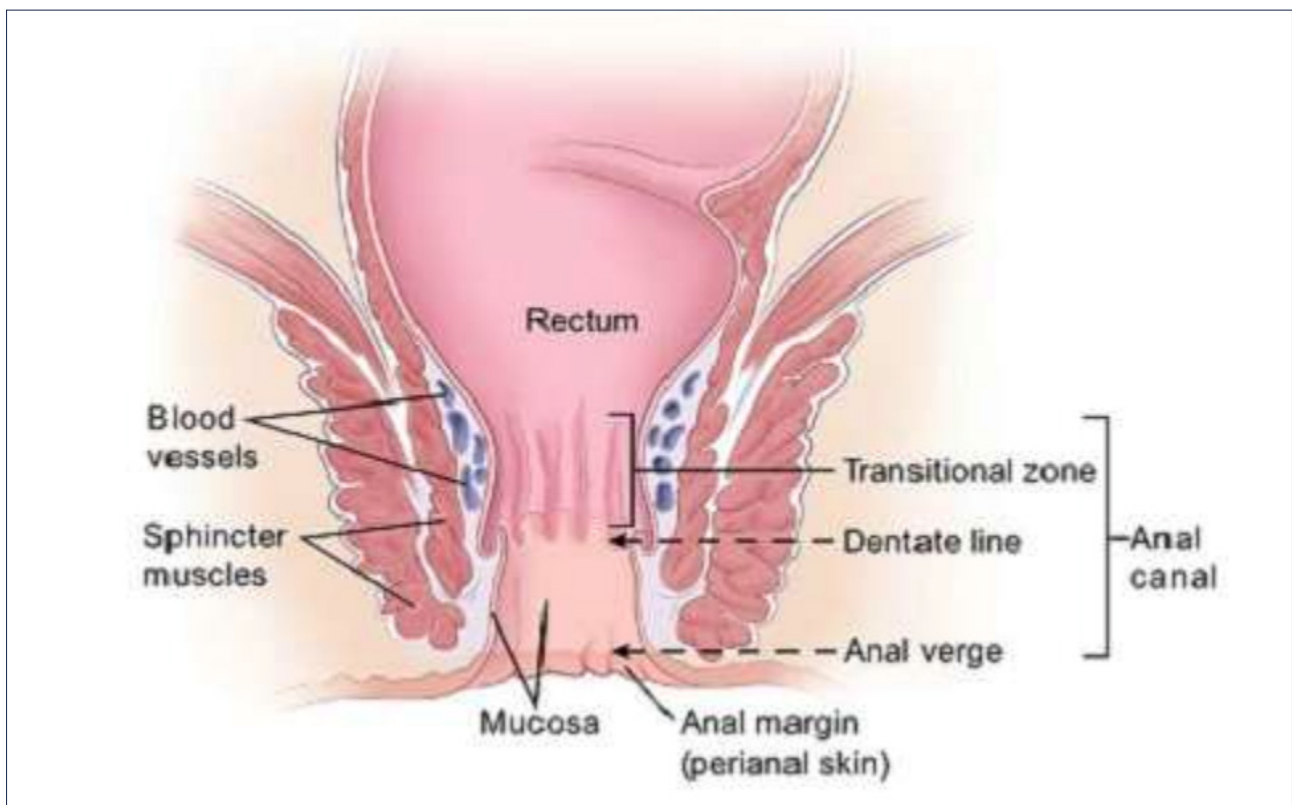
Cervical cancer treatment depends on the stage of the disease and this requires investigation to ascertain whether the disease has spread to the regional pelvic lymph nodes or further. Stage 1 (limited to the cervix) may be treated with surgery with larger tumours requiring radiotherapy and chemotherapy.

Anal cancer

The below information may be outdated, please refer to the latest [Anal Cancer Screening Guidelines for People Living with HIV](#).

Anal cancer is defined as a cancer arising either from the squamous or glandular epithelium of the anus. The vast majority are SCCs, (36) with the remainder coded as adenocarcinomas, neuroendocrine neoplasm, malignant melanoma, mesenchymal tumours and lymphoma. (36-39) Anal cancers are distinguished anatomically as being of the *anal canal* (arising from the canal which extends between the rectum to perianal skin) or *perianal* (arising from the skin within 5 cm diameter from the anal verge) (Figure 3).

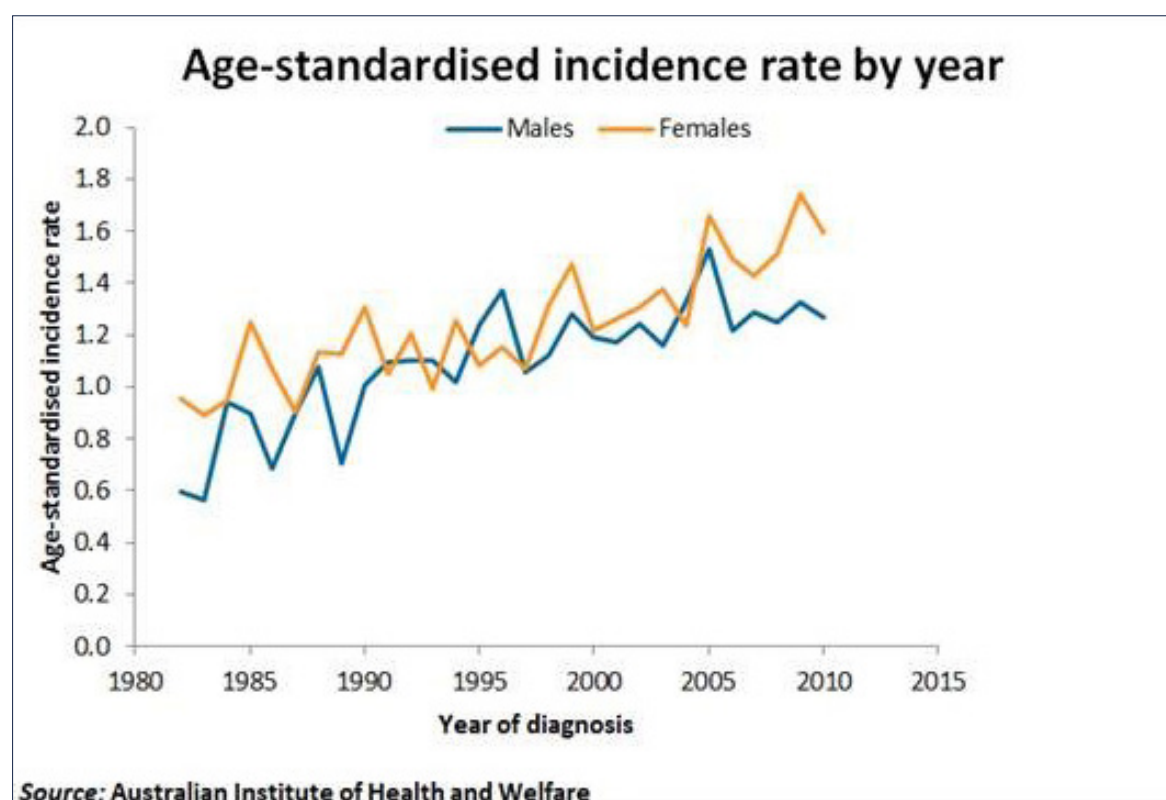
Figure 3. Anatomy of the anal canal (40)



CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Anal cancer is relatively rare in the general population with incidence rates between 1 to 2 per 100,000 person-years, though rates are rising over time (Figure 4). (36, 38, 41-43) However, for men who have sex with men (MSM) who have HIV infection, a recent meta-analysis estimated a pooled incidence rate of 77.8 per 100,000 person-years. (44) This is comparable with other common cancers in the general Australian population. (45)

Figure 4. Australian age-standardized incidence rate of anal cancer by gender (43)



Squamous cell carcinoma is the commonest (85%) form of anal cancer and is primarily caused by HPV infection. (46-49) Additional risk factors are receptive anal intercourse (before the age of 30), (49-51) higher lifetime number of sexual partners, (50, 51) current cigarette smoking, (48, 52, 53) genital warts, (50, 53) and immunosuppression (HIV, post-organ transplantation). (49, 54-56) Anal fistulae and epithelial trauma may also be associated, possibly because they increase access of HPV to the basement membrane. (57-59)

An increased incidence of anal cancer in the last 30 years has been attributed to changes in sexual behavioural patterns, (60, 61) including increased anal sex (61, 62) and increased partner numbers for both MSM and women, as well as the increased number of people with HIV infection. (63) A recent cancer registry study in the United Kingdom has shown a 126% increase of anal carcinoma incidence in women comparing the time periods 2006-2010 to 1990-1994; whereas in men the increase was only 69% with the male to female ratio being 10:18. (64)

Screening

There are no consistent guidelines on how to screen for anal cancer or pre-cancerous lesions. If available, anal cytology with or without high resolution anoscopy has been recommended to detect anal cancer precursor lesions (analogous to cervical cancer). (65) There is ongoing research (including a large randomized controlled trial in the United States) to determine the effectiveness of this screening modality.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

As evidence gathers for screening using anal cytology, those people at highest risk of anal cancer are recommended to have an annual digital anorectal examination (DARE). (66-68) Early anal cancer detection is associated with better morbidity and mortality outcomes. (41, 69, 70) Resources for performing DARE are available on the following websites: www.anal.org.au/clinician and <https://youtu.be/KDUcJHdz-Sk>.

Clinical presentation

Anal cancer may present as rectal bleeding, anal or perineal pain, a painful/hard/friable mass, pruritus ani, faecal incontinence, anal fistula, anal discharge and ulceration. (71-75) Up to 80% of anal cancers may be symptomatic at the time of diagnosis. (76) However, symptoms may be present at a mean time of 22 weeks before diagnosis is made. (72) In a large UK cohort of 8,640 people with HIV infection (40,126 patient years of follow up), a significant majority of anal cancer cases were diagnosed late; 38% had cancers larger than 5 cm, 31% had nodal disease and 6% had distal metastases. (77) In evaluating 585 anal cancer patients in the UK, only 13% of anal canal tumours and 10% of anal margin tumours were smaller than 2 cm. (78) A series of 128 cases of anal cancers in Victoria reported that 52% of anal cancers were externally visible at diagnosis with a mean tumor size of 3.6 cm. (72)

Diagnosis

A biopsy of any suspicious lesions should be conducted to confirm the diagnosis together with staging investigations such as CT, MRI or PET scan. For more details, see (79).

Management

Cancers of the perianal skin and those of the anal canal have different outcomes. (80) Early stage perianal lesions can usually be treated by surgical excision whereas the anal canal lesions require chemoradiotherapy (79, 80). The prognosis depends on the site, size of the lesion (<2cm, 2-5cm, >5cm) and whether there is nodal involvement or metastases. The 5-year survival for anal cancer is approximately 70%, (81) with a better prognosis for early disease (i.e. 70-92% 5-year survival rate for Stage I disease). (82) It is not yet known if detection at the microinvasive stage is associated with a better long-term prognosis. In people with HIV infection, anal cancer prognosis and treatment toxicities are similar to those of the general population. (83)

Oropharyngeal cancer

Oropharyngeal cancer (OPC) is one of the most common head and neck squamous cell carcinomas globally. (84) OPC includes cancer of the tonsils, tonsillar crypt and pillars, base of tongue and oropharynx. Traditional risk factors are smoking and excessive alcohol use (85) but in the past two decades, there is a rise in HPV-associated OPC in developed countries among non-smoking individuals, aged 35-55 years. (86, 87) More males are affected compared to females with a ratio of approximately 3:1. (88, 89) HPV causes approximately 70% of OPC in the United States. (90) In particular, HPV-16 is associated with 90% of HPV-associated OPC. (90) Compared to individuals with HPV-negative OPC, those with HPV-associated OPC are younger with a median age of 54 years, have less exposure to tobacco and alcohol, and have better five-year survival (82% vs. 35% in HPV-negative cancers). (91, 92)

Screening

There is currently no consensus on screening for OPC and, consequently, precancerous lesion may not be recognised. Salivary oral rinse with or without abrasion may be used to detect HPV DNA. (93) However, the

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

presence of HPV does not equate with definite risk of progression to cancer. HPV is found in the oropharynx of healthy adults and the vast majority will clear the virus naturally and without any symptoms. Further, oral HPV infection may lie dormant for many years. (94) The United States National Health and Nutrition Examination Survey (NHANES) estimates that prevalence of any HPV in adults aged 18 to 69 years was 7.3%. (95)

Clinical presentation

There are no definitive symptoms pathognomonic for OPC. Potential symptoms may include an unhealing sore or ulcer, discoloration in the soft tissues, difficult or painful swallowing, persistent sore throat or hoarse voice, earache, swollen cervical lymph nodes, and a swelling or lump. Individuals may also have loss of appetite and/or weight, and general malaise.

Diagnosis

Examination under anaesthesia is recommended but not mandatory. Histologic diagnosis from a biopsy of the tissue sample is needed, especially for those undergoing curative treatments. HPV testing is recommended for all OPC. Staging investigations includes MRI or CT scan.

Management

Radiotherapy is the mainstay of treatment though the stage of cancer will determine the optimal modality: chemotherapy, radiotherapy and/or surgical resection. In recent years, use of minimally invasive surgery has resulted in good survival rates. (96, 97) More details of management guidelines can be found elsewhere. (98)

Vulval cancer

Squamous cell carcinoma of the vulva (VSCC) is a rare cancer. Some are associated with HPV-related precursor lesions (vulval intraepithelial neoplasia usual type) especially those associated with HPV 16. (99) However, most cancers are not related to HPV infection. For instance, lichen sclerosus is a non-HPV related skin condition with an increased risk of development of vulval neoplasia-differentiated VIN (dVIN). (100) Other chronic inflammatory dermatoses may also be associated with dVIN which is more likely to occur in older post-menopausal women. (101) There is an increased risk of vulvar cancer if there has been previous cervical or vaginal cancer. Tumor size and P53 positivity are linked to a poorer prognosis and increased mortality compared to HPV p16 positive cancers. (102)

Screening

There are no recommendations regarding screening for vulval cancer.

Clinical Presentation

Women may present with either as a lump or ulcer, itching or soreness or as a skin lesion such as a mole. Some women may present with enlarged inguinal lymph nodes.

Diagnosis

Diagnosis is made by biopsy with histopathological examination of tissue.

Management

The treatment depends on the stage of the disease and may involve surgery alone or with chemoradiotherapy.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Vaginal cancer

Vaginal cancer is extremely rare and is usually related to HPV infection, (103) but may rarely be caused by melanoma, sarcoma or adenocarcinoma or be due to metastatic disease. It occurs mainly in older women and the risk is increased if there have been other HPV-related genital cancers.

Screening

There are no recommendations regarding screening for vaginal cancer.

Clinical presentation

There may be no symptoms or the patient may notice a hard lump, bleeding or an odorous vaginal discharge or complain of genital pain.

Diagnosis

Diagnosis is made by biopsy with histopathological examination of tissue.

Management

Treatment depends on the stage of the disease and involves surgical excision and radiotherapy. (104) Advanced cases may also receive chemotherapy. (105) Prognosis is generally poor despite these treatments. (103)

Penile cancer

Penile cancers are rare but have significant morbidity and mortality when detected in late stages. Squamous cell cancers cause over 90% of penile cancers and may be related to HPV infection or to phimosis and/or penile chronic inflammation. Incidence in the US is 0.7 per 100,000 men (106) and 0.8 per 100,000 men in Australia. (107) In the developing world, incidence is higher at 4.4 per 100,000 men. (108, 109) The peak incidence is during the seventh decade of life. (110)

Risk factors for penile SCC include HPV infection, increasing age, smoking tobacco, immunodeficiency, phimosis and men who are uncircumcised. (110, 111) Approximately half (48%) of penile cancers are associated with HPV, especially types 16 and 18. (112)

High risk HPV types can cause a precursor lesion, penile intraepithelial neoplasia (PeIN). Undifferentiated PeIN is commonly associated with HPV infection whereas differentiated PeIN is associated with non-viral factors such as chronic inflammation, lichen sclerosis or phimosis. (113, 114) The mechanisms whereby PeIN progresses to invasive penile carcinoma are yet to be elucidated.

Screening

To date, there remains no consensus on how to screen for penile cancer. Consider specialist referral for any persistent penile lesion after treatment for STIs is completed.

Clinical presentation

Clinically, PeIN may be subdivided as erythroplasia of Queyrat, Bowen disease, and bowenoid papulosis. Erythroplasia of Queyrat lesions have the highest likelihood of progressing to carcinoma. Penile squamous cell cancers can present in a variety of ways, including a non-healing ulcer or mass, discharge, bleeding, phimosis, change in colour or rash of penile skin.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Diagnosis

Biopsy of any suspicious lesion is recommended.

Management

Management depends on the stage of the cancer at diagnosis. If diagnosed early, especially for carcinoma-in-situ lesions, laser surgery, cryotherapy or fluorouracil cream may be considered. Otherwise, the patient will require surgery, radiotherapy and chemotherapy. (115) In certain circumstances, penile-preserving surgery may be possible. (116)

The role of vaccination in preventing HPV-associated malignancies

Prophylactic vaccination against HPV has been publicly funded in Australia since 2007 and three HPV vaccines are currently registered for use (Table 1). Since early 2018, the 9-valent HPV vaccine (Gardasil®9, Seqirus/Merck & Co) has been available on the National Immunisation Program (NIP) for all 9-14 year olds using a two dose schedule. For immunocompromised individuals aged 9-45 years, including people with HIV infection, a three dose schedule is recommended (at 0, 2 and 6 months). (117)

Table 1. Prophylactic HPV vaccines registered in Australia

Vaccine	HPV types covered*	Safe for people with HIV infection	Funded by NIP for people with HIV infection
Gardasil®9	6, 11, 16, 18, 31, 33, 45, 52, 58	Yes	9-45 year olds (3 doses)
Gardasil®	6, 11, 16, 18	Yes	N/A
Cervarix®	16, 18	Yes	N/A

*High-risk (oncogenic) HPV types are in bold font

All currently registered HPV vaccines are made using recombinant protein technology to assemble the HPV L1 viral capsid protein into virus-like particles, which are very immunogenic. They are not live vaccines and therefore safe for immunocompromised individuals including people with HIV infection.

While there are no specific data published for Gardasil®9 in HIV-infected individuals, there is ample evidence of immunogenicity of Gardasil® and Cervarix®9 in HIV-infected men, (118) women, (119, 120) adolescents (121) and children. (122) Furthermore, even in HIV-infected individuals, cross-reactive antibodies against non-vaccine HPV types are detected. (122-124) The adverse event profile of HPV vaccines is similar to the HIV-uninfected population (mainly injection site pain). There are no adverse effects of HPV vaccines on HIV viral load or CD4+ T cell counts. (125, 126)

These vaccines are only effective at preventing initial HPV infection in a type-specific fashion. (127) Hence their efficacy is predicated on being administered before an individual has been exposed to a particular HPV type. For people with HIV infection older than 45 years, a potential benefit may still be obtained by vaccination, dependent on their individual risk of future HPV exposure and disease. People with HIV infection may choose to be vaccinated at their own cost, after weighing up the cost versus benefits of vaccination in discussion with a health care provider that understands their individual circumstances. (128)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Dermatological Conditions

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Last reviewed: Jan 2024

Next review due: March 2029

Acknowledgement: We would like to acknowledge Alexis Lara Rivero, Mark Kelly, Cassy Workman & Margot Whitfeld as the original authors of this section and David Wong for providing independent review of the current version.

Introduction

Dermatological conditions may present at any stage of human immunodeficiency virus (HIV) infection. Cutaneous manifestations may be the initial sign of HIV infection as part of a seroconversion illness, patients may develop drug reactions, or infectious, inflammatory or neoplastic disease as part of their immune dysregulation.

Since the advent of combination antiretroviral therapy (ART), dermatological presentations are increasingly encountered in the setting of immune reconstitution inflammatory syndrome (IRIS). Furthermore, due to longer life-expectancy and improvements in HIV-associated mortality due to ART, there has been a greater appreciation of dermatological issues arising in people living with HIV (PLWHIV). (1)

Although some skin conditions occur almost exclusively in PLWHIV, the spectrum of dermatological conditions is otherwise similar to that found in the general population. These general dermatological problems may be atypical in presentation however. Depending on the degree of immunodeficiency they are often less responsive to the usual therapies or require unique management considerations.

Clinical History Taking and Physical Examination

As with any clinical presentation, history taking may offer clues to diagnosis (Table 2). Note the distribution, type of rash and any other associated physical findings including: oral, hair, nail and genital changes.

Table 2: History essentials in the setting of cutaneous presentations

HIV status	Current and nadir CD4 cell count, and viral load results
History	Medical and surgical history
Medications	Current and recent medical therapy including ART, complementary therapy and over-the-counter medications
Contacts	With children and adults experiencing similar symptoms Sexual contacts With pets, wildlife
Occupation	Associated exposure
Travel	Recent and past, and travel history if relevant

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Viral infections

Many viral infections, including those presenting with or limited to cutaneous involvement, occur more frequently in PLWHIV. (2) Common viral skin infections include those caused by Herpesviridae (including herpes simplex-1 and -2 and varicella zoster viruses), human papilloma viruses and Pox viruses. Given the underlying immunodeficiency in this demographic, viral infections may present atypically leading to delayed diagnosis; have a more severe clinical course; or be more resistant to treatments. (3-5)

Herpes simplex virus

Serological studies estimate approximately 67% and 16% of the global population are living with Herpes Simplex Virus (HSV)-1 and -2, respectively. (6, 7). Both HSV-1 and -2 are typically acquired in childhood or early adulthood, primarily through vertical or sexual transmission, and are never cleared. (8) In the immunocompetent population, HSV infection is typically latent and asymptomatic, although asymptomatic viral shedding (particularly for HSV-1) means ongoing sexual transmission is common. Multiple population studies have observed a bimodal association between HSV and HIV infection, resulting from a combination of behavioural risk factors and viral synergy. (9-12)

Clinical presentation

Herpes simplex virus (HSV) types 1 and 2 can result in highly varied mucocutaneous manifestations. Most commonly, oral (*herpes labialis*) and genital sites (*herpes genitalis*) present with characteristic vesicular or pustular lesions with an erythematous base. (13). Primary infection may also be associated with systemic symptoms such as fever and malaise. Other, less common presentations may include crops of vesicles on non-mucosal skin (*herpes gladiatorum* or *herpes folliculitis*), digits (*herpetic whitlow*), or disseminated superinfection in the context of underlying eczematous conditions (*eczema herpeticum*). Extracutaneous involvement may also occur including *herpetic keratoconjunctivitis* and *herpes encephalitis*.

In PLWHIV, mucocutaneous flares of HSV may be more extensive, recurrent or slower to resolve spontaneously compared to immunocompetent individuals. (4) Furthermore, atypical HSV lesions may develop including larger, more widespread and deeper cutaneous involvement, resulting in necrotising ulcers or verrucous lesions. (13, 14) The presence of herpes ulcers for 1 month or more in PLWHIV is associated with advanced stages of infection with CD4+ T-cell counts below 200 cells/ μ L, and is therefore considered an AIDS-defining illness. (15-17)

Diagnosis

The diagnosis of mucocutaneous HSV may be made on clinical grounds alone in the majority of cases. Vesicular fluid should be swabbed to confirm the presence of HSV using polymerase chain reaction (PCR) or nucleic acid amplification testing (NAAT), and exclude other alternate or concurrent viral pathogens (including varicella, discussed below) as well as bacterial co-infection. (18) In cases of treatment-refractory HSV infection, viral culture or genotyping of swabbed vesicles may be required for resistance analysis (19). In cases of atypical ulcerative or verrucous lesions, biopsy may be required. (17) It should be noted that HSV serology has low sensitivity in diagnosing acute infection and has limited clinical utility (20).

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Management and Prevention

There is no difference in management between HSV-1 and HSV-2 infection. Few randomised, controlled trials have been performed in PLWHIV. Aciclovir, famciclovir and valaciclovir have all been shown to be safe and effective as both intermittent and continuous therapy for HSV-2 clinical and subclinical infection in HIV-positive individuals. (21)

In the majority of situations, mucocutaneous HSV responds to oral therapy with aciclovir (400 mg three times a day); valaciclovir (1g twice a day); or famciclovir (250 mg three times a day). Primary episodes are treated for 7 to 10 days; recurrent episodes are treated for 5 days (21). Higher doses may be useful with aciclovir 800 mg twice a day or valaciclovir 1g three times a day. Treatment of aciclovir-resistant HSV should be guided by Infectious Diseases specialists using resistance genotyping, and may include non-thymidine kinase dependent therapies such as foscarnet or cidofovir (22).

Chronic antiviral suppressive therapy is suggested for PLWHIV who experience frequent and severe recurrences of mucocutaneous HSV infection (23-25). Valaciclovir (500 mg twice a day) or famciclovir (500 mg twice a day) is recommended as maintenance therapy for secondary prophylaxis. (21) In addition, PLWHIV and HSV-2 co-infection who are sexually active should be advised of the association between HSV-2 reactivation and mucosal HIV-1 shedding and risk of onward sexual transmission if they do not have an undetectable viral load on ART (11). Of note, incidence of the AIDS-defining clinical presentation of HSV necrotic ulcers steeply declined following introduction of ART (26).

Varicella zoster virus

Varicella zoster virus (VZV) may result in cutaneous disease in primary infection as well as secondary reactivation in the context of immune latency, where it is referred to as herpes zoster (HZ). (27) HZ occurs up to 20-fold more frequently in PLWHIV compared to their seronegative counterparts (28) particularly among men who have sex with men and those with CD4+ counts below 200 cells/μL. (29) Moreover, recurrent HZ is estimated to occur in 27% of patients with advanced HIV, and is significantly reduced by ART. (29) Although mortality from varicella infection is somewhat higher in adults, children living with HIV have a significant mortality rate from primary varicella infection and may also develop severe complications.

Clinical presentation

The cutaneous presentation of primary and secondary VZV in patients with HIV commonly follows a typical course, with crops of pruritic papules and vesicles on an erythematous base that become generalised in primary varicella and follow a dermatomal distribution in HZ. (30) In the setting of more advanced HIV infection, primary varicella is often more florid with a pronounced systemic prodrome (malaise, headache, fever and myalgia), has a prolonged course, and has a greater incidence of systemic complications such as encephalitis, pneumonitis and hepatitis. (30)

The classical rash of HZ is grouped vesicles or bullae, involving one or more dermatomes, evolving into pustular and haemorrhagic lesions within a few days. Most patients have prodromal pain in the affected dermatome preceding vesicular eruption. Disseminated HZ is defined by more than 20 vesicles outside the area of the primary and adjacent dermatomes or those involvement over three contiguous dermatomes, and is rare but has been reported in the setting of advanced HIV infection. (31) Subsequently, crusting occurs with the development of hypo- or hyperpigmentation as well as atrophic scarring. (32) The diagnosis of HZ in the distribution of the ophthalmic division of the trigeminal nerve is important, as it can cause uveitis and keratitis.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Following resolution of HZV, 5-20% of patients may develop post-herpetic neuralgia, characterised by persistent burning pain or allodynia in the affected dermatome. (33, 34)

Diagnosis

The diagnosis of VZV infection is usually clinical, however VZV PCR of vesicular fluid should be used for confirmation. VZV IgM is detected in acute chickenpox and in about 70% of people with HZ, whereas VZV IgG cannot differentiate acute and past infection or prior immunisation. (35).

Management, prevention and vaccination

Antiviral treatment for primary VZV infection is indicated in neonates, children and adults with HIV infection or other immunodeficiencies, as well those with severe disease. These include oral valaciclovir, famciclovir or aciclovir (dosages and durations provided in Table 3). Treatment should begin within 24–48 hours of onset, however in immunocompromised patients (including people living with HIV) antivirals are indicated regardless of rash duration.

Aciclovir, valaciclovir and famciclovir are efficacious in acute HZ, and should be used in ophthalmic HZ and can ameliorate postherpetic neuralgia. In immunocompromised populations such as PLWHIV, oral antivirals should be commenced even if onset is greater than 72 hours. (21) All three drugs are effective and with a similar safety profile, however valaciclovir and famciclovir may be associated with reduced risk of post-herpetic neuralgia. (36)

Management of systemic VZV infection or disseminated HZ requires intravenous aciclovir and should be guided by Infectious Diseases specialists with appropriate subspecialty advice, for example Neurology for encephalitis or Ophthalmology for keratitis. (37) Aciclovir-resistant varicella zoster infection is rare, especially in the post ART era, but when it does occur it is associated with significant mortality and morbidity. These patients usually have advanced disease with CD4 cell counts below 20 cells/ μ L. The presence of atypical lesions or a failed clinical response should prompt evaluation for aciclovir susceptibility. Foscarnet is recommended for the treatment of aciclovir-resistant zoster infection (38).

The live-attenuated varicella vaccine has been demonstrated to be safe and immunogenic in both adults and children living with HIV, with no reported case of vaccine-associated infection. (39-41) Australian guidelines recommend children over 12 months with HIV and age-specific CD4+ count of >15% total lymphocytes; as well as adults with HIV who are seronegative for varicella and with a CD4+ count >200 cells/ μ L receive two doses of the monovalent varicella vaccine at least three months apart. (42) Combination vaccines, such as the measles-mumps-rubella-varicella vaccine, have not been evaluated for safety in immunocompromised peoples and are therefore not recommended.

In such immunocompromised patients, recombinant vaccines against HZ are preferred over live-attenuated variants due to risk of disseminated vaccine strain VZV infection associated with the latter. Recombinant vaccination against HZ is recommended by Australian guidelines and funded for immunocompromised adults over 18 years old, including 'untreated or advanced HIV', or any adult over 50 years old. (42) However, in adults living with HIV who have CD4+ counts greater than 200 cells/ μ L, live-attenuated vaccination has not been associated with vaccine-related infection, and may be considered if recombinant vaccines are not accessible. As of 2024, The varicella zoster virus recombinant vaccine (RZV) is now recommended for adults with HIV and CD4+ count < 200 cells/ μ L in the National Immunisation Program (43).

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Zoster immunoglobulin is indicated for patients with HIV infection within 96 hours to 10 days of significant first VZV exposure (e.g. household or classroom contact) and who do not have immunity against varicella (44). Protection from HZV immunoglobulins may last for approximately 3 weeks, or alternatively aciclovir can be given up to 7 days post exposure (45). Recurrent HZV despite vaccination and adequate suppression of HIV viral load may benefit from VZV suppression using oral aciclovir, (46) however this is not an approved indication for aciclovir in Australia.

Table 3: Oral antiviral medications for herpes zoster

Medication	Dosage	Duration of treatment	Most common side effect	Precaution and contraindication
Aciclovir	800 mg 5 times a day	Primary VZV: 7 days HZV: 7-10 days or until lesions heal	Nausea, gastrointestinal side effects	Dose adjust for renal impairment if creatinine clearance < 25mL/min
Valaciclovir	1000 mg 3 times a day	Primary VZV: 7 days HZV: 7 days or until lesions heal	Nausea	Dose adjust for renal insufficiency, if creatinine clearance < 50mL/min.
Famciclovir	500 mg 3 times a day	Primary VZV: 7 days HZ: 7 days or until lesions heal	Nausea, headache	Dose adjust for renal insufficiency if creatinine clearance < 60mL/min In immunocompromised patients, a 10 day treatment course is recommended.

Source: Adapted from Australian Therapeutic Guidelines 2023. (21, 37)

Cytomegalovirus and Epstein-Bar Virus

Other herpesviridae including cytomegalovirus (CMV) and Epstein-Bar virus (EBV) do not typically present with chronic mucocutaneous lesions. In PLWHIV, mucocutaneous CMV infection is regarded as an AIDS-defining condition. (15)

Clinical Presentation

In PLWHIV and CD4+ count below 200 cells/ μ L, both CMV and EBV infection may result in chronic mucosal or perianal ulceration, correlating with the degree of immunosuppression. (47) Chronic oral mucosal EBV infection has been implicated in cases of premalignant hairy leukoplakia, which presents as adherent white plaques on the lateral tongue. (48) In advanced HIV, extensive prurigo nodularis-like lesions secondary to CMV have been reported. (49)

Diagnosis

In cases of chronic mucocutaneous ulceration suspected to be secondary to CMV or EBV infection, biopsy for histopathological assessment is necessary to make the diagnosis.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Management

Improvement of mucocutaneous lesions of CMV and EBV following commencement of ART have been reported in the setting of advanced HIV infection. (48) Systemic antiviral therapy is indicated for CMV infection in immunocompromised patients, and may involve oral valganciclovir or intravenous ganciclovir for up to six weeks. Oral valganciclovir may be continued as secondary prophylaxis in cases of recurrent disease or in cases with CD4+ count below 100 cells/μL. (50)

Human papilloma virus (warts)

In general, human papillomavirus (HPV) infections are considered benign. However, HPV subtypes 16, 18 and several others have oncogenic potential and have been shown to be associated with malignant transformation. (51) Neoplastic transformation to squamous cell carcinoma can occur in association with HPV infection of the skin, oral mucosa cervix, vulva, penis and anogenital mucosa. Precursor lesions to HPV-associated squamous carcinoma of the cervix, vulva, penis and anus are termed high-grade squamous intraepithelial lesions (HSIL). Previous terminology such as anal intraepithelial neoplasia (AIN) are no longer routinely used. (52)

Clinical presentation

Infection of the skin by low-risk HPV genotypes results in development of verrucae, or 'warts'. Clinical features vary by anatomic site, and may vary from flat papules (typically on the face or dorsal hands), clustered papules (usually on plantar surfaces) or filiform lesions (frequently on the scalp or beard area). (53) Although warts may be larger or more numerous in PLWHIV, most commonly the warts look like those found in the general population. While most cases are asymptomatic, some patients may experience pruritus, mild burning or bleeding. (54)

In the anogenital areas however, it can be more difficult with both common genital warts (*condyloma accuminatum*, usually secondary to low-risk HPV types 6 and 11) as well as other lesions due to other HPV subtypes. (55, 56) For example, Bowenoid papulosis is a HPV-associated papular eruption typically involving the penis or vulva which clinically mimics genital warts but histologically resembles HSIL and is caused by high-risk genotypes (including 16, 18, 31 and 33). (57) Penile, anal or vulval HSIL, due to high-risk HPV subtypes, otherwise often presents as erythematous lesions which may be associated with pain, bleeding or pruritus. (58) These may be difficult to differentiate from invasive carcinoma of these anatomical sites, which can develop from HSIL precursors, and thus features including rapid growth or ulceration should raise clinical suspicion. (52)

Diagnosis

The diagnosis of HPV warts is usually clinical. A biopsy may be helpful in establishing a diagnosis, particularly in verrucal lesions unresponsive to therapy or when warts have unusual features, such as hyperpigmentation, ulceration, rapid growth or excessive bleeding. (59) At mucosal sites, premalignant lesions (e.g. penile or vulval HSIL) caused by HPV can be confirmed by whitening of the mucosa when acetic acid is applied. Cytologic examination is used for mucosal evaluation as well as HPV genotyping to identify high-risk subtypes. (60, 61)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Management and prevention

Treatment of cutaneous and anogenital warts is directed on the alleviation of signs and symptoms with traditional treatment modalities focusing on the destruction of infected tissue. First-line treatments for warts include cryotherapy or keratolytics such as topical salicylic acid-based preparations, either separately or in combination. (53) Refractory warts may require referral for off-label therapies, such as imiquimod, cantharidin, podophyllin, podophyllotoxin, laser or surgery. Intralesional and intramuscular HPV vaccination has also demonstrated high complete clearance rates for cutaneous warts (82% and 63%, respectively) in a population without concomitant HIV. (62)

Despite the fact that patients with HIV infection tend to have larger or more numerous warts which may be more refractory to standard treatments, data does not support altered approaches to treatment for PLWHIV. (54) Topical imiquimod has been shown to be safe and effective for anogenital warts in men living with HIV, with a randomised trial showing higher rates of >50% clinical improvement compared to placebo (38% versus 14%). (63) Best outcomes have been with application three times a week for 6-10 weeks until visible inflammation occurs and the warts disappear. Side effects can be controlled by decreasing the frequency of application. Recent evidence suggests topical cidofovir to be effective in treating anogenital warts and Bowenoid papulosis in patients with HIV infection. However, its cost limits its widespread use. (64, 65)

In immunocompetent populations, vaccines against high-risk HPV subtypes have been shown to reduce the incidence of associated anal and cervical cancer. (66, 67) These vaccines are safe and immunogenic in populations living with HIV, (68) however evidence for their efficacy in reducing HPV-associated malignancies in this group is limited due to their exclusion from clinical trials. The management, screening and monitoring of anogenital HSIL are described in section Oncological conditions.

Molluscum contagiosum

Molluscum contagiosum (MC) virus is a poxvirus that causes a localised cutaneous infection most often seen in children. MC is spread by direct skin-to-skin contact, occurring anywhere on the body except the palms of the hands and soles of the feet. In people living with HIV, prevalence of MC has been reported to be as high in 20% in adults and is likely to represent new transmission rather than reactivation. (69)

Clinical presentation

Classically, MC presents as dome shaped, flesh-coloured 2-6 mm papules with central umbilication (70) In PLWHIV who are virally suppressed, MC lesions may not differ clinically to people without HIV, whereas in advanced HIV can be more numerous, larger and verrucous in morphology. (71, 72) .

Diagnosis

The diagnosis of MC is usually clinical although a biopsy of the papules may be required if alternate diagnoses (eg mpox, cutaneous cryptococcus, talaromycosis, histoplasmosis) are being considered.

Management

MC is usually self-limiting and spontaneously resolves after a few months in immunocompetent hosts, supporting a watchful waiting approach. (70) In the setting of advanced HIV immunodeficiency, recalcitrant lesions often improve with immune reconstitution on ART. (73) General advice about the risks of autoinoculation and spreading should be given. Genital lesions should be definitively treated to prevent spread

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

by sexual contact. Active treatment options include enucleation, curettage, or cryotherapy. Topical therapies include: tretinoin cream or gel daily; benzoyl peroxide, podophyllin; trichloroacetic acid; cidofovir; silver nitrate or phenol. (70, 74, 75) .

Management and Prevention

Treatment of mpox is primarily supportive, with most cases resolving after three weeks. (76) Paraenteral nutrition and hydration may be required in patients unable to tolerate oral intake due to mucosal lesions. Antiviral treatments should be prescribed under the guidance of Infectious Diseases specialists, and may be required in severe cases or in patients with advanced immunodeficiency such as untreated HIV. In Australia, these may include anti-vaccinia immunoglobulins, tecovirimat (oral or intravenous) and cidofovir (intravenous or topical). (84)

Vaccination against mpox using repurposed smallpox vaccines is recommended by Australian guidelines for men who have sex with men at high risk for mpox (including HIV infection) and immunocompromised peoples. Patients who are immunocompromised, such as advanced HIV, are suggested to receive the inactivated vaccine (JYNNEOS®) rather than the live-attenuated vaccine (ACAM200TM). (85) Two doses of the inactivated vaccine has shown to be safe and sufficiently immunogenic in people living with HIV, (86) and may reduce the incidence of severe mpox infection. (87)

Diagnosis

The diagnosis of mpox requires confirmation by nucleic acid amplification testing (NAAT) using a sterile dry swab collected from lesional fluid or crust. Skin biopsy for NAAT and histopathological analysis can be helpful in patients without vesicles or crusts available to swab. (83)

Mpox

Mpox, previously termed monkeypox, is an orthopoxvirus infection predominately spread through sexual contact. In 2022 a global outbreak led to its declaration as a Public Health Emergency of International Concern by the WHO, with over 78,000 cases across 100 countries. (76) This outbreak disproportionately affected PLWHIV, who comprised approximately 40% of diagnosed cases. (77) To date, over 140 cases have been reported in Australia since May 2022. (78)

Clinical Presentation

Patients with mpox typically present with 2-5mm painful umbilicated papules and pseudopustules (containing solid debris rather than pus), typically affecting anogenital and perioral sites in the 2022 outbreak. (76, 79) Systemic symptoms such as fever, fatigue and headache may be present. Palpable lymphadenopathy may be detected on examination in up to 90% of cases. In PLWHIV, clinical manifestations may not differ substantially to people without HIV, (80, 81) however those with advanced immunodeficiency are at higher risk of disseminated rash, hospitalisation and death. (82)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Fungal infections

Dermatophyte infections

Dermatophytosis is most commonly due to *Trichophyton rubrum*, *Trychophytum mentagrophytes* or *Microsporum canis*. Patients living with HIV are not at increased risk of dermatophytosis, including those with advanced infection or low CD4+ counts. (88)

Clinical presentation

Cutaneous dermatophyte infection may affect the inguinal areas (*tinea cruris*), scalp (*tinea capitis*), body (*tinea corporis*) or nails (*tinea unguium*). Superficial dermatophyte infections can be atypical in patients with HIV, including widespread skin or nail involvement. (89) Dermatophyte infections may also present as multiple fluctuant erythematous ulcerative nodules, which can lead to permanent hair loss on the scalp. (90)

Diagnosis

Culture of the fungal skin or nail scraping may be required if the speciation of the fungus is required for directed antifungal treatment. Erroneous treatment with topical steroids may reduce available scale for scraping (*tinea incognito*) and biopsy for tissue culture may be required.

Management

Management of dermatophytoses does not differ for PLWHIV. Superficial disease can be initially treated topically. In children and adults (including pregnant women), localised tinea infections may be treated with topical terbinafine or miconazole. However, if this fails or if there is widespread, nail or dermal disease, systemic antifungal therapy is recommended. Duration of treatment depends on the type of therapy and the location of the fungal infection. Treatments of choice include terbinafine, griseofulvin and itraconazole. (91)

Candida infections

Clinical presentation

Oral candidiasis is the most common presentation of candida infection, presenting as white, exudative, plaques on the tongue, and oral mucosa. It can also present as the erythematous/atrophic erythematous form without white plaques which is often missed. (92) Other presentations include angular cheilitis with erythema and white scale, and chronic hyperplastic candidiasis with discrete leukoplakia.

Cutaneous candidiasis may develop in intertriginous sites, and presents as erythematous plaques with peripheral pustules. (93) Recurrent vulvovaginal candidiasis (VVC) may occur more frequently in HIV. (94) Symptoms of VVC may include pruritus, superficial dyspareunia and dysuria. The vulval component presents as erythema with papulopustules, and the vaginal infection is associated with white discharge, and erythematous plaques on the vaginal walls.

Diagnosis

The diagnosis of candidiasis is usually made clinically. Samples for microscopic examination and cultures are usually required when fungal resistance is suspected.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Management

Intraoral therapies such as nystatin or amphotericin lozenges are often used initially for oral candidiasis, topical clotrimazole for cutaneous candidiasis, and clotrimazole or miconazole pessaries for VVC. (92, 93) Systemic antifungal therapy may be required in refractory cases or in immunocompromised patients; fluconazole is the agent of choice at a dose of 150 mg single dose .

Malassezia infections

Malassezia has seven different subspecies that cause or contribute to a spectrum of conditions, with *M. symbodialis*, *M. globosa* and *M. furfur* the most common species isolated. These are commensal organisms on normal skin, however show greater diversity and immunoreactivity in patients with HIV leading to greater likelihood of associated cutaneous manifestations. (95)

Clinical presentation

Malassezia can present in the setting of HIV as pruritic pustules, plaques or papules on the face, chest, back and shoulders. Due to its morphology and distribution, *Malassezia* pustules may be confused with acne vulgaris however comedones are not present as with acne.

Diagnosis

The diagnosis relies on a KOH preparation test from skin scrapings or swabs from pustules.

Treatment

Topical ketoconazole and miconazole can be used initially but systemic fluconazole or itraconazole may be used if topical therapy fails.

Cryptococcosis

Cryptococcus neoformans is the most common invasive fungal infection in PLWHIV. Cutaneous disease due to *Cryptococcus* is not seen in immunocompetent people. Cryptococcosis in PLWHIV is an AIDS-defining illness. (15)

Clinical presentation

Approximately 10-20% of patients with HIV infection and cryptococcal infection have cutaneous lesions, which is a marker of disseminated infection. (95) These lesions can have varying morphologies including: erythematous papules, nodules, pustules, ulcers, herpetiform vesicles, indurated plaques or subcutaneous swelling.

Diagnosis

Skin biopsy is often required to confirm cutaneous cryptococcal infection. The diagnosis of cutaneous cryptococcal infection requires investigation for systemic disease.

Management and prevention

Cutaneous cryptococcosis without evidence of systemic involvement can be treated with oral fluconazole. If extracutaneous disease is found then the recommended treatment is intravenous amphotericin and flucytosine for at least 2 weeks, followed by oral fluconazole for at least 8 weeks. (21)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Parasitic infections

Scabies

Transmission of *Sarcoptes scabiei*, the causative mite for scabies, occurs by direct skin-to-skin contact with a person who has the infection or via fomites. The likelihood of transmission is higher when the parasite burden in the affected patient is bigger. Transmission via inanimate objects, such as shared clothing, is rare, but may occur in immunocompromised individuals. (96)

Clinical presentation

Classic scabies presents as papulovesicular lesions. The distribution varies, favouring the wrists, interdigital web spaces, elbows, axillae, breasts and genitals. Predominantly night-time pruritus is usually present. Excoriation may lead to bacterial superinfection including impetigo, cellulitis and, in some cases, fatal sepsis. (98) In PLWHIV, both the classic form and generalised, crusted (Norwegian) scabies can occur. The classic form can occur at any CD4 cell count, while crusted scabies is usually seen in patients with a CD4 cell count below 200 cells/ μ L. (99)

Diagnosis

The diagnosis is usually clinical and may be assisted by dermoscopy. (100) Definitive diagnosis of scabies is by microscopic examination of skin scrapings in potassium hydroxide 10% solution, demonstrating mites, ova or faeces. The skin is scraped with a sterile blade and the skin sample is placed in mineral oil for transport.

Management

People with a CD4 cell count over 200 cells/ μ L usually respond to a single total body application of topical permethrin (5%) left on for 8 to 14 hours, and repeated after 1 week. If permethrin is not available, benzyl benzoate 25% emulsion applied for 24-36 hours may be used. The lotion is usually applied once daily at night on 2 or 3 consecutive days. Sulphur 5-10% in cream or paraffin for 3 consecutive days and repeated in 1 week, may be another alternative option, particularly for neonates. (101) Treatment also involves hot water washing and drying of clothing and linen harbouring the mite, and prophylactic treatment for all household members and sexual contacts.

Often, topical treatment does not penetrate the lesions of crusted scabies sufficiently for eradication. Therefore, keratolytic treatment with topical salicylic acid 5-10% or urea 40% can be given concomitantly. (102) In adults, systemic therapy of oral ivermectin 200 μ g/kg in two doses two weeks apart can be given, and is recommended for immunocompromised patients including those with advanced HIV infection and CD4+ cell count below 200 cells/ μ L. However, topical permethrin has a faster onset of action in terms of itch control and reducing lesions count. (103)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Non-infectious disease

Seborrhoeic dermatitis

Seborrhoeic dermatitis is a very common non-infectious cutaneous presentation of HIV and is observed in 85% of patients with AIDS. (104) Increased severity and extent of involvement with poorer response to treatment occurs with progressive immunosuppression. *Malassezia* may have a role in the pathogenesis of this disease, with higher colonisation in patients with more severe clinical involvement. (105)

Clinical presentation

Patients have erythema and yellow-white greasy scaling of the sebaceous areas of the scalp, nasolabial folds, chest, back and intertriginous zone. The eruption is characterised by widespread, scaly, greasy, lesions and may progress to erythroderma. (106)

Diagnosis

Diagnosis is clinical. Histological and microbiological assessment may assist differentiation from psoriasis, dermatophytosis or atopic dermatitis.

Management

Initial therapy includes clotrimazole cream, or anti-dandruff shampoos containing ketoconazole or selenium sulfide which can be applied to affected areas and washed off. (107). Systemic therapy with oral antifungals or isotretinoin may be considered in severe cases.

Xerosis

The underlying cause of xerosis in HIV is unknown; it may in part be linked to poor nutritional status, polypharmacy, chronic illness and immunosuppression. It is cited as affecting approximately 30% of PLWHIV. (108) Xerosis and ichthyosiform changes of the skin have been considered by several authors as a marker for disease progression as it also correlates with CD4+ T lymphocyte count decline. (108)

Clinical presentation

There are varying degrees of xerosis, but it is generally characterised by diffuse dryness of the skin with hyperpigmented scales and focal crusting. (109)

Diagnosis

Diagnosis is made on clinical assessment alone. Assessments of micronutrient status, such as vitamin A, B3, zinc and copper may be indicated. (110)

Management and prevention

Adequate nutrition is important. Dry skin care regimens are effective in the management of this condition, with emollients, including those with urea, lactic acid or salicylic acid.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Psoriasis

Psoriasis is a common inflammatory skin condition which affects 2-5% of PLWHIV compared to a prevalence of 1-2% in the general population. (111) Population studies have suggested PLWHIV are at increased risk of developing incident psoriasis, although this has not been demonstrated in the Australian population. (112) Psoriasis is associated with several systemic conditions including psoriatic arthritis (30%), metabolic syndrome (35%) and mental health disorders such as anxiety (17%) or depression (10%). (113)

Clinical presentation

Plaque psoriasis is characterised by well-defined, scaly and erythematous plaques which typically affects extensor surfaces. The erythema is classically described as 'salmon pink' in Caucasian patients, but may appear mulberry in darker skin tones. (114) Other clinical presentations include guttate psoriasis (diffuse small papules <10mm in diameter), erythrodermic psoriasis (involving >90% of body surface area), inverse psoriasis (affecting intertriginous sites such as the axillae, submammary or inguinal creases) and pustular psoriasis (presenting with sterile, pinpoint pustules). Finger or toenail changes such as pitting, discoloration or longitudinal ridging may be present in up to 50% of patients. (115)

HIV may alter the clinical presentation and course of psoriasis, and may increase in severity with the degree of immunocompromise. (116) More extensive involvement including erythroderma with increased frequency of acral lesions and inverse psoriasis may be present in the setting of HIV. (116)

Diagnosis

The diagnosis of psoriasis is clinical. Biopsy confirm the diagnosis however is not typically required. (117). Due to the association between psoriasis and metabolic syndrome, (118) international guidelines have recommended screening of cholesterol, blood glucose levels and body mass index in all patients with psoriasis. (113)

Management and prevention

Spontaneous remission to complete unresponsiveness to all therapy has been described for HIV-related psoriasis, particularly following commencement of ART and normalisation of CD4+ counts. (119, 120) Topical therapy includes emollients, coal tar, salicylic acid, vitamin D analogs, and corticosteroids. Referral to a dermatologist is indicated in cases refractory to topical therapies, with significant body surface involvement or to impairment of quality of life. (121) Systemic therapies include acitretin, methotrexate and cyclosporine (122) Phototherapy has been shown to be safe and effective in PLWHIV. (123, 124)

Oral small molecule inhibitors including apremilast or deucravactinib have demonstrated high efficacy in psoriasis, however evidence for their safety in patients with HIV is limited to case reports. (125, 126) Biologics targeting specific inflammatory pathways have emerged as highly effective treatments for psoriasis with superior safety profiles compared to classical immunosuppressants. (127) In Australia, patients are eligible for biologics for psoriasis should they have severe disease and fail or have contraindications to multiple standard systemic treatments. (128) Of note, clinical trials for all these novel therapies in psoriasis excluded PLWHIV, however small real-world studies have not shown an adverse effect on viral load or CD4+ cell counts. (129)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Pityriasis rubra pilaris

Pityriasis rubra pilaris (PRP) refers to a group of rare inflammatory skin disorders with clinical and histological similarities to plaque psoriasis. (130) There are six clinical subtypes, with Type VI, discussed herein, being proposed in 1995 as a unique HIV-associated dermatosis. (131) Due to its rarity and potential for misclassification as psoriasis, data on the incidence of PRP in people living with HIV is unknown.

Clinical presentation

Classic, Type I PRP is characterised by orange-red plaques with fine scale, which develops over weeks-to-months in a rostrocaudal fashion. Typical features which may differentiate it from psoriasis include keratotic follicular papules and 'islands of sparing', referring to areas of uninvolved normal skin interspersed between otherwise generalised plaques. (130) Erythroderma (with >90% body surface area involvement) and waxy yellow scaling of the palms and soles (palmoplantar keratoderma) may also develop.

Diagnosis

Diagnosis of PRP, including the HIV-associated Type VI subtype, relies on clinical findings and skin biopsy histopathological correlation. Up to 60% of PRP cases in retrospective studies were initially misdiagnosed as other inflammatory skin disorders, most commonly psoriasis, highlighting the diagnostic challenge in this disorder. (132)

Management

Among patients with PRP in the setting of newly diagnosed HIV infection, commencement of ART alone has been reported to induce cutaneous remission. (133, 134) Due to its rarity, management guidelines are based on retrospective studies and case series, and may include topical steroids, retinoids and vitamin D analogs in cases with limited cutaneous involvement, and systemic retinoids, methotrexate, cyclosporine and biologics (particularly infliximab). (130)

Eosinophilic folliculitis, pruritic papular eruption and other inflammatory folliculitides

Eosinophilic folliculitis (EF), previously referred to as Ofuji's disease, is a common intensely pruritic condition often occurring in advanced HIV or the setting of IRIS, commonly 3-6 months post commencement of ART. (135)

Although some believe that eosinophilic folliculitis and pruritic papular eruption (PPE) are part of the same disease spectrum, the distribution of both diseases are different. (135, 136) PPE occurs more frequently in acral and photoexposed sites, and may follow a history of arthropod bites. As such, PPE is theorised to represent cutaneous hypersensitivity to arthropod antigens secondary to HIV-mediated immune dysregulation. Similar to EF, there is an association between PPE development and degree of HIV-associated immunosuppression. (137)

Clinical presentation

Eosinophilic folliculitis presents as intensely pruritic 2-3 mm erythematous oedematous urticarial papules centred on follicles and may have pustules. The distribution is typically over the forehead, neck, shoulders, trunk and upper arms. In women living with HIV, PPE may more predominantly involve

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

the face and therefore mimic acne excorioriae. (138) Due to the associated pruritus, excoriations with secondary *Staphylococcal* infection, prurigo nodularis, lichen simplex chronicus and postinflammatory pigmentary changes are common. (134)

PPE appears as multiple papules, typically symmetric, on the trunk and extensor surfaces of the extremities, as well as on the face, with sparing of the palms and soles. (135) Because of the chronic nature of PPE, like with EF, papules are often excoriated and develop post-inflammatory hyperpigmentation and scarring. Over time, severe inflammation exacerbated by persistent scratching causes the papules to become nodular in appearance. (136)

Diagnosis

The differential diagnosis is difficult and includes the common causes found in patients without HIV such as insect bite reactions, scabies, dermatitis herpetiformis, drug reactions, atopic dermatitis and bacterial folliculitis. Skin biopsy for histopathological assessment be helpful, however EF and PPE have overlapping histological features and thus should be used primarily to support clinical diagnoses. (136)

Management

Depending on the cause, management varies, particularly if an infective cause such as scabies is found. Eosinophilic folliculitis and pruritic papular eruption can be difficult to manage with the pruritus often unresponsive to traditional therapies. Case reports of both EF and PPE remission following commencement of ART have been reported. (139, 140) Treatment options for eosinophilic folliculitis and pruritic papular eruption are similar and aim to reduce skin inflammation, including with emollients, potent topical corticosteroids, oral antihistamines, oral antibiotics, antifungals, antiscabies and phototherapy treatments all trialled.

World Health Organisation guidelines emphasise that in children, adolescents, pregnant women and adults with HIV infection who develop PPE or EF, ART should be considered as the primary treatment. If PPE or EF appears after the introduction of ART, it should not be discontinued. If there is no response or a failure in response to the treatments described above, other causes of papular eruptions of HIV must be considered. (142)

Serious adverse drug eruptions including Stevens - Johnson syndrome and toxic epidermal necrolysis

Drug reaction, eosinophilia and systemic symptoms (DRESS)

Drug reaction, eosinophilia and systemic symptoms (DRESS) is a rare severe cutaneous adverse reaction (SCAR) seen more commonly in PLWHIV. (143) DRESS can develop as a SCAR to medications, including ART agents such as abacavir or raltegravir which demonstrate association with HLA genotypes HLA-B*5701 and HLA-B*53:01, respectively. (144-146)

Clinical presentation

The disease is characterised by cutaneous eruption which can take on any morphology, fever, lymphadenopathy and the presence of eosinophilia or atypical lymphocytes and solid organ inflammation on laboratory investigation. Common end organs affected include the heart, lung, kidneys and liver. Mortality approaches 20% if untreated, usually as a result of hepatotoxicity. (143)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Diagnosis

The diagnosis is usually clinical, and may be aided by the REGISCAR scoring system. (147) Skin biopsies usually reflect the morphology of the cutaneous eruption but are not specific to DRESS. The eosinophilia may be delayed, developing days after the first skin signs are noted.

Management

Identification and cessation of the causative medication is paramount. High dose corticosteroids, eg prednisolone 1mg/kg/day are the cornerstone of treatment. This is usually tapered over a period of 6-12 weeks. Guidelines do not suggest differing treatment for DRESS in PLWHIV. Following the acute phase, DRESS patients are at risk of autoimmune sequelae such as diabetes mellitus type I and thyroid disease and should be serially monitored. (148)

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are part of the spectrum of SCAR. The incidence is higher in patients with HIV infection than in the general population due to higher rates of polypharmacy and underlying immune dysregulation. (149, 150) There have been well documented case reports of Stevens- Johnson syndrome and TEN in the setting of HIV treatment with protease inhibitors and, most commonly, nevirapine. (151)

Clinical presentation

Patients with SJS/TEN may present with a prodrome of fever, stinging eyes, painful swallowing, followed by development of dusky macules which progress to erosions and bullae. Epidermal detachment is common, which may lead to massive fluid loss and electrolyte imbalance. Any mucosal surface may be affected including the eyes, aerodigestive tract and genitalia. SJS is characterised by <10% body surface area involvement, TEN by >30% and SJS/TEN overlap by 10-30% coverage. (152)

Diagnosis

A skin biopsy is usually obtained for definitive diagnosis given the morbidity and mortality associated with this condition. Severity scoring such as with the SCORTEN criteria may be helpful for prognostication. (153)

Management

Stevens-Johnson syndrome has an attributable mortality of 5% and TEN an overall mortality of 30%. (153) If SJS/TEN is considered, patients should be transferred to a tertiary centre, and ideally one with an HDU/ICU or Burns Unit. Discontinuation of the offending drug is essential. Drugs initiated in the last 1 to 3 weeks before illness should be considered as potential causes including all drugs the patient is receiving, including over-the-counter and non-prescription as well as herbal and traditional medicines.

Supportive measures include wound care, maintenance of fluid, electrolyte and temperature homeostasis, and multidisciplinary specialist input (e.g ophthalmology, urology, pain team etc). Some units use high doses of intravenous immunoglobulins or etanercept as therapy for TEN, including in PLWHIV; however, more evidence of its effectiveness is needed. (154, 155) The use of systemic corticosteroids is controversial and prophylactic antibiotics are not recommended. (156)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

HIV-related opportunistic infections (OI) in the central nervous system (CNS)

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Last Reviewed: November 2019

Introduction

People with HIV (PWH) presenting with central nervous system (CNS) manifestations require careful assessment as the differentials are broad. Key factors in the history and examination to narrow down the diagnostic possibilities include a sudden vs. insidious onset; an acute or vs. sub-acute vs chronic course; the presence or absence of associated features such as fevers, confusion, headache, memory loss, and localising neurological deficits; local epidemiology, and the degree of immunosuppression associated with HIV. OIs are more common with advanced HIV though malignancies such as primary CNS lymphoma or metastatic disease, and other non-infective conditions need to be considered. Most CNS OIs such as cryptococcal meningitis and meningoencephalitis, and the rarer OIs in our region, such as tuberculous meningitis (TBM), toxoplasmosis, and cytomegalovirus (CMV) encephalitis are associated with systemic infective symptoms. In contrast, the rare, progressive multifocal leucoencephalopathy (PML) typically has minimal infective features. Clearly, “common” CNS infections that occur in immunocompetent persons such as varicella zoster virus (VZV) encephalitis, enterovirus infections, and bacterial meningitis, can also occur in people with HIV (PWH). Dual pathology can also occur.

This chapter focuses on the two classical CNS OIs – cryptococcal meningitis and PML and is targeted at general practitioners and nurse practitioners working in Australasia. For detailed inpatient care, readers should consult definitive texts and guidelines, including the various guidelines for cryptococcosis (Global guidelines published by the European Congress of Medical Mycology (ECMM) (1), HIV-guidelines by the US Center for disease control (CDC) (2), HIV guidelines by European AIDS EACS (3), Australasian haematology-Oncology antifungal guidelines.(4) For PML and other OIs, please refer to the HIV-guidelines by the US CDC. (2)

Cryptococcal meningitis/ meningoencephalitis

Cryptococcal disease (cryptococcosis) is caused by *Cryptococcus neoformans* – *Cryptococcus gattii* complex, a ubiquitous environmental yeast that is endemic in many countries including Australia. While cryptococcosis can affect many organs, cryptococcal meningoencephalitis is the most frequently recognised, and most severe form with mortality rates, ranging from 24%-47% at 10 weeks.(5-8)

Clinical presentation

Patients typically present with an acute, subacute or chronic meningitis or meningoencephalitis Signs and symptoms include headache, nausea, fever, altered consciousness, cranial neuropathy, memory loss, confusion, meningeal irritation signs, nausea and vomiting, seizures, visual and hearing deficits, and coma. Occasionally, CNS symptoms may be subtle so the absence of CNS symptoms in a patient with positive serum cryptococcal antigen does not exclude CNS involvement.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Diagnosis

The diagnosis of cryptococcal meningoencephalitis is confirmed with a lumbar puncture. Typically, the opening pressure is high (more than 20 cmH₂O) and the cerebrospinal fluid (CSF) analysis reveals a lymphocytosis, with a positive CSF cryptococcal antigen (CrAg), and a positive India ink. Brain imaging such as CT and MRI may show meningeal enhancement, ventricular compression, or cryptococcomas. Pulmonary lesions (typically lung nodules) are often found incidentally. All patients with a positive serum CrAg, those who have cultured *Cryptococcus* spp. in their sputum, or has a pulmonary lesion suspicious for cryptococcosis, should be thoroughly investigated to consider CNS involvement, including brain and chest imaging, lumbar puncture, and blood culture. (1)

Management

Appropriate antifungal therapy and optimal management of raised intracranial pressure are the two key pillars of cryptococcal meningoencephalitis management. Antifungal therapy in cryptococcosis is traditionally divided into three phases – induction, consolidation and maintenance. Induction with liposomal amphotericin (3-4 mg/kg/day) and 5-flucytosine (100 mg/kg/day in 3-4 divided doses) remains the most optimal regimen for induction treatment of cryptococcal meningoencephalitis in resource-rich settings such as Australia. This is usually given for 2 weeks, with consideration for a more extended course in select clinical settings. Liposomal amphotericin while less toxic than conventional amphotericin, is still associated with renal impairment, hypokalaemia and hypomagnesaemia, thus pre-emptive aggressive fluid, potassium and magnesium replacement is recommended. 5-Flucytosine is associated with cytopenias.

Of note, the single dose of liposomal amphotericin 10 mg/kg given with the backbone of 14 days of Fluconazole 1200 mg daily and 5-Flucytosine 100 mg/kg/day in 3-4 divided doses (sometimes referred to as the Ambition-cm regimen) as induction therapy was compared against sub-optimal induction regimens, (9) and is recommended in resource-limited settings, (10) but not so, in resource-rich settings.

The general practitioner is likely to be involved predominantly in the maintenance and consolidation phases of cryptococcal meningoencephalitis therapy. Here, the mainstay is fluconazole 400-800 mg daily in consolidation and 200 mg daily in the maintenance phase. Maintenance therapy may be ceased after 12 months of antifungal therapy in people who are on ART with CD4 count > 100 cells/mm³ and a suppressed viral load. Fluconazole should be restarted if the CD4 count drops below this threshold. (1)

The main risk of fluconazole is worsening liver function tests, gastrointestinal intolerance such as nausea, vomiting, abdominal pain, and diarrhoea, and also QTc prolongation. The potential of drug-drug interaction should always be considered. Of note, alternative antifungal agents for these phases is rarely required. Any consideration of switching to an alternative therapy should be discussed with an expert.

Most patients with cryptococcal meningoencephalitis have raised intracranial pressure (ICP). This increased pressure is associated with cognitive impairment, neurological defects and increased short-term mortality. (11) Aggressive management of raised ICP with therapeutic lumbar punctures is recommended in international cryptococcal meningoencephalitis guidelines. Current recommendations for the management of raised ICP suggests repeated daily CSF drainage until opening pressure is stable, and drainage until CSF closing pressure is ≤ 20 cmH₂O or < 50% of the initial opening pressure. (1)

There are no prospective treatment studies on isolated pulmonary cryptococcosis. In principle, asymptomatic or mild-to-moderate pulmonary cryptococcosis may be treated with 400-800 mg fluconazole daily for 6-12 months while those with severe symptoms, diffuse infiltrates on imaging, and those with concomitant CNS disease should be treated as for CNS disease. (1)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Timing of antiretroviral therapy commencement

The timing of ART commencement in the setting of any newly diagnosed opportunistic infection has been long debated where the risk of immune reconstitution inflammatory syndrome (IRIS) in early ART commencement is measured against the ongoing risk of co-infections in late ART commencement. In cryptococcal meningoencephalitis, two small and one large randomised controlled trial cautioned against very early ART initiation, with most guidelines recommending deferring till 4-6 weeks after cryptococcal meningoencephalitis presentation but noting the importance of individualisation of care. In principle, patients treated with optimal induction antifungal therapy (such as liposomal amphotericin and 5-FC in our settings) clear their CSF of cryptococcosis earlier, and studies have shown that patients who have been able to sterilise their CSF (i.e. attain CSF culture negativity) prior to ART commencement have improved clinical outcomes, including a lower rate of microbiological relapse and C-IRIS. (12)

Taken together, current evidence suggests that very early commencement of ART (in the first 11 days after cryptococcal meningoencephalitis diagnosis) is likely harmful. Equally, deliberate delay of antiretroviral therapy commencement to > 5 or 6 weeks after cryptococcal meningoencephalitis diagnosis risks losses in follow-up. It is likely that patients could be risk-stratified – patients who demonstrate good clinical improvement, have normalised their CSF opening pressure and have sterilised their CSF are not likely to require a delay of > 5-6 weeks.

Neurological deterioration post-ART commencement

Patients with cryptococcal meningoencephalitis are known to have symptomatic relapse despite being on adequate antifungal therapy and ART and may re-present with worsening headaches, new seizures or sudden loss of conscious state. Differentiating cryptococcal microbiological relapse from cryptococcosis-associated immune reconstitution inflammatory syndrome (C-IRIS) and other infective and non-infective cases is important to guide ongoing management.

A thorough history and examination, and a repeat lumbar puncture is recommended to measure opening pressure, and CSF should be sent for biochemistry, cell counts, cryptococcal culture and other molecular tests as necessary. In addition, brain imaging including CT and MRI scans may be necessary to look for focal brain lesions or meningeal enhancement. A positive CSF cryptococcal culture suggests microbiological relapse – re-induction of antifungal therapy, therapeutic LPs, and paired antifungal susceptibility testing with the initial isolate are recommended.

Note that while CSF and serum cryptococcal antigen is often performed, the antigen tests will remain positive for months to years, thus a high (even a higher) titre does not necessarily indicate microbiological relapse. Similarly, a CSF with a positive gram stain or India ink for *Cryptococcus spp.*, is not necessarily indicative of microbiological relapse as dead Cryptococci are often seen for a prolonged period.

In patients with C-IRIS, symptomatic management with analgesia including non-steroidal medication, and regular therapeutic LPs, often suffice. In some cases, steroids (Prednisolone 0.5-1.0 mg/kg/day, weaned over 4-6 weeks, may be considered). Steroid-refractory C-IRIS requires expert discussion including for the role of alternative agents such as tumour necrosis factor (TNF) blockers and others.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Progressive multifocal leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) is a demyelinating disease of the CNS caused by reactivation of John Cunningham virus (JCV). This rare condition is associated with advanced immunosuppression almost exclusively – malignancy, HIV, organ transplantation, and immunomodulatory agents.

Clinical features

The demyelination involves white matter and can involve grey matter. In classical PML, the signs and symptoms typically develop and progress over several weeks or months. As in the name, the multifocal involvement results in a myriad of neurological deficits including cognitive impairment, sensory or motor deficits, gait disturbance, visual disturbance, speech changes, seizures, difficulty swallowing, and altered mentation. Clinical examination may reveal hemiparesis, hemineglect, visual field defects (including homonymous hemianopia), cerebellar signs and gait disturbance. The presentation of PML is notable for the absence of fever in the patient. Classical PML is usually progressive and fatal.

Other forms of potentially “milder” JC virus infection are increasingly recognised such as those with a single lesion, JCV encephalopathy, JCN meningitis, and JCV cerebellar granule cell neuronopathy.

Diagnosis

MRI brain and CSF analysis for JCV by polymerase chain reaction (PCR) are key to the diagnosis of PML. Typical clinical and radiological findings alongside a positive JCV PCR in the CSF are adequate for a probable diagnosis of PML. The degree of JCV viral load may have prognostic implications.

A brain biopsy may be necessary to confidently exclude other pathologies, particularly in atypical cases or those with unifocal lesions. The insidious nature of PML raises the possibility of concurrent HIV encephalopathy, primary CNS lymphoma or concurrent OIs such as toxoplasmosis – features on MRI brain, the presence of JCV, Epstein-Barr virus (EBV), Toxoplasma PCR, HIV viral load, and ultimately a brain biopsy can help distinguish these conditions.

Management

Unfortunately, there is no specific treatment for PML. Overall prognosis is poor. PWH who are ART-naïve and develop PML should commence ART (preferably with good CNS penetration). ART serves to immune restore and has in some cases led to modest clinical response, noting the risk of PML-IRIS.

A repeat LP to look for a drop of JCV viral load may guide treatment response. The timing of follow-up assessments should be guided by clinical progress.

Agents such as maraviroc, mirtazapine, mefloquine have been tried with no obvious benefit. Of late, there has been interest in considering checkpoint inhibitors such as nivolumab and pembrolizumab, (13) and JCV-specific T-cells therapy. (14) These remain under investigation and require expert discussion.

Early discussions on goals-of-care and symptomatic and supportive care are encouraged.

Timing of antiretroviral therapy commencement

As discussed above, ART should be commenced early in the setting of HIV-PML co-infection as this is key to immune restoration.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Neurological deterioration post-ART commencement

Patients with PML can continue to progressively deteriorate despite ART. It can be difficult distinguishing natural progression of PML from PML-IRIS, where the latter may benefit from steroid therapy. PML-IRIS typically has MRI changes suggestive of progressive oedema

If a patient continues to have progressive CNS decline despite virological and immunological response to ART, consideration should be given to a brain biopsy, particularly if the initial diagnosis of PML was presumptive and not virologically proven.

Summary

The diagnosis and management of CNS OIs can be complex. Please seek help from local and international experts where needed.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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6. Other HIV-Associated Disease

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Haematological disorders in people with HIV infection

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Last reviewed: October 2019

Introduction

Despite significant reductions in all complications of HIV infection since the introduction of combination antiretroviral therapy (cART), haematological disorders remain common.⁽¹⁾ Common problems are cytopenias, dysproteinaemia, lymphadenopathy and splenomegaly, and thromboembolic disease. The majority of cytopenias respond to ART.⁽²⁾

Anaemia

Anaemia is a common problem and increases in frequency with stage of HIV infection, ranging from 3% of asymptomatic patients to 12% of patients with CD4+ T cell counts of <200 cells/μL (or a CD4+ T cell percentage of <14% of lymphocytes) and 37% of patients with the acquired immunodeficiency syndrome (AIDS) in one large surveillance study.⁽³⁾ Anaemia has been associated with reduced survival in a number of studies, independent of other risk factors such as CD4+ T cell count and HIV viral load.^(3,4) The cause for this association has not been determined. This relationship is more pronounced in patients who remain anaemic after commencing cART. ⁽⁵⁾ Causes of anaemia are often multifactorial. Common causes of anaemia include anaemia of inflammatory disease (previously termed anaemia of chronic disease), drugs such as zidovudine, cotrimoxazole, amphotericin B, ganciclovir, ribavirin and dapsone, and both opportunistic and non-opportunistic infections. Other causes are malignancy (lymphoma and Kaposi's sarcoma involving the gastrointestinal tract) and hypersplenism (often associated with liver disease such as chronic viral hepatitis). Rarer, important causes include Castleman's disease, human parvovirus B19 infection, thrombotic thrombocytopenic purpura haemophagocytic syndrome. Anaemia of inflammatory disease may be due to HIV infection, other infections or cancer. Zidovudine and lamivudine may cause a macrocytosis.^(1,6) Low B12 levels are not uncommon but true B12 deficiency is rare.⁽⁷⁾ Similarly, while direct antiglobulin tests are often positive, ranging from 18 to 43% of people with HIV infection,⁽⁸⁾ autoimmune haemolytic anaemia is rare.⁽⁹⁾

The ideal treatment for anaemia is to identify and manage the underlying cause (e.g. treat HIV or other infections or remove causative drugs). Human parvovirus B19 infection is a rare but interesting cause of pure red cell aplasia in severely immunodeficient patients; it responds to cART and intravenous immunoglobulin therapy.⁽¹⁾ If the cause of the anaemia cannot be corrected, then exogenous erythropoietin may improve haemoglobin levels and quality of life.^(10,11) However, it is not effective in patients with high endogenous levels (>500 IU/L). Treatment with erythropoietin may reduce the risk of mortality while blood transfusion therapy may increase this risk.^(12,13) Consequently, only patients with symptomatic anaemia without a correctable cause should be considered for transfusion.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Thrombocytopenia and immune thrombocytopenic purpura

Thrombocytopenia is commonly observed in people with HIV infection with immune thrombocytopenic purpura (ITP) the most common cause of severe thrombocytopenia (platelet count $< 30 \times 10^9/L$). It may occur in 30% or more of patients with AIDS(13) and can occur at any time during HIV infection. In the antiretroviral era, risk factors include HIV viral load > 400 copies/mL, hepatitis C virus co-infection and cirrhosis.(14) It may be seen before other clinical manifestations of HIV infection. Therefore, HIV antibody testing is recommended in the assessment of new cases of thrombocytopenia. Platelet depletion in HIV-associated ITP has several causes. Immune complexes of antibodies to HIV glycoprotein (gp) 120 may bind the platelet membrane GPIIb/IIIa complex(15) and it appears that megakaryocytes may be directly infected by HIV.(1) Platelet survival is decreased, especially in patients with only mild-to-moderate depletion of CD4+ T cells, as is platelet production.(1) Other common causes of thrombocytopenia in HIV patients are drugs, such as ganciclovir, cotrimoxazole and rifabutin, infections such as *Mycobacterium avium* complex (MAC), lymphoma and hypersplenism (most commonly due to liver disease). Rarer causes that appear directly related to HIV infection are thrombotic microangiopathies, thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome. Bleeding is uncommon in ITP unless the platelet count is $< 30 \times 10^9/L$. However, patients with co-existing haemophilia or other coagulopathies should be treated if platelet counts fall below $50 \times 10^9/L$.(16) The treatment of choice for ITP is cART. Corticosteroids are effective but long-term use is not desirable due to immunosuppression. Other drugs such as dapsone and danazol can be effective. Intravenous immunoglobulin is very effective in increasing platelet counts in the short term but is expensive. Splenectomy may be successful for refractory cases and does not increase risk of progression to AIDS.(16) The thrombopoietin receptor agonists, romiplostim and eltrombopag may also be effective and considered for patients with refractory ITP (17) who are not fit for splenectomy. For other causes of thrombocytopenia, treatment of the underlying cause is usually effective. Support with platelet transfusions should only be considered for patients at immediate risk of bleeding as the effect of transfusion is short lived and platelet allo-antibodies rapidly develop, limiting the effectiveness of future transfusions.

Neutropenia, pancytopenia and myelodysplasia

Neutropenia is common in HIV infection (16% of patients in one study of over 130,00 individuals in a primary care setting) and should trigger testing for HIV infection. (18) Neutropenia may be due to HIV infection itself, autoimmune neutropenia, infections such as MAC and tuberculosis (TB), marrow infiltration by malignancy (commonly lymphoma), hypersplenism and drugs. Treatment is directed at the underlying cause: ART for HIV infection; antibiotics for infection; and the withdrawal of potentially causative drugs. Granulocyte colony stimulating factor (G-CSF) will usually correct severe neutropenia in refractory cases and may allow marrow suppressive drugs such as ganciclovir to be continued until infection has resolved. Infection or undiagnosed fever associated with severe neutropenia (neutrophil count $< 0.5 \times 10^9/L$) should be considered a medical emergency with immediate commencement of broad-spectrum antibiotics and supportive therapies such as G-CSF.(1)

All of the causes of individual cytopenias may produce a generalised pancytopenia. Late HIV infection commonly causes a myelodysplasia-type syndrome with impaired bone marrow function. Pancytopenia with severe lymphopenia and eosinophilia are commonly observed in the blood. Examination of the bone marrow commonly demonstrates normal or increased cellularity suggesting the impaired marrow function is due to inhibition of cellular maturation and production. Marrow plasmacytosis, lymphoid aggregates, granulomata and fibrosis are common.(19)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Paraproteinaemia

An increase in immunoglobulin production occurs as part of the immune dysfunction caused by HIV infection and monoclonal paraproteins have been reported in as many as 7% of people with HIV infection. They do not appear to be clinically significant and may persist despite ART.(20) Similarly, cryoglobulinaemia has been reported in HIV infection, again without clinical significance. Over 90% of HIV patients with cryoglobulinaemia are co-infected with hepatitis C virus and HIV infection does not appear to be a causative factor.(21)

Thromboembolic disease

Thrombosis has been reported in up to 2% of people with HIV infection. Risk factors for this group are age over 45 years, advanced stage of HIV infection, co-existing opportunistic infections, hospitalisation, and therapy with indinavir and megestrol acetate.(22) A number of potentially pro-thrombotic abnormalities have been reported in association with HIV infection, including decreased levels of (a) antithrombin (seen in HIV nephropathy), (b) free protein S, (c) protein C and (d) heparin cofactor II; lupus anticoagulant and anticardiolipin antibodies; co-existent malignant, inflammatory and autoimmune disorders; as well as vascular damage due to injecting drug use, vascular catheters and CMV infection.(23) Lupus anticoagulant or anticardiolipin antibodies are weakly associated with venous thrombosis but cerebrovascular accidents, bone and skin necrosis and brachial artery thrombosis have been reported.(1)

Investigations

Bone marrow examination should be undertaken for any unexplained moderate-to-severe anaemia or isolated cytopenia or pancytopenia and for pyrexia of unknown origin where initial tests are unhelpful. Specimens should be sent for special microbial cultures, such as MAC, flow cytometry to examine to help exclude lymphoma, as well as for morphological examination.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Heart disease in HIV infection

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Last reviewed: November 2019

Introduction

The arrival of effective antiretroviral therapy (ART) has meant that there are many HIV-infected people living to advanced age. Therefore, diseases more associated with the middle and older years will achieve increasing importance as co-morbidities of HIV infection. In the time before effective ART there were a number of cardiac/vascular conditions more commonly seen in HIV-infected patients than in uninfected patients from similar backgrounds; these included dilated cardiomyopathy, pulmonary hypertension and pericardial effusions. Happily, these are seen less frequently since the arrival of effective ART. Nonetheless, these diagnoses are important to consider in patients with appropriate physical signs. Arrhythmias occur often in the setting of cardiovascular disease (CVD) and should be assessed and treated accordingly. Additionally, cardiac electrical dysfunction may be precipitated by antiretroviral drugs and their interactions with other medications.

Pulmonary hypertension

Pulmonary arterial hypertension (PAH) in the setting of HIV infection recently acquired its own specific category in the Updated Classification of Pulmonary Hypertension. (1) It consistently has been found in 0.5% of HIV-infected people, a figure unchanged by the widespread use of effective ART (2) and represents a rate about a thousand times greater than that of idiopathic pulmonary hypertension as reported in the general population. Hospital discharge data suggests that PAH is under-recognised in comparison to known prevalence rates. (3) Pathological features are similar to idiopathic PAH. Viral particles from HIV are not found in affected tissues suggesting that the pathogenesis is likely a consequence of HIV-induced inflammation or other systemic changes. There may also be a contribution from other viral infections. High HIV viral load and low CD4+ T cell count appear to be predictive of HIV-associated PAH. (4) Findings on gender differences have been variable but male intravenous drug users seem to be particularly at risk. There is experimental evidence for an additive effect of cocaine. Recent evidence has suggested a particular pathogenic role for Endothelin-1. (5) HIV infection may first be recognized in patients admitted with an initial diagnosis of idiopathic PAH. (6) As in the general community, PAH often presents late (NYHA Class II or IV).

Published guidelines do not recommend routine screening for PAH in the HIV-infected population but do highlight the need for consideration of PAH in patients with unexplained dyspnea. Initial investigations should include transthoracic echocardiography (which may also identify other cardiac causes of dyspnea). Definitive diagnosis of PAH requires right heart catheterization to demonstrate elevated pulmonary artery pressures in the presence of normal 'wedge' (left atrial) pressure. Whilst echocardiographic derived pulmonary systolic pressures of > 40mmHg have been used to identify patients with potential PAH, others have suggested that a lower cut off of 20mmHg may be prudent in order to avoid underdiagnosis. Patients with suspected PAH should be referred for specialist evaluation.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Management of HIV patients with PAH broadly follows the guidelines for PAH management in the general population. (1) In the HIV population with PAH, anticoagulation is not recommended. Calcium channel blockers appear to be less effective in PAH due to HIV infection. Treatment with phosphodiesterase inhibitors may require dose adjustment due to drug-drug interactions. In a particular study of HIV-infected patients with PAH, a long-term benefit was demonstrated with bosentan. (7) Lung transplantation has been successfully undertaken in cases with otherwise uncontrolled PAH.

Pericardial effusion and cardiomyopathy

Early in the HIV epidemic, high rates (11%) of pericardial effusion were noted in patients with HIV infection (8). With the advent of ART, the condition became much less common and in one study of 802 patients (of whom 85% were taking ART), only two (0.25%) were found to have echocardiographic evidence of a pericardial effusion and in neither case was cardiac function compromised. (9) However, in Africa pericardial effusions are likely to be the first manifestation of HIV/AIDS related cardiac disease, often significantly large enough to cause tamponade, of which 70% can be due to *Mycobacterium tuberculosis* infection. (10)

Cardiomyopathy in HIV-infected patients is thought to be multi-factorial, possibly resulting from a) direct infection of the myocardium with HIV (with or without myocarditis), b) the release of pro-inflammatory cytokines, c) opportunistic infections including cardiotropic viruses, d) nutritional disorders, and e) drug toxicity. (11) Data from early in the epidemic suggested cardiomyopathy (measured as systolic dysfunction, usually as the ejection fraction) was much more common than in current times. A meta-analysis of more than 2200 asymptomatic HIV patients well-controlled on ART put the rate of systolic dysfunction at 8.3%, but diastolic dysfunction was present in 43.4%. Systolic dysfunction was associated with high serum CRP levels, smoking and previous myocardial infarction, while diastolic dysfunction was more common in older patients and those with hypertension. (12)

Despite reductions in the incidence of both pericardial effusions and systolic dysfunction, these conditions should still be considered in the setting of HIV infection when someone presents with dyspnea, cardiomegaly and a raised jugular venous pressure, especially when CD4+ T cell counts are low.

Treatment entails optimising control of HIV replication, where necessary, with the addition of standard measures for the management of pericardial effusion and cardiomyopathy as appropriate. When end-stage cardiac failure results from any cause, consideration for cardiac transplantation should be entertained, as HIV infection is not a contraindication. (13)

Cardiac malignancy

Malignant conditions of the heart are rare but have been seen in HIV-infected patients, particularly in those with more advanced immunodeficiency. Non-Hodgkin's lymphoma and Kaposi's sarcoma have both been reported to affect the heart. The impact of ART has been reported to be most profound on KS of the heart, reducing the prevalence from up to 28% (on autopsy studies) to being largely unseen. (14)

Infective endocarditis

HIV infection is not seen as a particular risk factor for infective endocarditis (IE), however it can occur and, in a similar way to the HIV-uninfected population, it is more frequently seen in those people who inject drugs. The advent of ART does not seem to have had a large impact on prevalence of IE in this particular population. (15) However, in a US nationwide study of IE, the prevalence of HIV infection amongst IE patients fell from 4.8% in 1998 to 1.5% in 2009 (16) for reasons that are not entirely clear.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Cardiac arrhythmias

In a large US study of more than 30,000 veterans, 2.6% developed atrial fibrillation (AF) over a median time of 6.8 years. This was significantly more common (and independent of other risk factors) in those with lower CD4+ T cell counts and higher HIV viral loads. (17) As in all cases of AF, treatment is usually required. This may be rhythm or rate control. Rate control is most usually with a beta blocker. Digoxin is not frequently used in the management of AF but may be necessary since calcium channel blockers have the potential to interact with some antiretroviral drugs. Usual agents for rhythm control are flecainide (only in the absence of cardiac disease), sotalol or amiodarone. Pulmonary vein isolation (PVI) can be considered if the symptoms are hard to control, though recent evidence has not shown any superiority of PVI in terms of clinical outcomes. (18) The need for anticoagulation in the general population with AF is determined by their stroke risk score (eg ATRIA or CHAD2Vasc score). However, only a weak correlation between CHAD2Vasc score and thromboembolic events was shown in an HIV-infected population and warfarin use was not effective. (19) Nevertheless, given the weight of other evidence it is not appropriate to withhold anticoagulation on the basis of this one study, although it may be reasonable not to anticoagulate those patients with only borderline risk. Outcome trials with direct oral anticoagulant drugs, such as apixaban, have not included patients with HIV infection.

There have been mixed reports of HIV protease inhibitors (PIs) having a detrimental effect on electrical conduction in the heart; some studies found QT prolongation (20) while others did not. (21) While it is not necessary to perform an ECG on everyone commencing PIs, it would be advisable to do so in patients with CVD risk factors, both before commencing treatment and a few months afterwards, to see if there is a discernable effect. Care should be taken when prescribing other drugs that may also exacerbate QT prolongation and arrhythmias, including macrolides, fluoroquinolones, triazole and imidazole antifungal agents, pentamidine and methadone. (22)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Rheumatological disease in patients with HIV infection

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Last reviewed: August 2019

Introduction

In the general population, rheumatological conditions can arise in any age group and are often chronic and progressive. As HIV-infected patients taking antiretroviral therapy (ART) can now achieve almost normal life-expectancy, it is to be expected that diseases affecting joints, muscles and connective tissue will have a greater impact in this group than previously. That said, some rheumatological conditions have always had particular impact in patients with HIV infection and may appear during a primary HIV infection syndrome or any time thereafter. Prompt diagnosis and management can usually reduce the symptoms and prevent, or at least slow, the progression of the condition. Many rheumatological diseases are best treated with immunosuppressive agents, more recently including 'biologic agents', and in general, all types of therapy should be considered, especially if the HIV infection is controlled by ART.

The major rheumatological conditions that may be experienced by HIV patients are listed in table 1.

Table 1. List of rheumatological conditions found in HIV-infected patients. (1)

Myalgia and Arthralgia

Arthritis

- HIV-related arthritis
- Osteoarthritis
- Painful Arc Syndrome
- Reactive arthritis
- Psoriatic arthritis

Gout

- Rheumatoid arthritis
- ART-associated arthritis

Avascular necrosis

Diffuse Infiltrative Lymphocytosis Syndrome

Vasculitis

Systemic Lupus Erythematosus

Bacterial Infections

- Septic arthritis
- Pyomyositis
- Osteomyelitis

Polymyositis and other myopathies

1. Adapted from Espinoza (1)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Myalgia and arthralgia

In primary HIV infection syndrome, myalgia is quite commonly experienced, occurring in 30% of a Korean cohort, (2) though previously it has been noted to be present in up to a half of patients and that the symptoms could persist for weeks or even months. (3) Arthralgia is less common, occurring in approximately a quarter of patients and is very variable in its severity, (4) though it was relatively rare in the Korean study. (2) Both of these symptoms are best managed with simple analgesia, such as paracetamol, or anti-inflammatories, such as non-steroidal anti-inflammatory drugs (NSAIDs), and rest.

Arthritis

HIV-related arthritis

Weeks or even years after primary HIV infection syndrome is complete, a condition referred to as HIV-related arthritis may occur. (5) Most commonly this affects large joints of the upper limbs and knees, in an asymmetric pattern. This can usually be managed by rest, NSAIDs and paracetamol, though occasionally the pain is severe or persistent enough to warrant an intra-articular corticosteroid injection. Less commonly, HIV-related arthritis may mimic rheumatoid arthritis with a symmetrical polyarthropathy that may become destructive. (6)

Osteoarthritis

While not recognised as being particularly associated with HIV infection, osteoarthritis (OA) is likely to become more apparent as the HIV-infected population reaches old age. Four cases of OA in HIV-infected patients were described by Larcher et al (7) and it was suggested that it may be a manifestation of early senescence in HIV-infected people. The presentations were typical for the condition (eg. pain, stiffness, Heberden's nodes etc) and the patients received standard treatment.

Painful Arc Syndrome

This acute and severe syndrome mainly affects large joints and may cause intense pain for two or three hours or even several days. It may require NSAIDs or even hospitalisation and opiates. Berman described the phenomenon early in the HIV epidemic in the US and Argentina (8, 9) but it did not feature prominently in similar studies that followed. (10)

Spondyloarthropathies

The spondyloarthropathies affect the spine and sacro-iliac joints and mainly occur in men. HLA-B27 positivity is common (in Caucasians) but patients are rheumatoid factor negative, making this part of the so-called 'seronegative' arthropathy group.

Reactive arthritis

This is usually an oligoarthritis, with enthesitis (inflammation of the periarticular connective tissue, particularly tendons, ligaments, joint capsules and fascial bands), affecting the lower limbs and frequently occurring with skin pathology, such as circinate balanitis and keratoderma blenorrhagica. (11) It often follows a genital or gastrointestinal tract infection that occurred 1-6 weeks earlier, including Chlamydia trachomatis, Campylobacter, Salmonella, Shigella and Yersinia species infections. (12) This condition was well-described in the early years of the HIV epidemic but its frequency may have declined with the advent of ART (13) despite increasing diagnoses of chlamydial infections in this group. (14) The triad of reactive arthritis, conjunctivitis and urethritis still occurs but is no longer called Reiter's syndrome.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

The symptoms may last for just a few weeks in some patients but not infrequently there may be debility for many months. When only one joint is involved, septic arthritis may be suspected. To further confuse the situation joint aspiration may yield significant numbers of leukocytes that might be predominantly neutrophils (though the joint fluid would usually not have the purulent appearance expected of septic arthritis. Precipitating gastro-intestinal infections, such as *Campylobacter* infection, will usually have long settled and not need treatment, however, screening for *Chlamydia trachomatis* infection of the genitourinary tract, and treatment of it if found, is recommended.

The arthritis itself usually responds to NSAIDs and simple analgesia but more severe, complex and chronic disease may require a specialist rheumatological opinion and disease modifying agents such as sulfasalazine and even methotrexate. Both oral and injectable corticosteroids have been used (12) though care should be used in their co-administration with ART. For example, triamcinolone when used with ritonavir or cobicistat has caused iatrogenic Cushing's syndrome (which may itself cause myalgia and arthralgia). (15)

Psoriatic arthritis

Psoriasis is an inflammatory skin condition that affects 2-4% of the general population. Skin disease and the arthritis that may be associated with it, has been observed more frequently in HIV-infected people. (16) Dermatologists are alert to requesting HIV testing especially when the psoriasis is severe and different forms of the disease (for example, guttate and pustular psoriasis) occur concurrently. (17) Psoriasis worsens with progression of HIV infection and depletion of CD4+ T-cells, particularly when the count is lower than 100/mL. Similarly, psoriatic arthritis can be exacerbated in this profound immunodeficient state. Psoriatic arthritis may take the form of a spondyloarthritis affecting the spine and sacro-iliac joints or may preferentially cause peripheral small joint disease (resulting in the classic appearance of 'sausage digits').

Treatment should be to both suppress HIV replication and normalise immune status with ART and to suppress joint inflammation. As the joint inflammation can be very destructive, immunosuppressive therapy is often needed, including methotrexate and even cyclosporine. Relatively little known about the long-term consequences of using TNF inhibitors but case reports and small observational studies make a good case for them being safe. (18) Early referral to a dermatologist and/or rheumatologist is often beneficial.

Gout

A recent case-control prevalence survey from the UK found that gout was common in HIV-infected patients, particularly amongst black men of African origin, and that hypertension was a significant risk factor for disease occurrence. The authors found that non-nucleoside reverse transcriptase inhibitors might be protective against gout. (19) Several anti-retroviral drugs, including ritonavir and nucleoside reverse transcriptase inhibitors, have been associated with high uric acid levels and, sometimes even gout itself. (20) Gout has also been reported as an immune reconstitution inflammatory condition. (21) Acute gout requires anti-inflammatory therapy for the arthritis followed by removal of precipitating factors and uric acid lowering medication when the attack has settled.

Rheumatoid arthritis

Rheumatoid arthritis (RA) is typically a symmetrical, small joint, erosive polyarthropathy that affects women more than men. RA may also affect the spine and large joints and have significant extra-articular manifestations, including splenomegaly (as in Felty's syndrome) and pulmonary fibrosis. RA is often referred to as a 'seropositive arthritis' because the serum of most affected patients contains rheumatoid factor (autoantibodies to

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

immunoglobulins). However, both rheumatoid factor and cyclic citrullinated peptide (CCP) autoantibodies (a more specific marker for RA) may be falsely positive in HIV-infected individuals. (22) The inflammatory process in RA is mediated by CD4+ T-cells and therefore early in the HIV epidemic it was thought that RA would be alleviated by HIV infection. (23) However, it has become clear that HIV-infected patients may experience RA at any time during the course of their life, including as an immune reconstitution disorder, though this is rare. (24)

The treatment for RA in HIV-infected patients should follow the course of all RA patients and no particular agents are contra-indicated. While many of the agents are immunosuppressive, they can be used with safety and success. Limited data on the long-term effects and complications of 'biologic' agents are available but they appear to be largely safe, especially when HIV infection is controlled. (25)

ART-associated arthritis/arthralgia

There have been reports of arthralgia with many if not most of the antiretroviral drugs now available. Of the protease inhibitors, indinavir was a particular risk for arthritis, though others also caused similar symptoms (20). For example, although still a rare observation, arthralgia was a common reason for interrupting PrEP (tenofovir/lamivudine) during the pre-exposure HIV prophylaxis (PROUD) study. (26) For patients on ART, arthralgia is a rare reason to change regimen.

Avascular necrosis of bone

HIV-infection can increase the risk of acquiring avascular necrosis (AVN) of bone (otherwise known as aseptic necrosis) by more than 100-fold over the non-infected population. (27) In addition to HIV infection itself, other risks include taking ART, smoking, hyperlipidaemia, corticosteroid use, vasculitis and anti-phospholipid syndrome. (28) AVN mainly affects the femoral head but can occur in the knee (femoral condyles and tibial plateaux), humeral head, talus and elsewhere. There may be no symptoms especially early on and AVN of the hip, for example, can be an incidental radiological finding. Later, however, there may be progressive groin pain; at first just felt when weight-bearing, but later occurring at rest. It is best diagnosed by magnetic resonance imaging. Treatment remains controversial and many pharmacological and non-pharmacological modalities have been trialled. Pain control is important and non-operative therapies are preferred, though surgery is often needed. Joint replacements have been found to be necessary at a younger age in HIV-infected patients compared to non-infected patients (61% vs 8% of 22-50 year-olds). (29)

Diffuse infiltrative lymphocytosis syndrome

There is a wide variety of vasculitis diagnoses recorded in HIV-infected patients affecting vessels of all sizes. It has been suggested that an excess of CD8+ T-cells may trigger the vessel inflammation, possibly related to opportunistic infections in the context of severe CD4+ T cell depletion. Infections by *Toxoplasma gondii*, *Pneumocystis jiroveci*, cytomegalovirus and varicella zoster virus have been implicated and the vasculitis can involve the gut, lungs, central nervous system and skin. (33, 34) Corticosteroids are the mainstay of treatment of vasculitis and sometimes very large doses are needed if the condition is severe or life-threatening.

Vasculitis

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Pneumocystis jiroveci, cytomegalovirus and varicella zoster virus have been implicated and the vasculitis can involve the gut, lungs, central nervous system and skin. (33, 34) Corticosteroids are the mainstay of treatment of vasculitis and sometimes very large doses are needed if the condition is severe or life-threatening.

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a chronic autoimmune condition, characterised by the production of multiple autoantibodies, with a wide variety of inflammatory manifestations including disease of the skin, lungs, kidneys, heart, nervous system, joints and other connective tissue (such as pleura and pericardium). In addition, it can interfere with the production of all blood cell types. SLE predominantly affects women. The literature describes relatively few cases of concomitant SLE and HIV infection with very variable disease manifestations. For example, both improvement and flares of SLE have been observed in the setting of HIV infection. (31, 35) Immunosuppression with corticosteroid and immunomodulating agents are often needed. Importantly, false positive antibody results are known to occur in both conditions i.e. SLE patients may have a false positive HIV-antibody test and HIV-infected patients may produce low levels of autoantibodies commonly present in patients with SLE. (36)

Bacterial Infections of joints and connective tissue

Septic arthritis

Acute bacterial infection of joints is quite rare in HIV-infected patients and when it does occur, it is more likely in people who inject drugs. As is the case in the general population, *Staphylococcus* and *Streptococcus* are the commonest organisms found. (3) Early diagnosis with diagnostic aspiration revealing purulent synovial fluid should be promptly followed by orthopaedic referral and joint washout. Repeat joint washout may be required, in addition to intravenous antibiotics, which are usually followed by oral antibiotic therapy. As antibiotics are usually required for several weeks, the specific diagnosis that aspiration, culture and sensitivity testing can yield is critically important. Other causes of septic arthritis include gonococcal septic arthritis, though a recent review noted this to be rare in the setting of HIV infection. (37)

Pyomyositis

Bacterial infections of muscles have been rarely reported in HIV-infected patients in the last few years. As is typical for the disease in any population, pyomyositis may present as a single (or multiple) abscess(es), either spontaneously or after trauma (eg. intramuscular injection). Gram positive organisms especially *Staphylococcus aureus* are the most common bacteria found. The disease course may be indolent at first but later present with increasing symptoms of infection, such as fever, pain and swelling. Imaging and surgical drainage are both diagnostically and therapeutically essential. (38) Occasionally the pyomyositis may be part of an immune reconstitution inflammatory syndrome associated with *Mycobacterium tuberculosis* infection. (39)

Osteomyelitis

Osteomyelitis in patients with HIV infection may be acute or chronic and be the result of haematogenous or contiguous spread. Again, *Staphylococcus aureus* is the most common organism to cause the disease though there are many reports of other pathogens, such as *Salmonella*, *Nocardia* and fungi such as *Cryptococcus* and *Candida*. (40) In some settings tuberculous osteomyelitis has been common and it may particularly involve the spine causing bone, joint and sometimes serious neurological pathology. (38)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

In a staphylococcal infection, a positive blood culture sometimes identifies the organism causing the bone pain, however a targeted bone biopsy might be necessary. In chronic osteomyelitis, surgery is frequently needed to remove a piece of dead bone (a sequestrum) that forms the nidus of the infection and this creates an excellent opportunity for cultures to be undertaken. This procedure is best performed when the patient is not on antibiotics. As with non-HIV-infected patients, chronic osteomyelitis may require a short course of intravenous antibiotics followed by weeks to months of oral antibiotics. In contrast, acute osteomyelitis may not need surgical debridement but respond to few weeks of targeted intravenous antibiotics followed by a short oral tail. Atypical organisms (eg. fungi, mycobacteria) may necessitate much longer durations of therapy. (41)

Myopathy

Polymyositis and other myopathies

Mild self-limiting myalgia may occur quite commonly during a primary HIV infection syndrome but severe rhabdomyolysis at that time has also been reported. (42) Later, and at any time in the course of untreated HIV infection, several different myopathies may manifest with symptoms such as wasting, pain and weakness, which may range from mild to severe and debilitating. The serum creatinine kinase level may be significantly elevated and a biopsy may show inflammation with leukocytic infiltrates, vacuolation, atrophy and sometimes necrosis, although changes can be quite mild. (43, 44) There are some specific histological diagnoses associated with HIV infection, the commonest being isolated mitochondrial polymyositis, followed by classic polymyositis and then non-specific myositis. (45) Inclusion body myositis, dermatomyositis and some necrotising myopathies are also reported. (46) Treatment often includes at least moderately high dose corticosteroids with the addition of immunosuppressive agents such as azathioprine and methotrexate. (32) Though once thought to be harmful, exercise programs may help some milder inflammatory polymyositis conditions. (47)

Nemaline Rod myopathy is a rare condition that appears as a sporadic late-onset disease but can also be associated with HIV infection. (48) The proximal muscle weakness and atrophy is associated with the presence of nemaline bodies or rods within the muscle cells. When associated with HIV infection the disease may respond to corticosteroids, intravenous immunoglobulin and plasmapheresis. (49)

HIV infection has been associated with a wasting myopathy that occurs in advanced disease with little or no inflammatory response in the muscle and only modest rises in creatinine kinase. (32)

Zidovudine was the first antiretroviral drug to be reported to cause myopathy, when patients presented with myalgia, muscle tenderness and weakness. (31) This myopathy is mediated via mitochondrial disease and can be seen with the use of other nucleoside reverse transcriptase inhibitors but less commonly so. (50) Ceasing the drug is the best management strategy.

Lipid lowering 'statins' (HMG-CoA reductase inhibitors) can interact with protease inhibitors to achieve myopathic levels although pravastatin, atorvastatin, and rosuvastatin (at low doses) are probably safe. (51) Simvastatin was most associated with this phenomenon and is now rarely used whether the patient is on protease inhibitors or not. Other drugs that may cause myopathies in HIV-infected patients include beta-blockers, proton pump inhibitors, fluoroquinolones, sulphonamides and cocaine. (47)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Neurological Disease

Approach to neurological symptoms

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Last Reviewed: January 2024

When evaluating neurological presentations in context of HIV (Human immunodeficiency virus) the differential diagnosis is determined by the stage of HIV infection, previous treatment history, medication compliance, and objective evidence of involvement of the central and/or peripheral nervous system. This case study illustrates several diagnostic and management issues in approaching neurological symptoms in people living with HIV (PLWH). Details of the underlying conditions will be elucidated in the following section 'Neurological disorders in HIV infection'.

Case study – Neurological symptoms in an immunodeficient PLWH

Sebastian is a 58-year-old married man with HIV-1 infection. He has partially adhered to combined antiretroviral therapy (cART) and has progressed through multiple cART regimens, including nucleoside reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI) and protease inhibitors (PI) due to intolerable adverse drug reaction or virological failure. Sebastian is currently taking an antiretroviral drug regimen of tenofovir disoproxil fumarate, emtricitabine, and darunavir boosted with ritonavir. His most recent CD4 cell count is 70 cells/ μ L and HIV viral load is 79,432 (4.9 log₁₀) HIV RNA copies/mL. Sebastian has been poorly adherent to trimethoprim/sulfamethoxazole prophylaxis, evidenced by infrequently filled prescriptions. He is up to date with regular vaccinations. Sebastian has no known tuberculosis risk factors in terms of contacts or travel to endemic areas. He thinks he had syphilis treatment many years ago but cannot remember the details. He has a family history of myocardial infarction. He continues to smoke though is trying to quit. He has used methamphetamine in the past but not for several years.

Sebastian is referred to a HIV physician after his husband reported that he has had difficulty walking and recently 'isn't quite himself'. On review, he reports subjective cognitive slowness and gait disturbance. He and his husband confirm poor adherence to cART due to significant nausea with his current regimen. A directed history reveals he has experienced intermittent headaches and possibly fevers, although no rigors. He drinks a modest amount of alcohol and does not take illicit drugs or non-prescribed medications. Examination reveals a well appearing, overweight, normotensive, afebrile man with reduced pinprick and light touch sensation to the ankles bilaterally with preservation of bilateral ankle jerks. Heel-toe gait is impaired, with a tendency to fall to the left.

The serum *Toxoplasma gondii* immunoglobulin G antibody assay was negative and syphilis serology was non-reactive when last performed 2 years ago. Biochemical tests reveal normal serum electrolytes and renal function. Serum B12, folate and thyroid-stimulating-hormone levels are normal. HBA1c is not elevated at 5.5%. Hepatitis B surface antigen and hepatitis C serology is negative. Treponemal syphilis serology is non-reactive, with positive non-treponemal serology in keeping with previous infection. CMV serology demonstrates a negative IgM, a positive IgG, and the CMV viral load is undetectable.

MRI brain scan with spectroscopy (MRS) with gadolinium demonstrates diffuse T2 hyperintensities in periventricular and deep white matter with increased choline, myo-inositol and decreased n-acetyl aspartate (Figure 1) and no evidence of a mass lesion. Lumbar puncture (LP) reveals an opening pressure of 14 cm of water and the cerebrospinal

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

fluid (CSF) appears clear and colourless. CSF biochemistry reveals a normal glucose concentration and a raised protein concentration of 0.57 g/L (normal range 0.15-0.45 g/L). Microscopy of CSF reveals a mononuclear cell pleocytosis of 10/mm³, and no organisms are seen on Gram stain or India ink stain. Tests for CSF and serum cryptococcal antigen reveal titres of less than 1:4. Toxoplasma, HSV and VZV PCR testing is negative. CSF mycobacterial culture is pending. The CSF HIV viral load is 11,000 (4.04 log₁₀) HIV RNA copies/mL and the CSF beta 2-microglobulin concentration is 4 mg/L (0.2 – 1.5) and the neopterin level was 27 nmol/L (0 – 13). Formal neuropsychometric testing reveals deficits in attention and psychomotor processing speed.

Given the absence of an alternative cause for the neurological manifestations and the consistent clinical and laboratory findings, the physician makes a diagnosis of concurrent HIV associated neurocognitive disorder (HAND) and HIV sensory neuropathy. Serum and CSF genotypic HIV resistance assays demonstrate no evidence of resistance of NRTIs or integrase inhibitors. Following the availability of these results the HIV physician switches Sebastian's cART regimen to dolutegravir and tenofovir alafenamide/emtricitabine to improve tolerability, reduce pill burden thereby improving compliance and improving CNS penetration.

Table 1: Approach to the diagnosis of persistent headache, seizures, altered level of consciousness or focal neurological symptoms or signs in the immunodeficient patient with HIV infection

Initial assessment
History - History of treatment - Recent commencement of cART suggests immune reconstitution syndrome - Previous cART regimens and reasons for switch - Compliance with current and previous regimens - Toxicity, focusing on neurotoxicity - Adherence to trimethoprim/sulfamethoxazole prophylaxis – reduced likelihood of toxoplasmosis - Symptoms - Headache – persistent headache warrants investigation, even if mild in severity - Inattention, forgetfulness, slowed thinking, impaired handwriting - Social withdrawal and irritability - Temporal progression of neurological symptoms - Focal vs generalised neurological symptoms suggesting specific syndromes - Systemic and constitutional symptoms - Seizures - Past medical history - Previous neurological disease - Mental health history - Cardiovascular and metabolic comorbidities and management - Exposure history including tuberculosis risk factors, sexual history, dietary history (e.g. undercooked meat and risk of toxoplasmosis) - Collateral history where possible

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Examination

- Fevers
- Focal neurological signs
- Evidence of raised intracranial pressure
- Evidence of immunodeficiency e.g. oral candidiasis
- Evidence of disseminated disease process – vesicular rash, pulmonary signs of tuberculosis, evidence of retinitis
- Gait disturbance
- Weight
- Blood pressure

Investigations

- Previous CD4 T cell counts – informs differentials based on extent of immunosuppression
- Renal and hepatic function
- CD4 count, HIV viral load, previous genotypic resistance testing
- Serum toxoplasma IgM and IgG and previous results
- Serum syphilis serology with treponemal (TPPA, FTA) and non-treponemal testing (VDRL, RPR) and previous results
- Serum cryptococcal antigen titre
- Serum CMV IgM, IgG +/- CMV quantitative blood PCR
- Hepatitis B and C screening
- Neuroimaging – MRI with gadolinium and spectroscopy where available or CT with contrast
- Consideration of lumbar puncture – CSF microscopy, culture, protein, cryptococcal antigen, CSF HIV viral load +/- genotype, CSF syphilis serology, CMV, HSV, VZV, EBV, Toxoplasma PCRs

PICTURE OF MRS

Source: Bruce Brew, Immunology/HIV/Infectious Diseases Clinical Services Unit and Department of Neurology, St Vincent's Hospital, Sydney NSW. Used with permission.

Neurological disorders in HIV infection

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Last Reviewed: January 2024

Neurological complications of HIV (Human immunodeficiency virus) continue to commonly impact people living with HIV (PLWH) in the post combined antiretroviral therapy (cART) era. The spectrum of these disorders is diverse spanning the central nervous system (CNS) and peripheral nervous system, often concurrently. The proposed pathogenesis, clinical features, diagnosis and management of these conditions are discussed in this section.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

HIV associated central nervous system diseases

HIV associated neurocognitive disorder

HIV associated neurocognitive disorder (HAND) represents a significant burden upon PLWH in the post cART era. In a metanalysis of 35,513 PLWH, HAND is reported at a prevalence of 42.6%, (1) though it is less common in those with sustained viral suppression and early institution of cART. HAND adversely impacts PWLH with impaired quality of life, reduced independence with activities of daily living and increased mortality. (2,3)

HAND was defined by the Frascati criteria in 2007 in a tiered system stratified by extent of functional impairment and greater than one standard deviation below population means in at least two cognitive domains (complex attention, executive function, learning and memory, language, perceptual motor control and social cognition) on formal neurocognitive testing (4) (Table 1). These criteria categorised three syndromes of ascending severity: HIV-associated asymptomatic neurocognitive impairment (ANI), HIV-associated mild neurocognitive disorder (MND) and HIV-associated dementia (HAD), the latter of which is considered AIDS defining. (4) Epidemiological data has demonstrated an evolution in incidence of HAND since the uptake of cART with a significant reduction in HAD from 7% to 3% per year in immunocompromised patients, but static ANI and MND incidence ranging from 30 – 50%. (2) Some have questioned the clinical applicability of the Frascati criteria (5) and proposed the term HIV-associated brain injury. This has not been accepted for numerous reasons, not least of which relates to the identification of the legacy effect, referring to pre-existing HIV-mediated brain injury. It is unknown whether legacy brain injury is completely irreversible, noting recent data showing ongoing HIV replication of transcripts and whole virus despite standard assays showing “undetectable viral load”. (5,6) The senior author of this guideline (BJB) is leading a National Institutes of Health (USA) sponsored group to update the HAND criteria.

Table 1: Frascati criteria for diagnosis of HIV associated neurocognitive disorder (4)

Asymptomatic neurocognitive impairment (ANI)	Mild neurocognitive disorder (MND)	HIV-associated dementia (HAD)
No interference with ADLs	At least mild interference with ADLs	Marked interference with ADLs
At least 1.0 standard deviation below mean of normative population if at least 2 cognitive domains	At least 1.0 standard deviation below mean of normative population if at least 2 cognitive domains	At least 2.0 standard deviation below mean of normative population if at least 2 cognitive domains

The understanding of the pathogenesis of HAND is evolving with increasingly complex intercurrent mechanisms. (2) There are several key aspects. HIV infects the following brain cells: perivascular macrophages, microglia and astrocytes. (2) These cells have varied life spans ranging from months to many years; response to therapy may take months if not longer. HIV infection of astrocytes is restrictive – it does not produce whole virus but rather viral proteins that are not assembled into whole virus. (6) ART drugs have differing efficacy in macrophages, microglia and astrocytes. (6–9) Persistence of CNS HIV replication has been demonstrated despite plasma suppression, termed CSF escape, referring to detectable CSF HIV RNA in spite of undetectable plasma viral loads with distinct CSF HIV resistance profiles. (10–12)

Increasing mechanisms of neurotoxicity distinct to CNS viral replication are being elucidated in animal and cell models. (2) HIV RNA transcription has been demonstrated to continue in HIV infected myeloid cells and T cells in spite of effective cART using a novel assay. (6,8,9) This transcription includes production of HIV

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

proteins Tat, Nef and gp120 which are toxic to neurons and glial cells and precipitates neuroinflammation as well as systemic inflammation through T cell and monocyte/macrophage activation. (8,13,14) HIV mediated deleterious neuroinflammation secondary to interferon production and myeloid cell activation is proposed to cause neurodegeneration via neurotoxic inflammatory mediators (IL1 β , IL8, TNF, Quinolinic acid), mitochondrial dysfunction, oxidative stress and impaired autophagy. (2,15–18) Neurotoxicity secondary to antiretroviral drugs via direct or indirect mechanisms also possibly contributes to HAND. (2,19–21) Comorbid conditions are increasingly implicated in HAND including cardiovascular risk, visceral adiposity, the metabolic syndrome and insulin resistance. (22–26) Coinfection has been associated with increased risk of HAND including longitudinal impacts of Epstein bar virus (EBV) and Cytomegalovirus (CMV) infection. (27,28) This complex pathogenesis is a rapidly developing field. It remains to be seen whether viral replication occurring below current commercially available detection methods, with production of whole virus or only transcripts, drives HAND pathogenesis. There is also increased attention on the importance of comorbidities, especially vascular disease, and whether indeed comorbidities are the primary pathogenetic mechanism in the context of viral suppression in both blood and cerebrospinal fluid. (2,6,9,26) or are secondary to ongoing low-level HIV replication and transcription.

HAND manifests clinically with inattention, forgetfulness, slowed thinking, gait disturbance, impaired handwriting, apathy, social withdrawal and irritability. (29,30) Collateral history regarding longitudinal progression of these symptoms is vital. Progressive severe disease consistent with HAD manifests as dementia which if untreated progresses over weeks to months to mutism, incontinence and paraparesis. (31,32) Risk factors for HAND include age greater than 50 years, low nadir CD4 count (likely due to legacy brain injury), insulin resistance/ diabetes, hypertension and hyperlipidaemia, depression, mania and low education level. (2,31)

Diagnosis of HAND is complex, requiring a combination of detailed clinical and neurological evaluation, especially assessment of current and longitudinal HIV virological control and degree of immunosuppression (with nadir CD4 cell count if possible), and assessment of comorbid factors including metabolic diseases and psychiatric disorders. (32) This is supported by investigations with neuroimaging and consideration of CSF examination to assess for CSF viral escape or comorbid infection. Notably no single clinical feature or investigations is pathognomonic for HAND. If HAND is suspected, formal neurocognitive testing should be performed by a qualified neuropsychologist, where available. If this not possible then a MoCA test can be administered, noting that this test is relatively insensitive to HAND in its early stages as it is not time limited and may not detect the cognitive slowing and poor attention typical of early HAND. Serum investigations include assessment of HIV RNA viral load, CD4 count, and exclusion of concurrent conditions including syphilis, cryptococcal meningitis, and toxoplasmosis based on degree of immunocompromise further detailed below in 'HIV associated CNS disorders'. Neuroimaging should be performed with MRI to examine for classical changes of cerebral atrophy, T2 hyperintensities in periventricular and deep white matter. Where MR spectroscopy is available, it should be undertaken to assess for increased choline, myo-inositol and decreased n-acetyl aspartate (33) in the deep frontal white matter and caudate. CSF examination for protein, glucose, microscopy (including India ink), bacterial, mycobacterial and fungal culture, and CSF HIV RNA viral load should be performed, with a mononuclear pleocytosis being consistent with, but not specific for, HAND. Paired serum and CSF biomarkers such as neopterin (a marker of activated macrophage lineage cells) and B2 microglobulin (a marker primarily of lymphocytes) can be considered to support the diagnosis as these are elevated in HAND; whilst they are non-specific, they will often be elevated in HAND without other markers of inflammation. In the instance of CSF viral escape with detectable CSF HIV RNA and undetectable serum HIV RNA, a CSF HIV genotype should be attempted within the limits of available assays. (34)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Management of HAND is characterised by optimising virologic control with cART selection and maximising adherence, management of contributory comorbidities such as diabetic control and metabolic factors, and supportive interventions for functional impairment. Over the past decade there has been conflicting trial evidence regarding improved outcomes with intensification strategies for HAND with agents with high CNS penetration aiming to address ongoing HIV replication in the CNS reservoir. Most studies have been poorly designed yielding conflicting results. (35–47) A 2023 randomised, double blinded placebo-controlled trial of 191 patients to address cART intensification did not find any benefit of addition of dolutegravir or maraviroc for patients on suppressive cART. (48) However, there were again trial design and result analysis flaws that impair a definitive answer. (49) Notably this trial did not evaluate patients with confirmed CSF viral escape, and observational data have shown clinical improvement with improved neuropenetrant cART in this context (50). An additional issue to consider is that no studies thus far have assessed blood brain barrier impairment using MRI with advanced sequences or CSF studies, given HAND patients have varying degrees of blood brain barrier impairment allowing non-penetrating ARVs to enter the brain in some but not all patients. (51)

The CNS penetration effectiveness (CPE) score has been proposed as a tool for selecting optimal CNS active cART devised by Letendre et. al in 2007, with subsequent revision detailed in Table 2. (52) This schema stratifies ART with a score corresponding to CNS concentration, whereby a cART regimen with a total score of > 7 was considered to have high CNS penetration. This scoring system is limited: the methodology for CNS scoring is unclear, scores are categorical (a score of 3 is not 3 times better than 1), there is no accounting for drug-drug interactions or blood brain barrier impairment, there is a lack of scores for increasingly common agents such as bictegravir, cabotegravir and islatravir, and there is no accounting for potential neurotoxicity. Nonetheless, it can be used as a broad guide. Hence the choice of regimen must be individualised to the patient accounting for both benefit and toxicity. (2,19,20,53) Indeed, in an individual with poor adherence, any regimen that can be taken is better than none.

Management of HAND is mimetic of routine HIV management with cART selection based on genotypic confirmed susceptibility and strategies to optimise adherence, optimisation of metabolic and cardiovascular comorbidities and optimisation of CNS penetrance where possible. In the unusual circumstance of CSF viral escape, CSF HIV RNA genotype should be attempted and cART selection directed accordingly. Patients with significant functional impairment require allied health referral and referral to support/disability services such as the NDIS should be considered.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Table 2: Central nervous penetration (CPE) score; (increasing penetration with increasing score). NRTI – nucleoside reverse transcriptase inhibitor, NNRTI – non-nucleoside reverse transcriptase inhibitor, PI – protease inhibitor, /r – ritonavir boosted (52)

Antiretroviral agent	CNS penetration score (CPE)			
	4	3	2	1
NRTI	Zidovudine	Abacavir Emtracitabine	Didansoine Lamivudine Stavudine	Tenofovir Zalcitabine
NNRTI Nevirapine Delavirdine Efavirenz			Ertavirine	
PI	Indinavir/r	Davunavir/r Fosamprenavir/r Indinavir Lopinavir/r	Atazanavir Atazanavir/r Fosamprenavir	Nelfinavir Ritonavir Saquinavir Saquinavir/r Tipranavir/r
Entry inhibitor		Maraviroc		Ebuvirtide
Integrase inhibitor	Dolutegravir	Raltegravir	Elitegravir	

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

HIV-associated CNS opportunistic infections

Since the advent of cART CNS opportunistic infections have significantly declined, however they continue to cause significant morbidity and mortality in PLWH especially in those unaware of their HIV status. (54) A recent multicentre retrospective analysis of patients presenting with encephalitis demonstrated a one-year mortality of 31.3% in PLWH compared to 16.0% in HIV negative counterparts. (55) The following table summarises the clinical features, investigation and management of some common HIV-associated CNS pathogens pertinent to the Australian population. (54)

Table 3: Clinical features, diagnosis and management of common CNS opportunistic pathogens in PLWH (54–58)

HIV-associated CNS infection	Toxoplasmosis	Cryptococcal meningitis	Varicella zoster virus encephalitis	Herpes simplex virus encephalitis	Cytomegalovirus encephalitis	Invasive aspergillus	Progressive multifocal leukoencephalopathy	Tuberculous meningitis	Neurosyphilis
Pathogen	Toxoplasma gondii	Cryptococcus neoformans or gattii (less common)	Varicella zoster virus (VZV)	Herpes simplex virus (HSV)	Cytomegalovirus	Aspergillus spp.	JC virus	Mycobacterium tuberculosis	Treponema pallidum
Clinical features	cerebral abscess (subacute onset: visual field deficits, focal seizures, aphasia, hemiparesis / hemisensory deficits, confusion, movement disorders) diffuse encephalitis, chorioretinitis	Sub-acute onset, headaches, lethargy, fever, malaise, meningism (25% of cases), altered mental state	Encephalitis – lethargy, confusion, gait disturbance, headaches, cranial nerve palsy, ataxia, seizures, vesicular rash (frequently absent)	Encephalitis – lethargy, confusion, gait disturbance, headaches, cranial nerve palsy, ataxia, seizures, vesicular rash (frequently absent)	Encephalitis – lethargy, confusion, gait disturbance, headaches, cranial nerve palsy, ataxia, seizures, Retinitis – floaters, visual impairment, retinal detachment	Cranial nerve palsies, paraparesis, parathesis, altered mental status, seizures	Ataxia, hemiparesis, movement disorders, behavioural and cognitive abnormalities, cortical blindness, seizures (late) Rarely, there may be pure cerebellar involvement by JC without white matter disease – JCV neuronopathy	Fever, headache, impaired consciousness, meningism, lower cranial nerve palsies, hemiplegia, bulbar signs, sensory deficits	Hearing loss, acute hydrocephalus, seizures, hemiplegia, aphasia, cranial nerves palsies, argyll-robinson pupil, stroke syndromes, neuropsychiatric disturbance
Common CD4 count (cell/mm ³)	< 100	< 50 – 100	< 300	All stages	< 50	< 200	< 150	All stages; increased risk < 200	All stages
MRI	Ring-enhancing, brain lesions, often in basal ganglia, thalamus or dentate nucleus	Normal (2 – 8%), intracerebral masses, cortical and lacunar infarcts, pseudocyst, cerebritis, meningeal uptake	T2 hyperintensity and areas of restriction diffusion in cerebellum, thalami, cerebral cortex and basal ganglia	bilateral, asymmetric T2 hyperintensity and diffusion restriction of limbic and medial temporal lobes, more diffuse in advanced immunosuppression, T1 contrast enhancement in later disease	Linear periventricular hyperintensity with gadolinium enhancement, can be normal	Polylobulated mass with peripheral contrast enhancement, associated oedema adjacent structures and parenchyma	White matter hyperintensities of T2 and T1 FLAIR that are asymmetrical with particular involvement of the subcortical regions leading to a “scalloped” appearance. In the rare instance of JCV cerebellar neuronopathy there is only atrophy	Basilar exudates, arachnoiditis, tuberculomas of T2	Cerebral infarct (typically lacunar middle cerebral artery), nonspecific white matter lesions, cerebral gummas, or arteritis

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

CSF	Toxoplasma PCR positive but insensitive and CSF analysis is often not possible because of raised intracranial pressure	Cryptococcal antigen (92 – 100% sensitive, 84 – 98% specific), positive India ink staining, pleocytosis, high CSF protein, increased elevated CSF opening pressure (poor prognosis)	Lymphocytic pleocytosis, elevated protein, positive VZV PCR (can be negative), antiVZV IgM/ IgG	Lymphocytic pleocytosis, elevated protein, positive HSV-1 PCR, HSV-2 PCR	CMV PCR (95% sensitive, 85% specific), neutrophilic pleocytosis, elevated protein	Non-specific, often negative cultures	CSF JC virus PCR (98% specific, 76% sensitive), pleocytosis, elevated protein. Some individuals may have low levels of JCV therefore need to ensure PCR can detect 50-200 cpml	Can be normal (especially if CD4 <50), lymphocytic or neutrophilic pleocytosis < 100 cells/mm ³ (in contrast to lymphocytic in immunocompetent cases), highly elevated protein, low glucose, AFB smear, culture, GeneXpert PCR (79.5% sensitive), serial high volume sampling often required	CSF VDRL, elevated protein, lymphocytic pleocytosis. However, a significant proportion have a negative CSF VDRL
Serum Investigations (these may not be helpful if there is significant immune deficiency)	Toxoplasma IgM, IgG	Serum cryptococcal Antigen, mycolytic blood culture	VZV IgM + IgG	HSV 2 IgM + IgG	Quantitative CMV PCR, CMV serology	Serum aspergillus galactomannan and aspergillus PCR	JC Virus PCR blood	Nil specific	Serum TPPA,FTA, RPR, VDRL (can be negative)
Management	Pyrimethamine + (sulfadiazine or trimethoprim/ sulfamethoxazole) for 6 weeks followed by secondary prophylaxis	Induction (2 weeks): Liposomal amphotericin 3 – 4mg*kg daily + Flucytosine 25mg*kg QID for 2 weeks*; Consolidation (10 weeks): Fluconazole 400mg daily; Maintenance 200mg daily for at least 12 months; serial therapeutic lumbar puncture for intracranial hypertension *Single high dose liposomal amphotericin 10mg*kg + Flucytosine 100mg daily + Fluconazole 1200mg found to be non-inferior	IV Aciclovir 14 – 21 days	IV Aciclovir 14 – 21 days	Encephalitis -Ganciclovir 5mg*kg BD + / – Foscarnet 90mg*kg BD for 3 – 6 weeks (nil clinical trial data for combination therapy however considered in context of poor outcomes (Ref), role of valganciclovir unclear Retinitis – Valganciclovir 900mg BD for 3 weeks then 900mg daily	Voriconazole 6mg*kg BD loading for 2 doses then 4mg*kg BD; TDM monitoring aiming 1.0 – 5.0; poorly defined treatment duration	cART commencement/ optimisation but beware of IRIS requiring corticosteroids Whilst there is no specific therapy, T cell therapy is being trialled and limited data support pembrolizumab.	Four drug therapy induction phase for two months then maintenance two drug regimen for at least nine – twelve months. cART initiation delayed up to 8 weeks. Nil mortality benefit of adjunctive corticosteroids excluding for IRIS	Benzylpenicillin 10.8g q24hourly for 15 days

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Primary CNS Lymphoma (PCNSL)

PCNSL is a rare malignancy that affects the brain, leptomeninges, spinal cord or orbits. It is greatly increased in the PLWH compared to the general population, especially with CD4 < 100 cm/mm³ and is considered an AIDS defining illness. Overall incidence has reduced substantially in the post cART era however, unlike other HIV-associated lymphomas, PCNSL continues to have consistently worse outcomes in PLWH than the general population in spite of widespread use of cART. (59) Epstein-Barr virus is highly associated with the condition and is theorised to play a direct role in oncogenesis via immune dysregulation, expression of oncogenic proteins, dysregulated apoptosis and increased lymphocyte proliferation. (60)

PCNSL usually occurs in the brain with either solitary or less commonly multiple supratentorial lesions but can also affect the spinal cord. Clinical features include headache, constitutional symptoms (fevers, night sweats, malaise), weight loss seizures and specific neurological syndromes dependent on the site of the lesions. (60) MRI demonstrates T2 contrast enhancing lesions. CSF typically demonstrates elevated protein, lymphocytic pleocytosis, low glucose and positive CSF EBV PCR. (60) Diagnosis is established with CSF cytology, flow cytometry and histopathology of biopsy of lesions. Outcomes are unfortunately poor in PCNSL in PLWH with a 5 year survival of 14%. (59) Treatment regimens involve a combination of steroid therapy, high dose methotrexate and radiotherapy. (60)

HIV-associated spinal cord diseases

Prevalence of spinal cord disease in PLWH is largely unknown in the post cART era due to paucity of data. Historical postmortem analysis demonstrated spinal cord disease in at least 50% of patients with acquired immunodeficiency syndrome (AIDS). (61) HIV associated spinal cord disorders are mediated indirectly by inflammatory modulation, degeneration, or predisposition to opportunistic infection or neoplasm. Degree of immunosuppression or stage of HIV infection differentiates associated pathologies.

HIV associated transverse myelitis (TM)

Acute primary HIV TM is mediated by immune dysregulation from HIV virion CNS penetration and occurs with primary infection and seroconversion. (61) Classical features include back pain, urinary retention, lower extremity paraesthesia, spastic paraparesis, a band-like sensory level, hyperreflexia, and abnormal plantar responses in addition to constitutional signs of primary HIV or seroconversion (fevers, malaise, lymphadenopathy). CD4 counts are classically preserved (> 500 cell/mm³). Exclusion of other aetiologies of TM is essential, including other viral aetiologies and immune mediated disorders, with MRI and CSF examination. HIV associated TM is associated with a normal MRI or longitudinal T2 hyperintensity, and CSF shows a lymphocytic pleocytosis with normal or elevated protein and elevated CSF viral load. This disorder is often responsive to effective cART and reduction of CSF viral load with consideration of adjunctive pulsed steroids. (61)

Notably, a separate phenomenon of immune-mediated TM associated with HIV infection manifests as a central demyelinating disorder mimetic of multiple sclerosis (MS) or neuromyelitis optica (NMO). This disorder has been found to be present in early, controlled and uncontrolled disease. It remains unclear if this is a separate entity to MS/NMO, with similar clinical course including prodromal optic neuritis followed by paraesthesias, paraparesis and bladder dysfunction. Investigations demonstrate longitudinal T2 enhancement on MR imaging with or without T1 gadolinium enhancement, and CSF reveals a normal cell count or mild lymphocytic pleocytosis, elevated protein, oligoclonal bands and negative JC virus PCR. There is no consensus on treatment with variable response to cART, modest outcomes with steroids and steroid sparing immunomodulators and a paucity of data on MS immunotherapy.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Vacuolar myelopathy (VM)

HIV associated VM is a well described complication of AIDS with a historical prevalence estimated between 7 – 55%. (61) Current epidemiology is unknown but it is uncommon in the post cART era. VM is characterised by white matter spinal cord vacuolisation. Pathologically VM closely resembles subacute combined spinal cord degeneration and is associated with vitamin B12-dependent transmethylation and reduced levels of s-adenosyl-methionine. (62) VM often presents subacutely with indolent progression with spastic paraparesis with associated bladder and bowel dysfunction, although rapidly progressive courses have been described. Investigations are non-specific with spinal cord atrophy followed by normal or T2 hyperintensity on MRI and a normal or mild lymphocytic pleocytosis and elevated protein on CSF examination. Treatment is limited, with variable response to cART, modest and diminishing response to intravenous immunoglobulin (IVIG) and no benefit demonstrated with B12 or L-methionine administration. (61,63) VM is frequently associated with HAD, and in cART responsive cases the dominant pathology is a multinucleated giant cell myelitis similar to the pathology in the brain.

Infectious radiiculomyelitis

Radiculomyelitis in PLWH can be caused by multiple infectious aetiologies including Cytomegalovirus (CMV), Herpes zoster virus (HSV), Varicella zoster virus (VZV), spinal cord neurosyphilis and spinal cord Tuberculosis (TB). These have distinct clinical features, pre-disposing degree of immunosuppression, investigation findings and treatment which are detailed in the table 4.

Table 4: Clinical features, diagnosis and management of infectious aetiologies of radiculomyelitis in PLWH (54,61)

Aetiology of infectious myelitis	CMV	HSV	VZV	Spinal cord neurosyphilis	Spinal cord TB
Clinical features	Distinct sensory level, urinary retention, paraesthesias, asymmetric UMN weakness +/- polyradiculitis	Prodromal vesicular rash, perirectal pain, urinary retention, loss of rectal tone, ascending flaccid paraplegia	Progressive asymmetric motor and sensory impairment ipsilateral to dermatomal rash	Back pain, slowly progressive lower limb weakness, paraesthesias, urinary incontinence, hyperreflexia, sensory level extensor plantars	Subacute flaccid paralysis, lower extremity, bladder and bowel dysfunction
CD4 count	< 100	All stages, Increased severity < 200	< 300	All stages, increased risk < 350	All stages, increased risk < 200
MRI	Increased T2 and gadolinium enhancement on MRI of spinal cord	Increased T2 and gadolinium enhancement on MRI of conus medullaris and adjacent nerve roots	Extensive Increased T2 and gadolinium enhancement on MRI of spinal cord (extensive)	Extensive Increased T2 with discrete and irregular superficial enhancement	Variable based on syndrome: meningeal enhancement, loculated CSF, mass lesions, syringomyelia, Increased T2 spinal cord lesions

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

CSF	Neutrophilic pleocytosis, elevated protein, low glucose, high quantitative CMV DNA PCR	Lymphocytic pleocytosis, elevated protein, positive HSV PCR	Lymphocytic pleocytosis, elevated protein, positive VZV PCR (can be negative), antiVZV IgM/IgG	CSF VDRL, elevated protein, lymphocytic pleocytosis	Highly elevated protein, lymphocytic pleocytosis, low glucose, AFB, Mycobacterial cultures (low sensitivity), TB PCR (low sensitivity)
Treatment	IV Ganciclovir and/or IV Foscarnet	IV Aciclovir 14 – 21 days	IV Aciclovir 14 – 21 days	IV Benzylpenicillin 10.8g q24hourly for 15 days	TB therapy with CNS penetrating agents +/- steroid therapy, Delay cART initiation but commence within 2 months

HIV-associated diseases of the peripheral nervous system

HIV-associated sensory neuropathy

HIV-associated sensory neuropathy (HIV-SN) is a complication of HIV infection and antiretroviral therapy and continues to impact 38 – 57% of PLWH in the post cART era. (61) The proposed pathogenesis of HIV-SN involves primarily dorsal root ganglion infection/inflammation with mononuclear cellular infiltration, increased cytokine expression, and direct neurotoxic effects of viral proteins manifesting in axonal degeneration and reduced intraepidermal nerve fibre densities. (64–66) Genetic polymorphism in mitochondrial DNA, upregulated inflammatory cytokines and other inflammatory proteins such as CAMKK2, P2X7R and P2X4R have been associated with HIV-SN, however targeted therapies remain theoretical. (67) Multiple antiretrovirals are also associated with HIV-SN due to cumulative mitochondrial dysfunction and increased production of reactive oxygen species best characterised in the nucleoside reverse transcriptase inhibitors (stavudine, didanosine, zalcitabine). It is unclear whether protease inhibitors (indinavir, ritonavir, and saquinavir) can cause peripheral neuropathy directly, or more likely through metabolic disturbance especially insulin resistance. (65,68) Risk factors for HIV-SN include low CD4 count, age, height, duration of HIV, high viral load, DM, malnutrition, neurotoxic cART regimens, and African ethnicity. (65,66)

HIV-SN presents as a distal, symmetrical anaesthesia or hyperaesthesia with associated neuropathic pain in a glove and stocking distribution. (64–66) Ankle reflexes are often reduced or absent, however neurological examination can be normal. Supportive investigations include nerve conduction studies demonstrating axonal degeneration and skin biopsy revealing decreased epidermal nerve fibre density. (67) Exclusion of other aetiologies of peripheral neuropathy is crucial, such as nutritional deficiencies (B12, B6, thiamine, folate), diabetes, alcoholism, hypothyroidism, inflammatory disorders, paraneoplastic disorders and or other neurotoxic drugs (isoniazid, metronidazole, amiodarone, TNF-alpha inhibitors, heavy metals and chemotherapy agents such as vincristine, taxanes and platinum).

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Management of HIV-SN involves rationalising cART to minimise neurotoxic agents, optimising HIV control, optimising other contributors to peripheral neuropathy and symptomatic therapy to reduce neuropathic pain. (65) Therapeutic agents are similar for other causes of painful neuropathy including simple analgesia (paracetamol, non-steroidal anti-inflammatory drugs), tri-cyclic antidepressants, anticonvulsive drugs, selective serotonin and norepinephrine reuptake inhibitors (SNRIs), and opiate analgesia, detailed in Table 5. There is a paucity of HIV-SN specific trial data for many of these agents, with modest benefit versus placebo demonstrable for lamotrigine, gabapentin, and capsaicin and no benefit demonstrated for amitriptyline or pregabalin. (69–72) Unfortunately, even with multimodal symptomatic therapy for HIV-SN, pain control is often incomplete.

Table 5: Symptomatic Treatments for HIV-SN

Class	Agent and dose strategies	Evidence basis
Simple analgesia	Paracetamol 1g PO QID / TDS	Nil HIV-SN data
NSAIDs	Ibuprofen 400mg TDS, Meloxicam 15mg daily, Celebrex 100mg BD	Nil HIV-SN data
Antidepressants	SNRI: Duloxetine 60mg daily, Venlafaxine 37.5mg daily	Nil HIV-SN data, Benefit over placebo in painful diabetic neuropathy (73)
	TCA: Amitriptyline 10mg nocte Titrate to tolerance of cholinergic side effects	Nil benefit over placebo in RCT of 145 patients with HIV-SN (69) Benefit demonstrated in painful diabetic neuropathy over placebo, and non-inferior anticonvulsants and SNRIs (73)
Antiepileptic drugs (AED)	Lamotrigine (Find dose in paper)	Reduced pain scores vs placebo in patient receiving neurotoxic ART with HIV-SN (72)
	Gabapentin 400mg nocte Can be up-titrated to 3600mg daily over 4 weeks N.B. Non-PBS funded	Reduced pain scores and sleep interference vs placebo in HIV-SN (74)
	Pregabalin 75mg BD Can be up-titrated to 600mg daily, dose reduce in renal impairment	Nil benefit over placebo in mean pain scores with flexible dose regimen 150 – 600mg daily in HIV-SL (71)
	Other AED agents: Carbamazepine (limited by potential myelosuppression) and drug interactions, Sodium valproate (multiple drug interactions)	Nil HIV-SN data
Opiate analgesia	Tapentadol IR 50 – 100mg q4hourly PRN > Tapentadol MR BD, Oxycodone 5 – 10mg q4hourly PRN > Targin BD Transdermal Buprenorphine patch Trial immediate release prior to transition to long acting formulation for ongoing therapy. Reserve for severe pain and aim to minimise dose in light of risk of addiction	Nil specific data

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Acute and chronic inflammatory demyelinating polyneuropathy

Acute demyelinating polyneuropathy (AIDP), which closely resembles Guillain-Barré syndrome (GBS) is a rare but well recognised disease in PLWH. The pathogenesis of HIV associated AIDP is unknown. Proposed mechanisms include cell-mediated macrophage demyelination, perivascular T cell lymphocytic infiltration, antibody mediated neuronal damage secondary to molecular mimicry, and HIV neurotoxic proteins. (75) AIDP most commonly occurs in early HIV disease associated with seroconversion, early asymptomatic HIV or as an immune reconstitution disorder one to two months post cART commencement. (75) Chronic inflammatory demyelinating polyneuropathy (CIDP) may occur during any stage of HIV disease though it is exceedingly uncommon with advanced immunosuppression (CD4 count < 200 cm/mm³) where CMV is more likely as it can cause a radiculomyelopathy that can mimic AIDP/CIDP. (75)

AIDP and CIDP are characterised by progressive, ascending weakness with early loss of reflexes. HIV associated AIDP is generally monophasic with symptoms peaking at 4 weeks with recovery over months to years. Diagnosis is confirmed with nerve conduction studies demonstrating a demyelinating process, and CSF examination which may show classical albuminocytologic dissociation (elevated protein, total white cell count < 50 cells/uL) as in non-HIV associated AIDP/GBS or a mild mononuclear pleocytosis and elevated protein. CSF should also be investigated for opportunistic infection with CMV, VZV, and HSV in those cases where there is a radiculomyelopathy mimicking AIDP/CIDP.

The response to immune based therapies in HIV associated AIDP/CIDP is similar to non-HIV associated AIDP/CIDP, with early initiation of plasmapheresis and IVIG associated with improvement, and the addition of commencement cART with good CNS penetration (Table 2). (75) Unlike in non-HIV associated AIDP, steroids should be considered if AIDP occurs in context of IRIS. (75)

Mononeuritis multiplex

Mononeuritis multiplex is characterised by the acute onset of one or more nerve palsies. The likely underlying cause of mononeuritis multiplex varies at different stages of HIV disease. A relatively benign form of mononeuritis multiplex occurs early in the course of HIV infection, and commonly resolves spontaneously. (76,77) In patients with moderate immunosuppression (CD4 count 200-500 cells/mm³), mononeuritis multiplex may be related to immune complex disease secondary to hepatitis B virus (HBV), hepatitis C virus (HCV), vasculitis or malignancy either by infiltrative or paraneoplastic mechanisms. (76,77) In advanced HIV disease (CD4 count < 200 cells/mm³), mononeuritis multiplex is more likely to be due to nervous system involvement with an opportunistic infection, most commonly CMV. (76–78)

A presumptive diagnosis of mononeuritis multiplex can be made on clinical findings, but investigations should include serology tests for HBV, HCV, CMV, HSV, VZV and a serum quantitative CMV DNA PCR. CSF investigations include cytology, flow cytometry, and polymerase chain reaction (PCR) assays on the CSF for CMV, VZV and HSV. Other aetiologies of mononeuritis multiplex should be evaluated including diabetes, vasculitis.

Therapy for mononeuritis multiplex is directed towards the underlying mechanism, e.g. Ganciclovir for CMV or chemotherapy for malignancy, in addition to effective cART therapy. (76–78)

Further recommended reading

Brew BJ. HIV Neurology. Contemporary Neurology Series Oxford University Press 2001.

Brew BJ. The Neurology of HIV Infection. Handbook of Clinical Neurology Elsevier Press 2018.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Pulmonary Disease: Including Sarcoidosis and COPD

Introduction - HIV and Lung

HIV infection leads to a gradual but persistent loss of host immunity that results in a syndrome of immune dysregulation, dysfunction, and deficiency.(1) Initial infection with HIV leads to large depletion of CD4+ effector-memory lymphocytes from mucosal-associated lymphoid tissue. There is generalised immune activation leading to progressive decline in naïve and memory T cell pool that results in systemic CD4+ lymphocyte depletion during the chronic phase of the infection. HIV infection is also associated with B cell dysfunction, hypergammaglobulinemia, and defective specific antibody responses.(2) The combination of immune dysfunction, dysregulation, and depletion of CD4 + lymphocytes result in increased risk of infections in untreated patients. Among people living with HIV (PLHIV) treated with anti-retroviral therapy, chronic inflammation and immune activation decrease; however, immune activation can persist in patients who started ART at lower CD4+ cell counts or in those whose treatment is interrupted.(3, 4)

HIV infection causes alteration in several lines of host defenses in the lung and respiratory tract that contribute to an increased risk of lung complications.(1) HIV alters mucociliary function and soluble defense molecules in respiratory secretions. Within the lung parenchyma, innate and adaptive immune responses to pathogens may be impaired. For example, alveolar macrophages from HIV-infected individuals have been shown to be deficient in pathogen recognition. HIV also results in chronic stimulation and activation of inflammatory cells within the alveolar space(1, 5) The bronchoalveolar lavage (BAL) fluid from HIV infected individuals early in infection has demonstrated higher numbers of polyfunctional CD4+ T cells, in contrast to the depletion of CD4+ T cells seen in gut mucosa.(6) In early-to mid-stage disease, HIV infected individuals have increased numbers of HIV-specific CD8+ T lymphocytes which secrete high amounts of IFN-γ within the alveolar space.(7) Within the lung, HIV can infect the alveolar macrophages, T cells and fibroblasts. Evidence suggests that T cells may be a long-lived reservoir of infection within the lung.(8)

HIV is associated with a broad spectrum of lung diseases and many infectious and non-infectious complications have been described.(9-11) These include diseases that are AIDS-defining or HIV-associated such as Pneumocystis pneumonia and pulmonary tuberculosis, disorders that are not classified as AIDS-defining but are more common in patients with HIV infection (e.g., lung cancer, pulmonary arterial hypertension, and chronic obstructive pulmonary disease), and conditions whose association with HIV is inconclusive or coincidental (e.g., sarcoidosis). In addition, lung complications can result from immune reconstitution inflammatory syndrome (also called immune reconstitution syndrome), which may occur after initiation of ART(12).

As people living with HIV (PLHIV) are living longer, non-infectious complications and co-morbid conditions have increased in frequency in the last couple of decades.(13) The increased risk of non-infectious respiratory diseases in PLHIV was first demonstrated in a study from the United States by Crothers *et al.* Data from 33,420 HIV-infected and 66,840 age, sex, race, ethnicity, and size-matched HIV-uninfected veterans were analysed to determine the association of HIV with pulmonary diseases. The study demonstrated that the HIV infected cohort had a greater risk of chronic obstructive pulmonary disease, lung cancer, pulmonary hypertension and pulmonary fibrosis compared to HIV-uninfected cohort.(14) Subsequent studies have confirmed the findings of the study by Crothers *et al.*(15, 16) The rise in incidence of non- infectious lung complications in PLHIV has been shown in a nation-wide French study that examined the rates of hospitalisations due to non-infectious lung diseases between 2007 and 2013. The study demonstrated that there was a significant increase in incidence from 45.6% to 54.7% in people hospitalised with non-infectious lung diseases between 2007 and 2013.(17)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

HIV and COPD

Epidemiology and Risk factors

Chronic obstructive pulmonary disease (COPD) is a slowly progressive respiratory disorder that is characterised by incompletely reversible chronic airflow obstruction.(18) Smoking is the main risk factor. Other risk factors include occupational exposure to dust and chemicals, indoor air pollution or rarely genetic alpha-1-antitrypsin deficiency.(19) Active smoking and frequent exacerbations due to lower respiratory tract infections contribute to progressive disease. COPD encompasses two main entities, namely 1) chronic bronchitis which refers to an obstructive ventilatory pattern that is defined by the existence of chronic bronchitis with permanent obstructed of airways (forced expiratory volume in 1 s (FEV1) to forced vital capacity (FVC) ratio <70%) and 2) emphysema which is defined at the anatomical level by destruction of the walls of the alveolar sacs/ducts beyond the terminal bronchiole with an abnormal increase in size of distal airways. Both entities often occur together in patients with COPD and cause a chronic respiratory disorder.(19, 20)

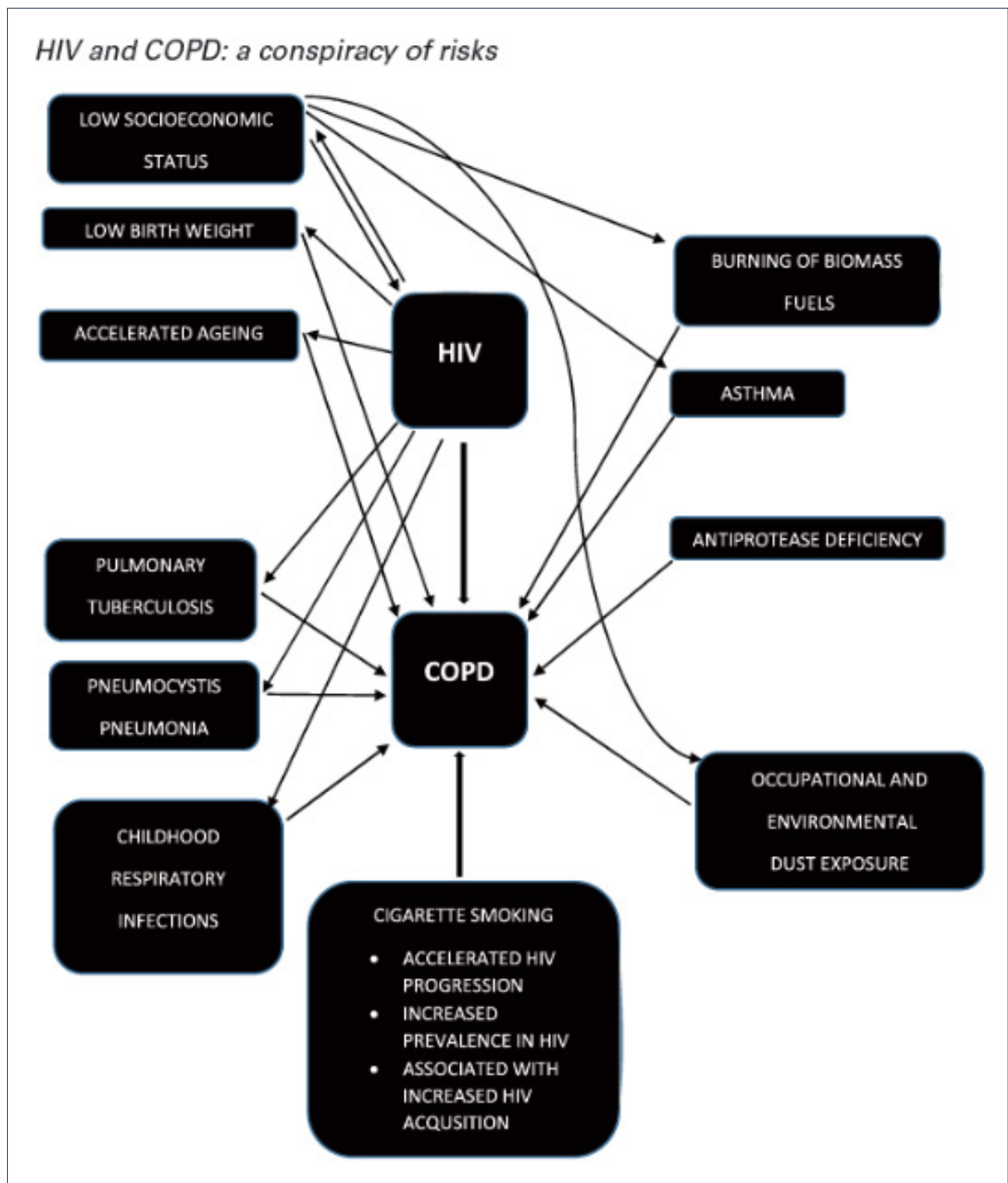
The global incidence of COPD has increased significantly in the last decade. It is now the third leading cause of death worldwide, causing 3.2 million deaths in 2019.(18) In recent years, the risk of people with HIV developing COPD has increased. Improved survival of people with HIV due to the widespread use of combined anti-retroviral therapy has meant that COPD has emerged as a disease of concern in this population.(21, 22) A systematic review and meta-analysis by Bigna JJ et al on the global prevalence of COPD in HIV population demonstrated that the prevalence of COPD varied from 5.6%-10.6% depending on the diagnostic criteria used. Generally diagnostic criteria that used CT scans showed higher prevalence than those that used spirometry. There was an association between HIV infection and COPD even after adjusting for tobacco consumption status.(23) This association was postulated to be caused by a complex interplay of various mechanisms including increased susceptibility to lung infections and colonisations, inadequate inflammatory response, increased oxidative stress, accumulation of cytotoxic lymphocytes in the lung tissue and recurrent pulmonary infections, particularly tuberculosis (Fig 1).(22)

In a study by Crothers et al, 1,014 veteran affairs cohort of HIV-infected persons and 713 HIV-uninfected cohorts were followed up for their COPD diagnosis. HIV remained an independent risk factor for COPD diagnosis by ICD-9 codes (odds ratio [OR]=1.47;95% confidence interval [CI]=1.01-2.13) and self-report (OR:1.58;95%CI:1.14-2.19). Though this study did not use spirometry to confirm the diagnosis of COPD, the results of this large study validates other smaller single or multicenter studies where spirometry was measured.(24) With regards to local prevalence in Australia, the Pulmonary Substudy of the Strategic Timing of AntiRetroviral Treatment (START) trial which included subjects from Australia amongst other countries in Europe and Israel reported a rate of 9.1% based on spirometry results. Cigarette smoking and age were significant risk factors for COPD in this population.(25)

The association of HIV and COPD in Sub-Saharan Africa is not well understood, despite the high prevalence of HIV in the region. There is paucity of data with a few published studies suggesting a higher prevalence.(26) A study from Uganda revealed a prevalence rate of COVID of 16.2% in the HIV population without significant gender difference. A large proportion of the population with COPD in this study were non-smokers. The main risk factor in this population included exposure to biomass, in poorly ventilated indoor kitchens. This also provides a plausible explanation for higher incidence rates in women and children. Biomass exposure is a known risk factor for COPD, particularly in low-income countries.(27) A community-based prevalence study in South Africa (SA) confirmed a high COPD prevalence of 23.1% in adults aged >40 years. It is postulated that in addition to smoking, other airborne exposures and a history of previous tuberculosis were all risk factors.(28) Additionally, in low-income countries other factors related to low socioeconomic status, eg. Pre and post-natal exposures to causative agents, nutritional deficiencies and low BMI may contribute to the development of COPD.(22)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Figure 1. Complex interplay of risk factors between HIV and COPD.



CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Diagnosis

Patients with suspected COPD, based on symptoms of chronic cough, sputum production or dyspnoea should have a spirometry, preferably with bronchodilator testing to determine persistent airflow limitation. The definition of persistent airflow limitation requires that the ratio of the forced expiratory volume in one second (FEV1) to the forced vital capacity (FVC) be less than 0.70 or a cut off of less than 95% of the lower limit of normal (LLN) can also be used.(31) Measurement of diffusing capacity should be measured, as patients with HIV are more likely to have a decrease in diffusing capacity despite an otherwise normal spirometry.(32) It is unclear exactly the reasons behind reduced DLCO in patients with HIV. Screening spirometry to detect COPD in asymptomatic populations is not recommend. Case-finding to diagnose individuals who have symptoms and risk factors should be pursued.(33) One study implementing screening spirometry in an outpatient clinic for PLWH found a high prevalence of symptoms and exposures consistent with COPD, and approximately one quarter of those who completed spirometry were diagnosed with COPD.(34)

Management

In the absence of specific guidelines on management of COPD in HIV patients, clinicians should follow the management guidelines proposed for the general population. Management of COPD is driven by symptoms and history of exacerbations, rather than the severity of airflow limitation or FEV1% predicted.(31) There are a number of symptom assessment tools available for use including the Medical Research Council (MRC) Dyspnoea score, COPD Control Questionnaire (CCQ) or COPD Assessment Test (CAT).(35) Smoking cessation should be prioritised for all patients with HIV, and specifically those with COPD to prevent further progression of disease.(31) All patients with COPD should receive the recommended pneumococcal vaccines and yearly recombinant influenza vaccine as per the Australian Immunisation Guideline.(36)

Pharmacotherapy for symptomatic COPD includes inhaled bronchodilators or in those with regular symptoms long-acting bronchodilators.(31) When choosing an agent, drug interactions with antiretroviral agents needs to be considered. Long-acting muscarinic antagonists (LAMA's), eg. tiotropium do not have known drug-drug interactions with antiretrovirals and are often be used as a first-line bronchodilator therapy in patients with HIV and COPD. An inhaled long-acting beta-agonist (LABA) is an alternative, although there can be some drug-drug interaction with some agents such as salmeterol. If symptoms persist on monotherapy, a combination of LAMA and LABA may be used. Inhaled corticosteroids (ICS) are reserved for patients who develop exacerbation of COPD, though drug-drug interaction, particularly with protease inhibitor such as ritonavir can be problematic. Careful monitoring is also required as high-dose ICS are associated with increased risk of oral candidiasis, bacterial pneumonia,(37) and tuberculosis.(38) The regular use of systemic steroids for COPD in people with HIV should preferably be avoided.

COPD is associated with poor physical function in patients with HIV.(39) Participation in pulmonary rehabilitation programme should be encouraged in patients with HIV and COPD. Pulmonary rehabilitation programs have shown to improve physical functioning in all patients with COPD, and the gains are largest in those who are symptomatic and have more severe disease.(31)

COPD is often associated with several comorbidities such as cardiovascular disease, muscle wasting, osteoporosis, depression/anxiety and lung cancer that will need to be managed or screened for appropriately. Many of these conditions occur in patients with HIV irrespective of their COPD status. Notably, many of these conditions also occur with increased frequency in PLWH. As survival of patients is improved with anti-retroviral therapy, COPD is likely to complicate the care and to adversely impact health-related quality of life, functional status, and mortality in an increasing proportion of patients with HIV.(40)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

HIV related effects on COPD

Both COPD and HIV are associated with increased inflammasome activation, susceptibility to oxidative stress and persistent activation or dysfunction of lung immune cells.(29) In addition to environmental risk factors such as smoking or biomass exposure, HIV likely leads to direct cytopathic effect or persistent immune activation which leads to inflammation and increased risk of COPD.(22) Though high HIV viral load in plasma correlate with high levels of inflammatory cytokines, neither suppressive anti-retroviral therapy nor HIV viral load consistently correlate with the incidence or progression of COPD.(21) The progression of HIV-related COPD correlate with elevated systemic markers of inflammation such as sCD14 and sCD163, which raises the possibility that these cells either serve as a site of HIV persistence or are activated by local tissue reservoirs that may not be adequately measured in the blood or BAL.(3) It is postulated that HIV infection leads to abnormal immune responses in the airway that impacts the capacity of the lung to regulate response to environmental toxins such as cigarette and biomass smoke. Hence, even mild exposures to the noxious substances that are not clinically relevant in a HIV-negative individual may lead to the development or earlier progression of COPD amongst HIV positive individuals.(21)

COPD may progress more rapidly in patients with HIV, particularly in those that are currently smoking and have poorly controlled HIV. People with HIV may have a greater risk of COPD exacerbation compared to people without HIV.(30)

Sarcoidosis

Sarcoidosis is a multisystem granulomatous disorder characterized pathologically by the presence of noncaseating granulomas in involved organs.(41) The disease is characterised by bilateral hilar adenopathy, pulmonary infiltrates and possible involvement of the skin, joints, or eyes. The diagnosis of sarcoidosis is established based on compatible clinical and radiologic findings supported by histologic evidence in one or more organs of noncaseating epithelioid-cell granulomas in the absence of other causes.(42) It is important that other causes of granulomatous inflammation such as infection are excluded before a diagnosis of Sarcoidosis can be made, particularly in the patient with HIV infection.(43) Evidence suggests that sarcoidosis results from environmental triggers and a susceptible genetic host.(41)

Sarcoidosis has been described in HIV patients both before and after the advent of highly active antiretroviral therapy (HAART).(42) A case series from France examined 11 subjects with sarcoidosis. Most were diagnosed after the commencement of HAART but in 3 cases, sarcoidosis was diagnosed prior to starting HAART. The manifestations in those with HIV were like those described in patients not infected with HIV.(44) Most of the subjects in this case series had a CD4 cell count above 200 cells/mm³. One patient had received IL-2 prior to the diagnosis of sarcoidosis, and one had received IFN-α therapy for chronic Hepatitis C. Other studies have emphasised the relationship of higher T cell counts to the diagnosis of sarcoidosis. (45) Furthermore, other explanations for granulomatous inflammation such as infection are more likely to be found in HIV-infected patients with peripheral CD4+ lymphocyte counts of < 200 cells/ mm³.(46)

The development of pulmonary sarcoidosis has been described as part of the Immune Reconstitution Inflammatory Syndrome (IRIS) following commencement of HAART.(47) Likewise, symptoms and signs of previously diagnosed sarcoidosis may flare after the commencement of HAART.(45) Clinicians should be aware of this possibility when commencing HAART in such patients. Management of sarcoidosis in HIV-infected persons should follow established guidelines for non-HIV-infected persons.(41)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Other pulmonary conditions

1. Interstitial lung disease (ILD)

Interstitial lung diseases such as NSIP and LIP are related to immune dysregulation and are now seen much less frequently due to the use of ART.(50)

Lymphocytic Interstitial Pneumonitis (LIP)

This has been described predominantly in children with low CD4 T-cell counts and is characterised by bilateral reticulonodular interstitial opacities in the middle and lower lung zones.(41) Other imaging findings include basal reticulation, ground-glass opacities, ill-defined centrilobular and subpleural nodules, thin-walled cysts, peribronchovascular interstitial thickening, and interlobular septal thickening. Cysts may result from bronchiolar obstruction by lymphocytic infiltrates with post-obstructive ectasia.(48) Diffuse hyperplasia of bronchus-associated lymphoid tissue is seen and the dominant microscopic feature of LIP is a diffuse, polyclonal lymphoid cell infiltrate surrounding airways and expanding the lung interstitium. LIP may be seen in association with autoimmune disorders.(48)

Nonspecific Interstitial Pneumonitis (NSIP)

This is a histological diagnosis, requiring the exclusion of other causes, and the condition may be part of the “lymphocytic pulmonary syndromes” associated with HIV infection.(49) NSIP is characterized by the presence of an interstitial infiltrate of lymphocytes, plasma cells, and macrophages. In severe cases, the infiltrate may extend into alveolar septae.(49) The presentation of NSIP is similar to that of pneumocystis pneumonia although it be present at higher CD4 cell counts. Chest radiographs may be normal although typical changes include ground-glass opacities and fibrosis. The condition may improve without specific therapy and may even be seen as an incidental finding on lung biopsy.(49, 50)

2. Bronchiectasis

Bronchiectasis is characterised by dilatation of airways, impaired mucociliary clearance and recurrent infection. Bronchiectasis rates have been reported to be increased in both paediatric and adult populations living with HIV.(46, 51) In the pre-ART era, a US study reported a 6% prevalence of bronchiectasis in a group of HIV-infected children. Studies from Africa report higher rates of bronchiectasis in children.(52) Multiple pulmonary insults, include infection and immunodeficiency, can result in bronchiectasis. Such factors are associated with HIV infection however, some data suggest that HIV may predispose to bronchiectasis independently of infection, likely due to defects in innate immunity and accompanying airway neutrophilic inflammation.(52) Bronchiectasis in adolescents may be seen as a late complication of LIP.(46)

3. Cryptogenic Organising Pneumonia and Hypersensitivity Pneumonitis

Cryptogenic Organising Pneumonia is a pattern of lung tissue repair after injury. The condition may be idiopathic or a response to many different forms of lung injury including viral infections such as HIV. The condition may manifest with cough and dyspnoea, often as a syndrome of failure to improve after a previous infectious illness. The radiological appearances may be diverse, but often bilateral patchy or diffuse changes are seen in the presence of normal lung volumes.(53) The condition may be seen in association with *Pneumocystis jiroveci* pneumonia and may be a manifestation of IRIS.(50)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Hypersensitivity pneumonitis results from a disordered CD8+ inflammatory response to an extrinsic allergen. The condition was uncommonly associated with HIV infection, but with the advent of HAART, it has been described in HIV-infected individuals exposed to several agents, including efavirenz, dapsone and bleomycin. (49, 50) It may also be observed after the initiation of HAART. (54)

4. Pulmonary Arterial Hypertension (PAH)

PAH appears to be more common in individuals living with HIV. (50) Prevalence rates in persons living with HIV vary from 0.46% to 10%. (55,56) Symptoms of this disorder include progressive dyspnoea, chest pain and syncope. Examination shows features of pulmonary hypertension and chest radiology shows cardiomegaly and enlargement of the pulmonary arteries. (50) If the diagnosis is suspected, specialist referral and investigation is warranted. Outcomes in those with PAH and HIV appear to be worse than in those without HIV. One cohort reported a survival rate of 72% at 3 years, and cardiac function and CD4 counts both predictive of mortality. (57)

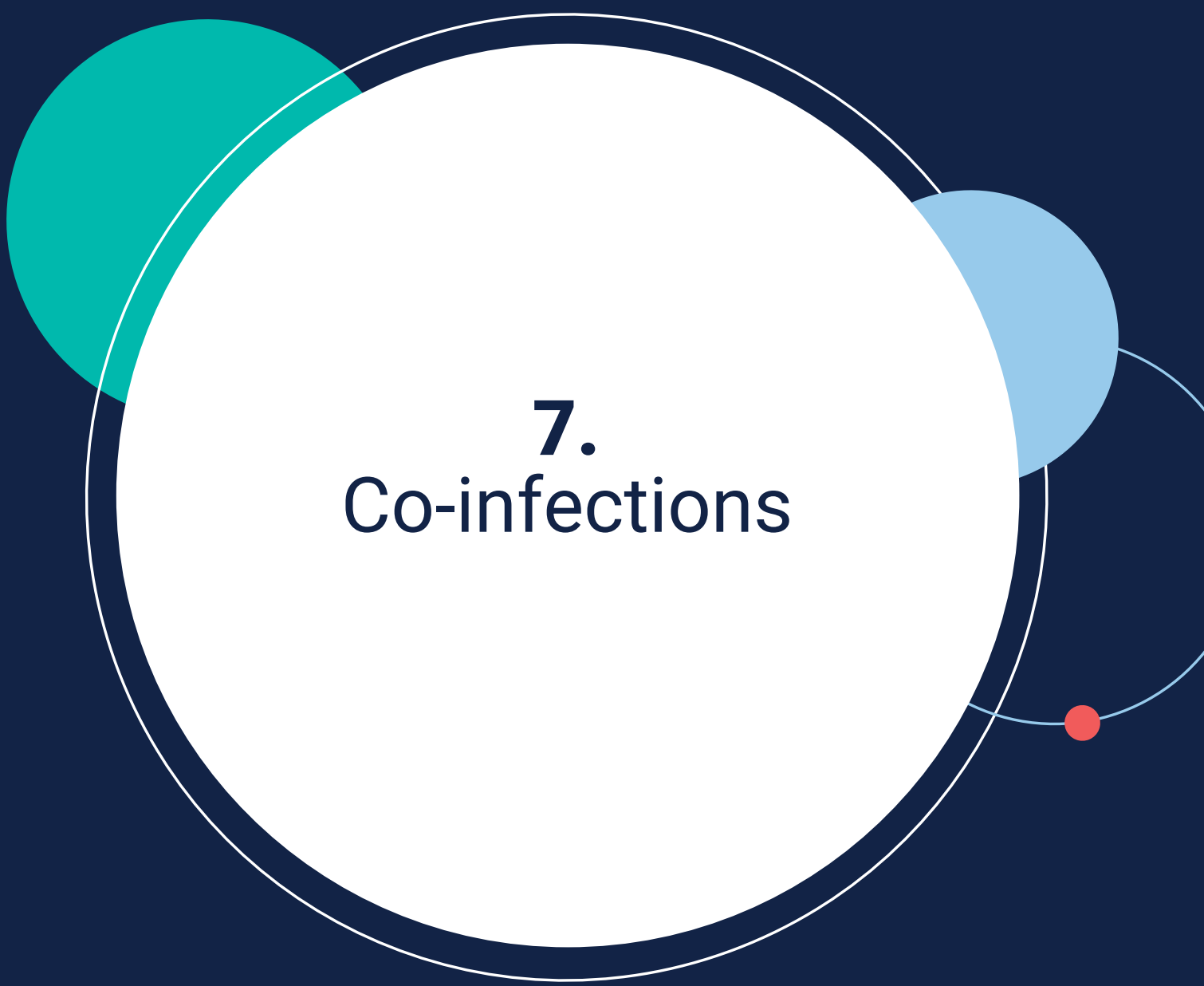
CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

References

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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7. Co-infections

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Sexually transmissible infections among people with HIV infection

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Last reviewed: October 2019

More recent Australian clinical guidelines on sexually transmissible infections are available.

Read the guidelines: <https://sti.guidelines.org.au/>

Introduction

The epidemiology of sexually transmissible infections (STIs) among Australian people with HIV infection varies widely, in keeping with the diverse demographic and behavioural characteristics of people with HIV infection in Australia. (1) Community-based cohort studies from the last decade found a higher incidence of most STIs among the group who bear a disproportionate burden of STIs in Australia: HIV-positive men who have sex with men (MSM) (2), and this finding remains consistent with recent Australian surveillance reports. (3) To our knowledge, there are no comparable data regarding STIs among non-MSM HIV-positive individuals in Australia.

Australian guidelines recommend STI testing (and, initially, vaccination for vaccine-preventable STIs) four times per year in asymptomatic MSM, and testing according to risk behaviour in other people with HIV infection. (4) The presence of some STIs is known to enhance transmission of HIV infection (5), however in the setting of HIV viral suppression, concurrent STIs do not appear to affect risk of HIV acquisition via condomless anal sex between serodiscordant gay male couples. (6, 7)

This chapter will discuss most STIs but focus on those where there are recognised differences in clinical presentation and management among HIV-positive individuals, namely lymphogranuloma venereum (LGV), syphilis and herpes simplex virus (HSV). Details of clinical presentation and guidelines for management of other STIs can be found online in the Australian STI Management Guidelines. (4) Human papillomavirus infection and associated malignancies in HIV-infected people, Hepatitis B virus co-infection and Hepatitis C virus co-infection are covered in detail in other chapters of this guide.

Neisseria gonorrhoeae and Chlamydia trachomatis infection

Epidemiology

Among MSM attending Australian sexual health clinics in 2017, chlamydia and gonorrhoea incidence was approximately 60% higher among HIV-positive MSM, compared with HIV-negative, MSM. (3) In the previous five years, chlamydia incidence increased by 25% and 43% among HIV-positive and HIV-negative MSM, respectively. Over the same time period, gonorrhoea incidence also increased among HIVpositive (31%) and HIVnegative (34%) MSM. (3)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

These increases were observed during a time of rapid HIV pre-exposure prophylaxis roll-out in several Australian jurisdictions. (8, 9) The concurrent increase in STI testing frequency undoubtedly contributed to these increases. Nonetheless, a significant increase in chlamydia incidence was observed in the Victorian PrEP Demonstration Project, even when adjusted for pre-PrEP STI testing frequency. (10)

Clinical presentation

In a US cross-sectional study of women hospitalised with pelvic inflammatory disease (PID), HIV-positive women had a more severe initial presentation and prolonged hospital course compared with hospitalised HIV-negative women (11). Nonetheless, there was no difference by HIV status in the prevalence of chlamydia and gonorrhoea detected during hospitalisation, or for treatment outcomes with standard therapeutic regimens. There have been no other published studies evaluating differences in clinical presentation, diagnosis, or response to treatment of gonococcal or chlamydial infections in patients with HIV infection. (12)

Management

Australian guidelines have recently changed to recommend 2g oral Azithromycin (previously 1g) plus 500mg IMI Ceftriaxone *statim* for treatment of pharyngeal gonococcal infections. Compared with uncomplicated anogenital infection (where treatment guidelines remain unchanged), treatment of pharyngeal gonorrhoea may be more likely to select for both ceftriaxone and azithromycin resistance due to lower levels of drug penetration at this site with treatment failures being observed, even in gonococcal strains susceptible to both antibiotics. The rise in low-level resistance to azithromycin among Australian gonococcal isolates is the basis for the recommendation to increase the dose of oral azithromycin. (4)

A recent systematic review and meta-analysis suggested that one week of oral doxycycline 100mg BD was superior to a single dose of Azithromycin 1g po *statim*, for treatment of rectal chlamydia in MSM (13) and a randomized clinical trial will soon definitely answer this question for treatment of asymptomatic rectal chlamydia in MSM. (14)

Lymphogranuloma venereum

Epidemiology

Lymphogranuloma venereum is caused by *Chlamydia trachomatis* (CT) serovars L1-3 and continues to affect MSM worldwide. (15) L2b is the serovar identified in the majority of LGV cases that have been diagnosed in Australia (16-21) and globally. (22-24)

Nationally, this infection is usually diagnosed in MSM, the vast majority of whom present with symptoms of proctitis (18, 20, 21, 25) with an incubation period of one to four weeks. (26) In addition, LGV has, historically, disproportionately affected those co-infected with HIV. (16, 20, 25, 27)

LGV was removed from the list of Australian nationally notifiable diseases in 2001 after 5 consecutive years with no LGV notifications. (28) Currently, it only remains notifiable to public health authorities in New South Wales, Queensland, Western Australia, the Northern Territory and Tasmania. Since that time, as with other jurisdictions globally (29-31), LGV diagnoses have markedly increased in Australia. (32, 33)

Chlamydia trachomatis transmission among MSM can occur via anogenital contact. However, given that the ratio of genital compared with anorectal LGV infections has been reported to be as high as 1 in 15 (34), other modes of transmission are likely. Although initially suggested (35), sharing sex toys and fisting have subsequently been dismissed. (36) Additionally, there is no evidence of differing tissue tropism between

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

anorectal and genital sites. (37, 38) *Chlamydiae* spp. in almost all natural animal hosts are transmitted faecal-orally and reside naturally in the gastrointestinal tract for long periods without causing disease or inflammation. (39) Mice infected orally with *Chlamydia muridarum* become infected in the lower gastrointestinal tract and are unable to clear the infection. (40) In addition, a report from four decades ago described neonates who were infected with perinatal nasopharyngeal and conjunctival CT subsequently testing positive on anorectal samples. (41) Thus, a recently proposed hypothesis for the large disparity between genital and anorectal infections is that oral infection acquired via “rimming” may lead to asymptomatic pharyngeal infection in MSM which passes through the gastrointestinal tract to the anorectum. Subsequently, L2 serovars may induce LGV proctitis or asymptomatic infection which could contribute to ongoing LGV transmission in the gay community. (42)

Clinical presentation

LGV is important to distinguish from non-LGV CT infection because of its frequently severe clinical presentation and sequelae, the need for a longer course of antibiotic therapy, and the possible consequence of enhanced HIV and Hepatitis C virus transmission. (26) The traditional presentation of LGV is a primary ulcerative genital lesion, leading to a secondary inguinal syndrome of buboes (painful unilateral inguino-femoral lymphadenopathy which may suppurate). (26) There are a few reports in Australia of penile ulcers progressing to inguinal bubo in men with HIV infection. (43, 44)

An important differential diagnosis of the painless anogenital ulcer of LGV is the primary chancre of syphilis (17) and consideration should be given to nucleic acid amplification testing (NAAT) of painless ulcers for LGV. In addition, there are multiple case reports in the literature of LGV being misdiagnosed as inflammatory bowel disease (45-51) and malignancies (52-55), leading to protracted symptoms due to inappropriate management and delayed LGV therapy.

Recently, genital LGV has also been described in HIV-negative Australian MSM on HIV pre-exposure prophylaxis (PrEP). (17) This observation highlights the possibility of increasing LGV diagnoses among HIV-negative MSM as a result of increasing unprotected anal intercourse between HIV-positive men and HIV-negative men on PrEP, as has been observed in Europe. (56)

If LGV proctocolitis is left untreated, perirectal abscesses, fistulas, strictures and stenosis of the rectum may occur with haemorrhoid-like swellings of obstructed rectal lymphatic tissue (“lymphorrhoids”). Oedema and sclerosing fibrosis resulting in strictures and fistulas can ultimately lead to elephantiasis. (22, 26) There is no evidence that the clinical severity or course of LGV infection is influenced by HIV status. (26)

A curious disparity exists between the clinical presentation of anorectal LGV among MSM in Europe compared with Australia. Between 5% and 53% of LGV infections identified during systematic anorectal testing of clinic attendees in several European jurisdictions have been asymptomatic. (29, 34, 57-60) In contrast, systematic genotyping of confirmed rectal CT infections among community-based cohorts (19) and clinic attendees (18, 21) has failed to identify a reservoir of asymptomatic rectal LGV in Australian MSM. Given frequent sexual activity during international travel of many MSM (61-63), the reason for this notable difference in asymptomatic LGV between MSM resident in Australia and those from overseas remains unclear. No commercial LGV assays are validated for use on rectal specimens (22), thus variability in performance of the multiple in-house or laboratory-developed assays used to diagnose LGV globally may be a possible explanation for this finding.

Management

In published studies of LGV treatment, the majority of participants have been HIV-positive. Treatment recommendations for LGV do not differ between HIV-positive and -negative individuals. (22, 26) One syndromic

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

management study of genital ulcer disease compared treatment outcomes by HIV status and showed no difference in response to treatment of genital ulcers by HIV status, including for ulcers caused by LGV. (64)

A systematic review and meta-analysis of doxycycline efficacy for rectal LGV in MSM, which included nine prospective and retrospective observational studies between 1940 and 2016, reported that among 282 MSM, most of whom were HIV-positive and symptomatic, the cure rate of doxycycline 100mg BD for 3 weeks was 98.5% (95% CI 96.3%–100%). (65) Nonetheless, treatment failures with this regimen have been reported among both HIV-positive and -negative MSM with inguinal LGV, more clinically severe and/or extensive rectal LGV infections. (24, 44, 66-68) In such cases, longer courses of doxycycline or alternative treatment with moxifloxacin have usually achieved clinical and microbial cure.

Recent data have suggested that shorter courses of 7-14 days of doxycycline may be curative for rectal LGV (69), although half of cases in this retrospective study were asymptomatic. An alternative is weekly azithromycin 1g orally for 3 weeks. (25, 70) However, insufficient evidence currently exists for these regimens to be recommended as first-line options for treatment of LGV and 3 weeks of doxycycline remains the recommended therapy. (4)

Mycoplasma genitalium infection

Epidemiology

Mycoplasma genitalium (MG) is considered a new and emerging sexually transmitted pathogen, (71) with an estimated global community prevalence of 1.3%. (72) The prevalence of MG infection in HIV-positive individuals has not been systematically investigated in Australia, however a meta-analysis of observational studies worldwide suggested HIV-positive individuals bear a disproportionate burden of MG infection. (73) Like several other STIs, MG infection may increase the shedding of HIV-1 virus from the cervix, (74) but the clinical implications of this finding have not been investigated.

Clinical presentation

MG causes urethritis in men and cervicitis in women. It is associated with PID and is a possible cause of preterm delivery, spontaneous abortion and infertility in women. (75) There is no evidence to suggest distinct clinical features are present or different management approaches are required in HIV-positive individuals.

Management

The prevalence of macrolide resistance is high in Australia, especially among MSM. (76) Doxycycline will only cure approximately one-third of MG infections, although Australian guidelines recommend a week of doxycycline 100mg po bd to reduce bacterial load, then resistance-guided therapy with either azithromycin 1g stat then 500mg daily for three days or, where macrolide resistance is confirmed or suspected, moxifloxacin 400mg po daily for 7 days. (4)

Trichomonas vaginalis infection

Epidemiology

Trichomonas vaginalis (TV) causes the most common curable STI globally (77) and is highly prevalent among the Australian indigenous population. (78) TV disproportionately affects older indigenous women living in remote settings, (4, 78) but is rarely diagnosed in urban Australia. (79-81) TV infection increases the

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

risk of HIV acquisition by 50% (77) and has been reported to increase genital shedding of HIV among co-infected individuals. (82) Nonetheless, the impact of TV treatment on reducing genital HIV shedding has been inconsistent among virologically suppressed individuals taking antiretroviral therapy (ART). (82, 83) Among women with HIV infection, TV infection is associated with an increased risk of PID. (84) In contrast to most other STIs, TV infection is rare among MSM. (85)

Clinical presentation

Up to 50% of women with genital TV infection are asymptomatic, whereas men are usually asymptomatic. (4) A frothy, malodorous vaginal discharge is the most common symptom in women, while urethral discharge and dysuria can rarely occur among men. (4) There is no evidence to suggest distinct clinical features are present or different management approaches are required in HIV-positive individuals.

Management

First-line treatment of uncomplicated genital TV infection is a stat oral dose of 2mg tinidazole or metronidazole. (4)

Syphilis

More recent Australian clinical guidelines on syphilis are available.

Read the guidelines: <https://sti.guidelines.org.au/sexually-transmissible-infections/syphilis/>

Epidemiology

Syphilis is caused by the spirochete *Treponema pallidum* subspecies *pallidum*. This obligate human pathogen is primarily transmitted via sexual contact between mucosal surfaces. In addition, cases of mother-to-child transmission of syphilis are being reported in the current epidemic. (86)

In Australia, syphilis disproportionately affects indigenous Australians and MSM populations. Among HIV-positive MSM attending sexual health clinics, the incidence of infectious syphilis approached 10% per year in 2015 and is currently over two-fold higher than the incidence among HIV-negative MSM. (3) Thus, current guidelines recommend testing for syphilis every three months among MSM with HIV infection. (87)

Epidemiological evidence supports the fact that incident syphilis infection increases sexual acquisition of HIV, via breaches in mucosa and/or skin during early syphilis infection (88) and the associated impact of local recruitment of CD4+ immune cells to the area. (89) This has been demonstrated in several studies, including the recent iPrEx HIV pre-exposure prophylaxis study, where incident syphilis infection was a risk factor for HIV acquisition. (90) As previously noted, in the setting of HIV viral suppression, concurrent STIs do not appear to affect risk of HIV acquisition via condomless anal sex between serodiscordant gay male couples. (6, 7)

Syphilis may also have a negative impact on chronic HIV infection. Early retrospective studies found that incident syphilis adversely affected both the immunological and virological status of HIV-infected people, leading to a reduction in CD4+ T cell counts and a rise in plasma HIV viral load. (91-93) However, some retrospective reports found no association between incident syphilis and changes in HIV viral load (94, 95) and a prospective study found that although incident syphilis infection was associated with a change in CD4+ T cell count, this was promptly reversed upon treatment of syphilis. In addition, the transient drop in CD4+ T cell count had no impact on disease trajectory, progression to AIDS or mortality. (96)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Clinical presentation

In general, the clinical manifestations of syphilis are similar in HIV-positive and -negative individuals. (4) However, important differences exist, as outlined below.

Infectious syphilis

In the US Syphilis and HIV cohort study, (97) HIV-infected individuals presenting with primary syphilis were more likely to have larger and more numerous chancres. In addition, secondary syphilis among HIV-infected individuals was more likely to present with concurrent chancres indicating an overlap between the primary and secondary stages. “Malignant” secondary syphilis, also known as “ulceronodular” syphilis, is a rare manifestation thought to be more common in HIV-infected individuals due to impaired cell-mediated immunity, which is characterised by disseminated papulopustular ulcers with a crusty base. (98)

Neurosyphilis

Syphilis of the central nervous system (CNS) can occur at any stage of disease with HIV infection being consistently demonstrated as a risk factor. Neurosyphilis is estimated to affect around 1-2% of syphilis/HIV co-infected individuals. (99) Most commonly, neurosyphilis is asymptomatic, defined by evidence of syphilis in the cerebrospinal fluid (CSF) without accompanying symptoms or clinical signs.

Symptomatic neurosyphilis is categorised below: (100)

- Early neurosyphilis: Approximately 10% of neurosyphilis in the early stage (months to 5 years) presents with meningovascular disease characterised by encephalitis and cerebrovascular injury. This may result in numerous clinical presentations including cerebral infarction, aseptic meningoencephalitis, cranial nerve palsy, gumma formation and myelitis.
- Late neurosyphilis: This usually manifest 10-30 years after initial infection and includes general paresis and tabes dorsalis, which are included in the case definition of tertiary syphilis. These result from direct parenchymal invasion of treponemes into the brain and spinal cord.
- Ocular & otologic syphilis: visual and hearing impairment from syphilis infection may occur as part of syphilitic meningovascular invasion.

Of note, the initiation of cART appears to be protective against the development of neurosyphilis. (101) Furthermore, there is evidence that cART increases the likelihood of successful treatment of neurosyphilis and reduces risk of treatment failure. (102, 103)

Diagnosis of syphilis in HIV-infected individuals

The standard algorithm for the serologic diagnosis and staging of syphilis infection using specific treponemal (e.g. enzyme immunoassay) and non-specific/non-treponemal (e.g. rapid plasma reagin) assays is appropriate for syphilis diagnosis irrespective of HIV status. (4) The diagnosis of neurosyphilis should be made only after considering the clinical history, examination, serology and CSF findings. No single feature is sufficiently accurate to diagnose or exclude a neurosyphilis diagnosis. However, when the index of suspicion is high, examination of the CSF via lumbar puncture (LP) remains the most useful diagnostic tool.

Although there is no international consensus on the precise timing of LP in the investigation of suspected neurosyphilis, the British Association for Sexual Health and HIV (BASHH) and The Centre for Disease Control and Prevention (CDC) provide a helpful framework which is summarised below: (104, 105)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

- All patients suspected of having neurosyphilis should undergo a thorough neurological examination.
- LP is indicated when patients with newly diagnosed syphilis present with neurological symptoms and/or abnormal neurological examination. This includes abnormal visual or auditory symptoms or signs which may indicate ocular or otologic syphilis, respectively.
- Routine CSF examination of patients with asymptomatic early or latent syphilis is *not* There is no evidence that performing a LP in patients without symptoms or signs suggestive of neurosyphilis improves long-term outcomes. However, LP should be considered in patients who have treatment failure despite adequate therapy as demonstrated by serial serology.
- Laboratory findings shown to be predictive of a CSF diagnosis of neurosyphilis among HIV-positive individual include a peripheral blood CD4+ T cell count of <350/mL and/or a RPR titre of >1:32. (106-108)

The interpretation of CSF findings in the HIV/syphilis co-infected individual can be complicated for several reasons. Firstly, certain CNS changes (namely pleiocytosis and elevated protein) can occur in HIV infection alone, thus may not in themselves indicate neurosyphilis in co-infected individuals. Secondly, due to the nature of the assays, tests detecting syphilis in the CNS are exquisitely sensitive to blood contamination and may yield false-positive results in such samples. (100) The BASHH guidelines suggest the following CSF criteria for the diagnosis of neurosyphilis: (105)

- Lymphocytic pleiocytosis:
 - 6-20 cells/microlitre in individuals on ART with undetectable HIV viral load or those with a blood CD4+ T cell count of <200/m
 - >20 cells/microlitre for all other HIV-infected individuals
- CSF Protein >0.45 g/L
- Non-treponemal test (e.g. CSF VDRL or RPR): reactive. These tests have poor *sensitivity* for the diagnosis of neurosyphilis (estimated 30-70%) but have *good specificity* unless the sample is contaminated with blood. (100)
- Treponemal test (e.g. CSF-TPPA): >1:320. These assays are sensitive but non-specific so they are useful in excluding the likelihood of neurosyphilis. Test sensitivity is reduced by blood contamination. (100)

Although NAATs are available in Australian reference laboratories, the diagnosis of neurosyphilis via NAAT is not currently recommended due to suboptimal assay performance on CSF samples. (109)

Management

Current Australian guidelines for penicillin-based treatment of syphilis are recommended irrespective of HIV status. (110) Briefly, primary, secondary & early latent (<2 years duration) syphilis is treated with benzathine benzylpenicillin 1.8 grams intramuscularly *statim* or procaine benzylpenicillin 1.5 grams intramuscularly daily for 10 days. The same therapy and dosages are indicated for syphilis of unknown duration or late-latent syphilis (>2 years), although for a longer duration: weekly for 3 weeks or daily for 15 days, respectively. The recommended treatment of neurosyphilis is with benzylpenicillin 1.8 grams intravenously every 4 hours for 15 days.

The Jarisch-Herxheimer (JH) reaction is a systemic inflammatory response to endotoxins released during spirochaete death following antimicrobial therapy and occurs in approximately one-third of individuals with early (infectious) syphilis. (111) The syndrome is characterised by fever, skin rash, arthralgia/myalgia and malaise within 24-48 hours of treatment. (112) Earlier evidence suggested there may be an increased risk of

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

the JH reaction in HIV-infected individuals. (113) However, a more recent prospective cohort study found no difference in risk of the JH reaction by HIV status. (111)

Treatment response is generally measured with serial serologic evaluation. Non-treponemal serology should be performed at 3, 6 and, if necessary, 12 months after treatment. (4) A four-fold decrease in RPR titre or reversion to non-reactivity indicates successful treatment. Earlier and/or more frequent follow-up serology should be performed in higher risk cases (including when non-first line therapy is used, in pregnancy or among those at high risk of re-infection). (104). Serological tests should ideally be performed in the same laboratory, to ensure comparability between serial RPR titres. When the expected serological treatment response fails to occur, such samples can thus be tested at the same time by the same laboratory scientist ("in parallel"). A slower decline in RPR titre may occur among HIV-positive individuals who are not established on ART following treatment. (114)

Treatment failure is suspected when the RPR test fails to decline four-fold, especially if re-infection can be reliably excluded. However, this could also be the result of the 'serofast state' when the test is reactive after 6-12 months of adequate treatment. There is no consensus as to whether this 'serofast state' leads to worse long-term outcomes or increased risk of tertiary neurosyphilis. (99) Although the risk of treatment failure is higher in HIV-infected individuals, the difference in clinical outcomes by HIV status appear minimal. (113)

Both UK and US guidelines recommend CSF examination in patients with suspected treatment failure as unrecognised neurosyphilis can be a reservoir of treponemes. If CSF examination excludes neurosyphilis as the cause of treatment failure then consideration of re-treatment with three doses of weekly intramuscular penicillin is recommended. (104, 105) Although a follow-up CSF examination is recommended 6-12 months post-treatment to demonstrate normalisation of CSF parameters, (114) there is a high correlation between the RPR titre in peripheral blood and normalisation of CSF changes. Thus, the serum RPR titre may be used as a surrogate marker for treatment response. (103)

Herpes simplex virus infection

Epidemiology

Anogenital herpes is caused by herpes simplex virus (HSV) type 1 (HSV1) or type 2 (HSV2). Infections caused by this virus are common across the world but there are variations in prevalence between countries and population groups.

HSV disease is not a notifiable disease in Australia so there are limited data regarding disease prevalence. A nationwide population seroprevalence survey of HSV infection from 1999-2000 found an overall HSV2 seroprevalence of 12%. (115) HSV2 seroprevalence was two-fold higher in females compared with males (16% vs 8%, respectively), 18% amongst indigenous Australians, and higher in metropolitan compared with remote areas (13% vs 9%). (115) The overall seroprevalence of HSV1 infection was 76%. (115)

Historically, HSV1 was the most common cause of orolabial herpes and HSV2 the most common cause of anogenital herpes. However, recent data from a large sexual health clinic in Melbourne suggests that HSV1 is now the most common cause of anogenital herpes among women, people younger than 28 years and MSM. (116)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

HSV2 infection may increase the risk of HIV acquisition. (117) HSV co-infection can increase transmission of HIV via activation of HIV replication with increased plasma and genital tract HIV RNA levels. (118) Conversely, suppression of HSV2 infection with valaciclovir has been found to reduce asymptomatic shedding of HIV in the female genital tract. (119) However, suppression with acyclovir does not appear to reduce the risk of HIV transmission, (120) thus should not be considered as an alternative to rapid initiation of ART in people diagnosed with HIV infection. Likewise, suppression of HSV infection with oral acyclovir does not reduce the risk of HIV acquisition, so suppressive therapy to reduce the risk of acquiring HIV among HSV2 seropositive individuals is not indicated. (121)

Clinical manifestations

Genital HSV disease typically presents in the anogenital area with blistering, ulceration and lymphangitis (especially in primary episodes). It is a common cause of proctitis in MSM, although only one-third of men will have externally visible ulcers. (16) Herpes proctitis is more common among HIV-positive, compared with HIV-negative, MSM. (16)

Prolonged symptoms with atypical appearing ulcers may be more common in people with HIV infection. (122) Chronic erosive ulcers and progressive hypertrophic genital herpes have been reported as part of an immune reconstitution inflammatory syndrome (IRIS) following ART initiation and have required treatment with less commonly used therapies including topical cidofovir, foscarnet, thalidomide and imiquimod. (122, 123, 124)

Serious non-genital presentations of HSV infection, such as keratitis, retinitis, encephalitis, hepatitis, and pneumonitis are more commonly reported in people with HIV infection. Although the clinical presentations are similar among HIV-negative individuals, they may be more severe and/or life threatening in people with HIV infection. (125)

The diagnosis of HSV infection is usually made by NAAT on a sample taken from a lesion, or rectal mucosa in the case of proctitis. HSV type-specific serology is not generally recommended for diagnosis, irrespective of HIV status. Type-specific serology may be useful in certain situations such as recurrent genital disease of unknown aetiology or to inform management decisions if a woman who has a first-recognised episode of HSV disease in pregnancy. (126)

Management

Among individuals with HSV infection, HIV co-infection increases the frequency of symptomatic reactivations and episodes of asymptomatic shedding, especially if the HIV-positive individual with moderate-to-severe immunodeficiency. (127, 128) Treatment with suppressive antivirals reduces the frequency of symptomatic recurrences among people with HIV infection experiencing frequent (> 6/year) outbreaks. (129) Long term ART use reduces the frequency of genital ulcer disease (130), although patients may experience an increase in symptoms at the time of ART initiation. (126) Effective ART does not appear to reduce the frequency of asymptomatic shedding of HSV. (131)

Treatment of genital herpes in people with HIV infection is with standard antiviral therapy. Occasionally, higher doses and prolonged duration of therapy may be required. Recommended regimens should be tailored to the severity of disease and degree of immunodeficiency: (126,132)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Oralabial HSV disease (duration: 5–10 days)

- Valaciclovir 500mg – 1 g PO BID
- Famciclovir 250 – 500 mg PO BID
- Acyclovir 400 mg PO TID

Initial or recurrent genital lesions (duration: 5–10 Days)

- Valaciclovir 500mg – 1 g PO BID
- Famciclovir 250mg – 500 mg PO BID (not licensed for use in first-episode of genital HSV disease in Australia)
- Acyclovir 400 mg PO, 3- 5 times daily

Severe mucocutaneous HSV disease

- Initial: acyclovir 5-10 mg/kg IV q8h
- Once lesions begin to heal, change to oral therapy as above.

Chronic suppressive therapy is indicated in people with HIV infection who have frequent or severe recurrences but may be less effective than in people who are HIV-negative. (129) Annual evaluation of ongoing need for suppressive therapy should occur. Recommended regimens include: (126, 132)

- Valaciclovir 500 mg PO BID
- Famciclovir 500 mg PO BID
- Acyclovir 400 mg PO BID

Drug resistant HSV has been reported among 5-7% of genital HSV lesions in HIV-positive individuals. (126) These drug-resistant isolates may be of reduced pathogenicity but can cause serious disease in immunodeficient individuals. Partially resistant strains of HSV may respond to higher doses of acyclovir but fully resistant strains will require alternative antiviral therapy with a different mode of action, such as foscarnet or cidofovir. Recommended regimens include: (132)

For acyclovir-resistant mucocutaneous HSV infections:

Preferred therapy:

- Foscarnet 80–120 mg/kg/day IV in 2–3 divided doses until clinical response

Alternative Therapy (Duration: 21–28 days or longer, based on clinical response):

- Topical trifluridine, or
- Topical cidofovir 1% gel, or
- Topical imiquimod 5% cream three times/week, or
- IV cidofovir 5 mg/kg IV once weekly

Conclusions

STIs continue to be an important issue among people with HIV infection in Australia, disproportionately affecting the MSM population. Comprehensive HIV management should include regular STI testing for all sexually-active people with HIV infection, tailored to their reported risk behaviours. Clinicians need to be aware of key differences in the epidemiology, clinical presentation and management of a number of these STIs.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Hepatitis C virus co-infection

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Last reviewed: 2024

More recent Australian clinical guidelines on Hepatitis C are available.

Read the guidelines: <https://hepcguidelines.org.au/>

Chronic Hepatitis C virus (HCV) infection is a major cause of chronic liver disease and an important public health concern in Australia. Around 25% of acute HCV infections will clear spontaneously within 6 months; however, the remaining 75% will progress to chronic disease and are at risk of progressive liver fibrosis leading to cirrhosis, liver failure, and hepatocellular carcinoma (HCC). Spontaneous clearance is often more common in younger people and females.(1) Chronic HCV infection can lead to the development of liver cirrhosis usually after 20-30 years of active infection. Progression is more rapid in people with significantly abnormal serum alanine aminotransferase (ALT) levels, older population groups at the time of acquisition,(2) and in people with cofactors for liver disease, such as alcohol misuse disorder; metabolic risk factors for metabolic dysfunction-associated steatosis liver disease (MASLD); and concurrent HIV and/or hepatitis B virus (HBV). Metabolic risk factors for MASLD include obesity, type 2 diabetes, hypertension, and dyslipidaemia. This has led to the World Health Organisation (WHO) setting a global target of HCV elimination by 2030.(3)

HCV is transmitted via the parenteral route, with the majority of new infections reported in people who inject drugs (PWID). People with haemophilia were previously considered at high risk of HCV transmission from receiving HCV-infected blood products. However, with the advent of better universal screening of blood products since 1990, new HCV infections from blood products are now considered rare. HCV can also be transmitted perinatally, and concurrent HIV in the mother increases the likelihood of HCV vertical transmission. HCV transmission via heterosexual intercourse is uncommon, but increased sexual (permucosal) transmission is recognised among men who have sex with men (MSM), especially in association with HIV.(4,5) Although the rate of HIV is low among Australian PWID, the prevalence of HCV infection is still high, such that PWID with HIV should be screened for likely concurrent HCV.(6) There is an associated increased rate of progressing to cirrhosis, increased risk of HCC, and mortality in people with HCV in the setting of HIV. The estimated incidence of HCV-HIV coinfection in Australia was reported to be 0.2 per 100 person-years in 2022.(7)

In Australia, since the early 1990s, the diagnosis of HCV infection requires a mandatory notification. In 2022, there were 6,728 HCV notifications in Australia, with 68% of the notifications being among males.(7) The number of HCV notifications in Australia has declined since 2016 after the listing of subsidised interferon-free direct-acting antiviral (DAA) therapy on the Pharmaceutical Benefits Scheme (PBS) in March 2016. In 2022, 5,210 people received DAA treatment through the PBS, and between the beginning of 2015 to the end of 2022, a total of 104,110 people received PBS-subsidised DAA treatment.(7) At the end of 2022, it was estimated that there were 74,400 people living with chronic HCV. This has declined from the estimated total of 117,814 people at the end of 2020(7) and is related to the availability of PBS-subsidised DAA treatment, reduction in the prevalence of injecting drug use, and improved harm reduction measures (e.g., needle and syringe programs and opioid substitution treatment uptake) among at-risk populations, such as PWID. The at-risk group and highly marginalised population, such as PWID, Aboriginal and Torres Strait Islander peoples, those in rural and

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

remote settings, and the prison population, remains particularly challenging in seeing effective engagement in treatment uptake. Models of care for the treatment of HCV infection in Australia have now taken on a multidisciplinary initiative, with specialist gastroenterologists, hepatologists, or infectious diseases physicians, general practitioners, or authorised nurse practitioners all eligible to prescribe DAA treatment under the PBS. This facilitates more timely, affordable, and equitable access to DAA treatment within Australia.

Several position statements and guidelines from major gastroenterology societies such as the European Association for the Study of the Liver (EASL), the American Association for the Study of Liver Diseases (AASLD), and the Gastroenterological Society of Australia (GESA) have been published and made available. This chapter has been formulated by referencing these international guidance statements and forms the basis of our recommendations for the treatment of HCV infection, with the aim to meet the set target of global elimination by 2030.

Hepatitis C in the setting of HIV

All people with HIV should be screened for HCV, and all people found to have concurrent HCV should be prioritised for treatment of HCV and be managed by a multidisciplinary team with experience in managing both conditions.

HIV-HCV is associated with a reduced HCV clearance rate⁽⁸⁾ and a higher rate of cirrhosis compared with people with HCV alone. After 10 years, the prevalence of cirrhosis in people with HIV-HCV was 14.9%, compared to only 2.6% in those with isolated HCV, in one study.⁽⁹⁾ While after 15 years, the prevalence of cirrhosis was 25% in people with HIV-HCV, compared to only 6.5% in those with isolated HCV.⁽¹⁰⁾

The impact of concurrent HIV-HCV is also observed in other population groups. HIV accelerates the progression of liver disease in people with haemophilia, and HCC occurs at a younger age and sooner in the time course in people with HIV-HCV.⁽²¹⁾ Progression of HIV-related immunodeficiency is also associated with HCV liver disease progression, with lower CD4 T-lymphocyte (CD4) cell counts found to correlate with hepatic fibrosis and liver failure.^(11,12) People with HIV-HCV and mild fibrosis on liver biopsy may experience significant progression of hepatic fibrosis over only a 3-year period.⁽¹³⁾ However, studies of the influence of HCV on the progression of HIV have been contradictory, with some studies suggesting an increase in HIV disease progression in people with concurrent HIV-HCV, while others demonstrated no influence on disease progression.⁽¹⁴⁾

Selection of DAA treatment of HCV in people with concurrent HIV-HCV is the same as the recommendations for people with isolated HCV. The only important consideration is choosing a DAA therapy regimen that minimises the potential drug-drug interaction and liver toxicity with current HIV antiretroviral therapy (ART) available. Careful evaluation of all relevant medications prior to commencement of DAA treatment is recommended. Management of HCV, treatment selection, and evaluating for potential drug-drug interactions will be discussed later in this chapter.

Diagnosis

Screening for HCV should be performed in people who have associated identifiable risk factors. Those with HCV are often asymptomatic, unless they have developed advanced liver disease. A major barrier to HCV elimination is that a substantial proportion of those who have acquired HCV are unaware of their status and not adequately screened and therefore, treatment is not made available for them. Identifiable risk factors include: PWID or who have ever injected drugs; people who are incarcerated; people with tattoos or body

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

piercings; people who have received a blood transfusion or organ transplant prior to 1990; people who have received blood products or plasma-derived clotting factor treatment products before 1993; children born to mothers with HCV; people with HIV or HBV; sexual partners of those with HCV or individuals at higher risk of sexual transmission including MSM; people with evidence of liver disease; people who have had a needle-stick injury; and migrants from high-prevalence areas (Egypt, Pakistan, Mediterranean and Eastern Europe, Africa and Asia).(15)

Recommended standard-of-care screening test includes HCV serology with anti-HCV antibody testing. Anti-HCV antibodies are detectable in whole blood serum or plasma by enzyme immunoassay (EIA) and are a biochemical indicator for exposure to HCV, whether it be a current or past infection. Anti-HCV antibodies will persist even after spontaneous clearance or treatment-induced viral clearance. Thus, if HCV serology is positive, current HCV infection should be confirmed via polymerase chain reaction (PCR) assay for HCV RNA on plasma or whole blood. False-negative assays are uncommon with third-generation EIA, but failure to detect HCV antibodies in people with HIV has been reported.(16) Patients who are Anti-HCV antibody-negative with evidence of liver disease, such as having an elevated serum transaminase level or a history of high-risk behaviours, should be evaluated for a detectable HCV RNA to exclude occult HCV infection. Patients diagnosed based on an isolated detectable HCV RNA in plasma or whole blood should have repeat testing for confirmation, as the incubation period for HCV infection is between 2 and 26 weeks.(17) HCV RNA testing should also be performed in seronegative people with possible early HCV infection, as the antibody response may be delayed by several months. The updated international consensus statements now recommend clinicians practice reflex testing, whenever possible, by requesting both anti-HCV antibodies and HCV RNA in the same plasma or whole blood sample, particularly in population groups considered most at-risk. This substantially increases the likelihood of adequately identifying people with active HCV and linking them in with subsequent treatment and follow-up in a timely and appropriate manner.(15,18)

Eligibility for PBS-subsidised DAA treatment requires documented evidence of chronic HCV infection, which has traditionally been defined as being anti-HCV antibody and HCV RNA positive for a duration longer than 6 months. However, in someone with a detectable HCV RNA on plasma or whole blood, treatment should not be delayed and a clinical assessment of chronicity can be inferred, unless an individual has a known recent exposure or in the absence of acute hepatitis.(15)

Documentation of HCV genotype is no longer a mandatory PBS criterion before prescribing DAA treatment, as currently available first-line treatments—sofosbuvir plus velpatasvir; glecaprevir plus pibrentasvir; and sofosbuvir plus velpatasvir plus voxilaprevir—are all pan-genotypic treatment regimens (meaning that they have been proven effective against multiple genotypes). There were several genotype-specific treatment regimens previously available, but these are now no longer marketed in Australia and therefore no longer relevant. However, documentation of HCV genotype may be useful in population groups at high risk of reinfection, where genotype switch would help differentiate reinfection from relapse.(15,18) History of any prior treatment for HCV, including the treatment regimen and duration course; adherence compliance; and response to treatment, should always be documented. These factors will influence future treatment decisions in the setting of reinfection or relapse.(15)

Annual HCV serological testing is recommended and should be continued for those who test seronegative but have ongoing risk factors for HCV transmission. In those who are seropositive but have undetectable HCV RNA, indicating a past infection, but with ongoing risk factors for HCV transmission, annual HCV RNA testing is recommended.(3)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Staging of liver disease

Adequate assessment of liver disease severity should be performed in all people with HCV before prescribing DAA treatment. The patient's cirrhosis status is a requirement when seeking PBS authority, and adequate assessment of liver disease severity helps determine clinical decisions surrounding: treatment priority; factors that may adversely affect treatment efficacy, and therefore the choice of DAA therapy and its duration course; and whether ongoing HCC surveillance post treatment is required.

Concurrent HBV or HIV is found in a higher prevalence in people with HCV compared to the general population, and both should also be tested for. Testing should be performed before initiation of HCV treatment, but confirmation of results should not delay commencement of treatment. If HBV and HIV testing is not performed prior to starting treatment, it should be performed within 4 weeks of starting DAA therapy. Vaccination against hepatitis A (HAV) and HBV (if seronegative) is recommended in all patients with HCV.(15,18)

Non-invasive testing consisting of a combination of serum biomarkers and transient elastography (e.g., FibroScan®; EchoSens, Paris) improves the accuracy of establishing liver staging of fibrosis, thus avoiding the need for a liver biopsy, and is now the recommended practice according to the international consensus statements.(15,18,19) It is important to stress that non-invasive assessment of liver fibrosis is not completely accurate, and interpretation of results should be corroborated with the clinical context. FibroScan® is readily available in the tertiary care setting, and its accuracy in diagnosing cirrhosis has been extensively validated in clinical studies in people with chronic HCV.(20,21) Shearwave elastography is now emerging as a diagnostic alternative to FibroScan®, with its benefits being that it can be performed at the same time as an ultrasound. However, shearwave elastography has not yet been extensively evaluated, and its validity tested, in the setting of HCV. Therefore, there should be caution in interpreting these results within this population cohort. Factors that may adversely affect the liver stiffness measurement (LSM) include obesity, elevated ALT levels, and post-prandial eating. These should be taken into consideration prior to testing.(18)

A new nomenclature of advanced chronic liver disease (ACLD) which does not require a liver biopsy has now been denoted to identify the population group who are likely representing severe fibrosis and cirrhosis based on LSM and platelet count. Patients with ACLD but without a prior decompensation event are denoted the term compensated (c) ACLD. A LSM by transient elastography of <10 kPa excludes ACLD, while values between 10 and 15 kPa are suggestive, and ≥15 kPa effectively rules in ACLD.(10) Transient elastography can further rule in clinically significant portal hypertension (CSPH). Presence of CSPH can be presumed in the presence of: LSM >25 kPa; LSM between 20 and 25 kPa plus a platelet count <150 ×10⁹/L; or a LSM between 15 and 20 kPa plus a platelet count <110 ×10⁹/L. CSPH is considered effectively excluded when LSM is <15 kPa plus platelet count >150 ×10⁹/L.(23) In the setting of CSPH, commencement of a non-selective beta blocker such as carvedilol is recommended for both primary prophylaxis against variceal haemorrhage and preventing decompensation events.(22-24) Caution should be exercised with the use of non-invasive tools to assess fibrosis stage post therapy, as this is considered less reliable in this clinical setting.(18)

There are numerous well-established fibrosis serum biomarkers that have been developed and are readily accessible, simple, and considered reliable. These include the aspartate aminotransferase (AST) to platelet ratio index (APRI) and Fibrosis-4 (FIB-4). The ease of use with these serum biomarker tools is that they can be calculated from routine blood tests. Both the APRI and FIB-4 calculation are similar, except FIB-4 considers patient age in addition.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Although the advancement of non-invasive testing means a liver biopsy is no longer recommended as routine screening, the need for liver histology is still reserved in situations of diagnostic uncertainty or incongruent non-invasive testing results leading to an indeterminant staging of fibrosis.(15,18)

In all people with cirrhosis (METAVIR score F4) or advanced (bridging) fibrosis (METAVIR score F3), they should be evaluated for hepatic decompensation, as this may impact treatment choice. They should also undergo liver ultrasound to exclude extrahepatic complications of cirrhosis and have routine screening for HCC. Ongoing surveillance for HCC with ultrasound every 6 months should be continued in people with F3 and F4 fibrosis, even after achieving post-treatment SVR, as the risk of HCC is only reduced and not abolished.(18)

Management

The primary goal of therapy is to cure HCV, defined by achieving SVR. There are multiple clinical benefits in achieving SVR including: preventing further transmission of HCV; preventing complications of HCV-related liver disease, such as hepatic inflammation, fibrosis, cirrhosis, and HCC, and extrahepatic diseases; it reduces all-cause mortality; improves individual quality of life and removes the social barriers that the stigma of having chronic HCV can lead to. HCV cure should include a collaborative and multidisciplinary approach, consisting of therapeutic treatment and readily available access to peer support; alcohol and drug counselling; and HCV transmission education programs. Education on the importance of adherence to treatment should be emphasised and should be done for every patient prior to treatment commencement.

Cure is defined as an undetectable HCV RNA in plasma or whole blood, tested at 12 (SVR12) or 24 weeks (SVR24) post completion of treatment course. Both endpoints are considered acceptable, however, there is emerging data that has shown an undetectable HCV RNA after only 4 weeks post completion of treatment (SVR4) can strongly predict the SVR12 result, thus providing an opportunity to test at any time point after 4 weeks.(25,26) SVR4 testing would be ideally suited and considered adequate in population groups considered high risk of being lost to follow up, such as those incarcerated but with release imminent.

HCV treatment should be considered for all people with current HCV.

Timing of therapy

Initiation of treatment should never be delayed, especially in people with HCV infection and those who have cirrhosis. Even if the remaining staging of liver disease workup has not yet been completed, this should not delay early initiation of treatment, and the rest of the workup may be scheduled concurrently or post-treatment completion. In patients with HIV-HCV, the general recommendation is that HIV should be fully suppressed and any HIV-related opportunistic infection treated, before initiating HCV treatment with DAA therapy.(15)

Prior to treatment initiation, a thorough review of the patient's medication list to identify any potential drug-drug interactions should be performed. This includes all prescribed medications, over-the-counter preparations, and recreational drugs. The possibility of drug-drug interactions should be assessed prior to treatment using the University of Liverpool's Hepatitis Drug Interactions website (www.hep-druginteractions.org). Identified interactions require clinical evaluation and decision regarding whether certain drugs are necessary and whether they can be temporarily stopped or switched to an alternative during the treatment period.(15,18)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Treatment selection

The current PBS-subsidised DAA treatment available in Australia includes: sofosbuvir plus velpatasvir (NS5B nucleotide inhibitor plus NS5A inhibitor), glecaprevir plus pibrentasvir (NS3 protease inhibitor plus NS5A inhibitor), and sofosbuvir plus velpatasvir plus voxilaprevir (NS5B nucleotide inhibitor plus NS5A inhibitor plus NS3 protease inhibitor). All three DAA combination regimens are pan-genotypic.

The Australian recommendations for the management of hepatitis C virus infection: a consensus statement (2022) provides a very comprehensive review of the recommended treatment regimens to which this chapter will base its summary of recommendations from (Table 1).⁽¹⁵⁾ First-line combination therapy for treatment-naïve people with compensated and decompensated liver disease living with HCV are sofosbuvir plus velpatasvir or glecaprevir plus pibrentasvir. For people who are non-responders to first-line combination treatment therapy of sofosbuvir plus velpatasvir or glecaprevir plus pibrentasvir, defined by a detectable HCV RNA despite treatment completion with first-line therapy, then a triple combination regimen of sofosbuvir plus velpatasvir plus voxilaprevir should be considered.

Recommended pan-genotypic treatment protocols for people with hepatitis C virus (HCV) infection and compensated liver disease, including people with HCV-HIV coinfection				
			Treatment duration	
Regimen	HCV genotype	Pill number	No cirrhosis	Cirrhosis
First-line regimens for people who are treatment-naïve				
Sofosbuvir 400 mg, orally, daily + Velpatasvir 100 mg, orally, daily	1–6	1 pill daily	12 weeks	12 weeks
Glecaprevir 300 mg, orally, daily + Pibrentasvir 120 mg, orally, daily	1–6	Once daily (3 pills)	8 weeks	8 weeks*
Regimen for people who do not respond to first-line therapy due to virological failure				
Sofosbuvir 400 mg, orally, daily + Velpatasvir 100 mg, orally, daily + Voxilaprevir 100 mg, orally, daily	1–6	1 pill daily	12 weeks	12 weeks

HIV = human immunodeficiency virus.

* A treatment duration of 12 weeks may be considered for patients with compensated cirrhosis, at the discretion of the prescriber.

Sofosbuvir (NS5B inhibitor) / velpatasvir (NS5A inhibitor)

Sofosbuvir (400 mg) plus velpatasvir (100 mg) is a fixed-dose combination formulated into a single tablet and administered once daily. It is considered safe in patients with cirrhosis. The recommended treatment duration is 12 weeks for all patients, irrespective of whether they have cirrhosis or not. Treatment with weight-based ribavirin, in addition to sofosbuvir plus velpatasvir, is recommended in patients with decompensated liver disease as it is shown to be associated with increased rates of SVR.⁽¹⁵⁾

Sofosbuvir plus velpatasvir is generally well tolerated with the most frequently reported adverse events including headache, fatigue, nausea, and nasopharyngitis.⁽²⁷⁾ It is also considered safe to be prescribed in patients with end-stage renal disease (ESRD) without need for any dose adjustments.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Glecaprevir (NS3 protease inhibitor) / pibrentasvir (NS5A inhibitor)

Glecaprevir (300 mg) plus pibrentasvir (120 mg) is a fixed-dose combination formulated into three tablets containing 100 mg of glecaprevir and 40 mg of pibrentasvir, administered as a once daily dose with food. Benefits to glecaprevir plus pibrentasvir is that treatment duration is shorter compared to sofosbuvir plus velpatasvir, at 8 compared to 12 weeks, for both patients who are treatment-naïve with or without compensated cirrhosis. A shorter treatment course is particularly beneficial in at-risk population groups considered high risk of being lost to follow-up and who would benefit with a shorter duration of treatment.

However, the use of glecaprevir plus pibrentasvir is contraindicated and should not be prescribed in patients with decompensated cirrhosis and in patients who are compensated but have had previous episodes of decompensation. This is because protease inhibitor-containing regimens are associated with higher protease inhibitor concentration and therefore, a higher risk of hepatic toxicity.(18)

Glecaprevir plus pibrentasvir is otherwise well tolerated in people with compensated cirrhosis and those without, with the most frequently reported adverse events being fatigue, headache, and nausea.(28)

Glecaprevir plus pibrentasvir is recommended first-line treatment for people with end-stage renal disease, including those on dialysis.(15)

Sofosbuvir (NS5B inhibitor) / velpatasvir (NS5A inhibitor) / voxilaprevir (NS3 protease inhibitor)

Sofosbuvir (400 mg) plus velpatasvir (100 mg) plus voxilaprevir (100 mg) is a fixed-dose triple-combination formulated into a single tablet and administered once daily with food. This regimen is reserved for people who fail to respond to first-line sofosbuvir plus velpatasvir or glecaprevir plus pibrentasvir as a salvage therapy and is not PBS-approved for treatment-naïve people. Recommended treatment duration is 12 weeks for all patients with or without cirrhosis.

Sofosbuvir plus velpatasvir plus voxilaprevir is also generally safe and well tolerated in people with compensated cirrhosis and in those without. The most frequently reported adverse events were headache, asthenia, nausea, fatigue, and diarrhoea. However, none of these adverse events reported frequency were >10%.(29)

Pregnancy and breastfeeding

There is a current paucity of published data on the safety and efficacy of HCV treatment in pregnant women and therefore treatment with DAA therapy is not recommended. All available PBS-listed DAA treatments are classed as Category B1. Ribavirin is a definite contraindication in pregnant women due to its teratogenicity risk and people on ribavirin should be counselled and put on contraceptive precautions during treatment and for 6 months post-treatment.

There is also limited published data on breastfeeding safety while on DAA treatment and is therefore also not recommended at this stage. However, there are no contraindications to breastfeeding in people with HCV with available data not showing any risk of mother-to-child transmissions.(30)

On-treatment monitoring

In treatment-naïve people with compensated cirrhosis or without cirrhosis on DAA therapy, extensive monitoring while on treatment is generally not required. Recommended follow-up requires a review at least 12 weeks after completion of therapy to test for SVR. However, more regular follow-up intervals can be tailored in certain populations who are considered at-risk, to optimise treatment adherence, monitor for any adverse events and potential drug-drug interactions.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

In people who are also receiving ribavirin, they do require regular monitoring of haemoglobin levels. In addition, these patients will generally have hepatic decompensation and so regular follow-up and serological liver function test monitoring is recommended.

HCC surveillance with 6-monthly liver ultrasound is recommended in all patients with cirrhosis. If HCV treatment was commenced on first diagnosis of cirrhosis, then a baseline liver ultrasound should be performed.

In the event of incomplete DAA adherence, this should be documented and its management algorithm will be addressed in the following section.

Management of incomplete DAA adherence

Poor adherence and an incomplete treatment course are relatively common, occurring in 11% to 40% who start treatment.⁽³¹⁻³³⁾ A risk assessment should always be an important consideration whenever someone is starting DAA therapy. In the event of treatment interruption, AASLD has developed a guidance statement on the management of DAA treatment interruptions in treatment-naïve patients, without cirrhosis or with compensated cirrhosis, receiving sofosbuvir plus velpatasvir or glecaprevir plus pibrentasvir (Figure 1),⁽¹⁹⁾ and the recommendations are in accordance to whether treatment interruption occurred before or after receiving 28 days of DAA treatment.

Interruptions before receiving 28 days of DAA therapy

If treatment has only been missed for ≤ 7 days, then treatment can be immediately restarted, and the patient should complete therapy for the originally planned duration.

If therapy is missed ≥ 8 days, then restart treatment immediately, but obtain an HCV RNA preferably on the same day of restarting. Restarting DAA should always take precedence over obtaining a repeat HCV RNA level. If the HCV RNA is undetectable, then the patient should complete the originally planned treatment duration. However, treatment extension for an additional 4 weeks (in addition to the originally planned duration) is recommended in patients with genotype 3 infection or compensated cirrhosis (regardless of HCV RNA status) and in all patients with a detectable HCV RNA.

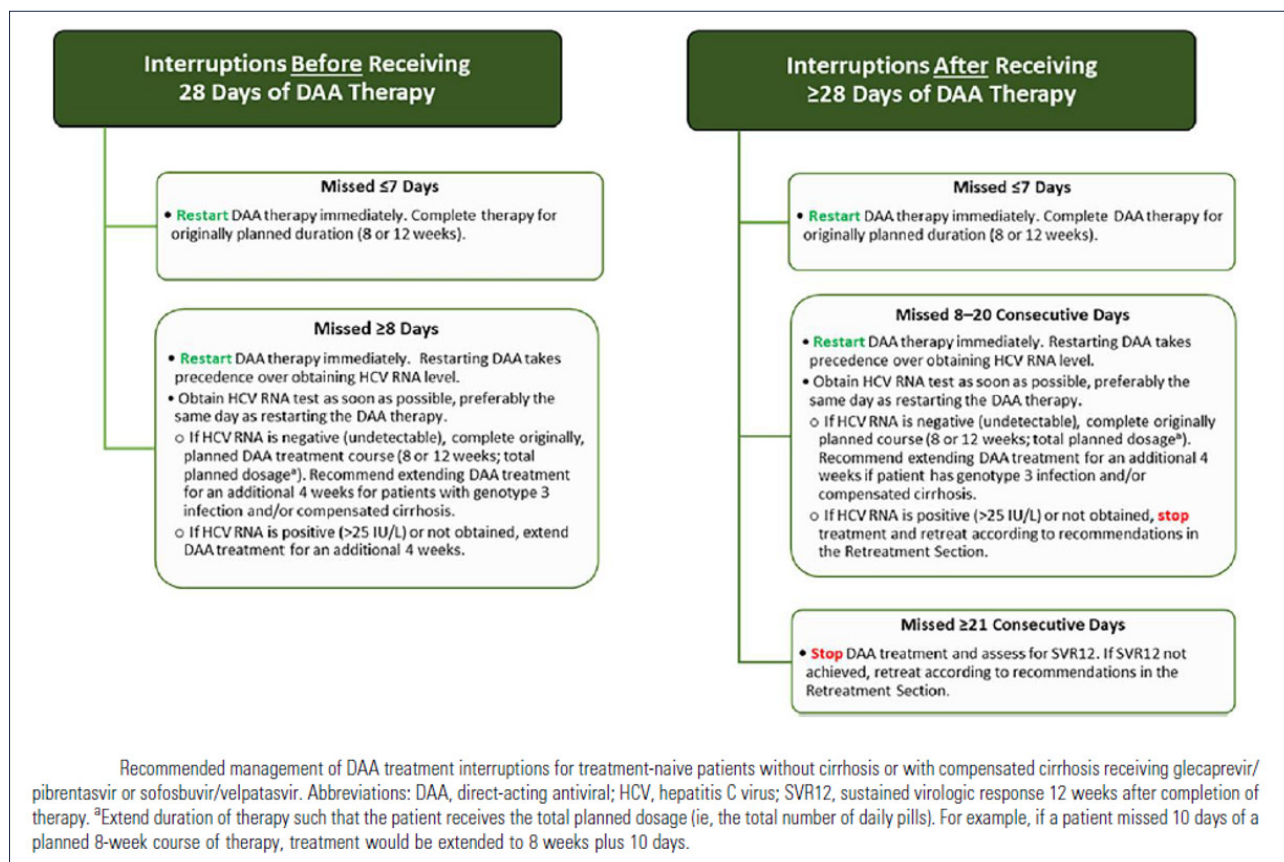
Interruptions after receiving ≥ 28 days of DAA therapy

If treatment has only been missed for ≤ 7 days, then treatment can be immediately restarted, and the patient should complete therapy for the originally planned duration.

If therapy is missed between 8-20 days, then restart treatment immediately, but obtain an HCV RNA preferably on the same day of restarting. Restarting DAA should always take precedence over obtaining a repeat HCV RNA level. If the HCV RNA is undetectable, then the patient should complete the originally planned treatment duration. Treatment extension for an additional 4 weeks (in addition to the originally planned duration) is recommended in patients with genotype 3 infection or compensated cirrhosis. However, if HCV RNA is detectable >25 IU/L or not obtained, then treatment should be stopped and retreatment needs to be prescribed.

When therapy is missed for ≥ 21 consecutive days, then treatment must also be stopped and SVR12 tested. If SVR12 is not achieved, then retreatment needs to be prescribed.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		



Post-treatment follow-up in population groups who achieve SVR

Patients without cirrhosis and who achieve SVR can be considered definitively cured from HCV. However, patients with advanced fibrosis (METAVIR score F3) or cirrhosis (METAVIR score F4) and who achieve SVR are recommended to continue indefinite HCC surveillance with liver ultrasound every 6 months.^(15,18)

In patients with pre-existing cofactors for liver disease, such as alcohol misuse disorder or metabolic risk factors for MASLD such as obesity, type 2 diabetes, hypertension, and dyslipidaemia, should be further evaluated +/- referral to a hepatology specialist.

People with a history of PWID, and recent or current PWID on opioid substitution therapy (OST), are recommended for at least annual HCV testing and also after any high-risk episode in PWIDs. The basis of this recommendation is due to the high prevalence of infection and reinfection in this population cohort.

People with HIV should have serological screening for HCV every 12 months. In people who are considered at high-risk of reacquisition of HCV, then they should have 3-6 monthly liver function test screening. A repeat HCV RNA should be performed whenever there is an unexplained transaminase level derangement.

Summary

Concurrent HCV-HIV is common and has historically contributed to the heavy burden of comorbidity and premature mortality for this population group. The currently available PBS-subsidised DAA treatment in Australia now offers a cure for the vast majority of those living with HCV, with added benefits in those also living with concurrent HIV in reducing the likelihood of liver disease progression.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Hepatitis B virus co-infection

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Last reviewed: November 2019

More recent Australian clinical guidance on Hepatitis B is available.

Read the guidance: <https://hepatitisb.org.au/>

Introduction

Hepatitis B virus (HBV) infection is an important infection in people with human immunodeficiency virus (HIV) infection because of the influence of HIV on the natural history of HBV infection. Antiviral therapies with activity against both viruses have enabled targeted therapy in people with co-infection without an increase in pill burden.

Epidemiology and pathogenesis

It is estimated that 257 million people worldwide, or approximately 5% of the global population, have chronic HBV infection. Areas of high endemicity for HBV infection, such as sub-Saharan Africa and Asia, are also most affected by the HIV pandemic.⁽¹⁾ HIV and HBV infections occur commonly together because of their shared routes of transmission. The prevalence of chronic HBV infection in people with HIV infection in Australia is approximately 5%.⁽²⁾

HBV is not directly cytopathic, and viral pathogenesis is largely immune mediated. Necroinflammatory changes in liver tissue that characterise chronic HBV infection are a result of cellular immune responses to viral antigens.⁽³⁾ Infection in endemic countries usually occurs very early in life, either through vertical or early horizontal transmission. The disease then passes through four different phases determined by the host immune response. These are the immune tolerant, immune clearance, immune control and immune escape phases and are characterised by varying levels of HBV viral load and necroinflammatory activity.⁽¹⁾ HIV infection significantly modifies this natural history as described below.

Diagnosis

Clinical decision-making in hepatitis B management resource:

<https://ashm.org.au/resources/decision-making-in-hepatitis-b/>

Serology

All people with HIV infection should be screened for HBV infection. Hepatitis B surface antigen (HBsAg) is the classic marker indicative of chronic infection. Although the detection of HBsAg is usually sufficiently sensitive to establish the presence of chronic HBV infection in the normal host, individuals may occasionally be negative for HBsAg, but still have active HBV replication, a phenomenon known as occult infection.⁽⁴⁾ It is recommended that all people with HIV infection should be tested with a panel of three serological tests to identify their serostatus: HBsAg, antibodies to HBV core antigen (anti-HBc) and antibodies to HBV surface antigen (anti-HBs). Patients found to be HBsAg positive should also have their e-antigen (HBeAg) status evaluated. People who are HBeAg positive usually have active replication, but some people who are negative

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

for HBeAg and positive for anti-HBe may also have active replication and active liver disease. The failure to synthesise HBeAg is due to the presence of mutations in the precore or core promoter regions. All people who are negative for all markers should be offered vaccination.

HBV DNA

If a person is HBsAg positive or has isolated anti-HBc (without HBsAg or anti-HBs) as their only marker of infection, he or she should be evaluated for active HBV replication using a sensitive assay for HBV DNA (also known as HBV viral load). The level of HBV DNA determines whether patients are at risk for transmission, progressive disease, liver cancer and immune reconstitution flares of hepatitis. HBV DNA should ideally be quantified by nucleic acid amplification assays, usually sensitive real time polymerase chain reaction (PCR).

In chronic HBV infection, robust evidence indicates that the HBV DNA level is strongly associated with the development of the two major clinical complications; cirrhosis and hepatocellular carcinoma.(5,6)

Disease progression

Effect of HIV on HBV disease progression

HIV co-infection results in considerable modification of the natural history of HBV infection.(7-9) Persistent HBV infection is more common in people with HIV infection, with the prevalence of chronic HBV infection estimated at 25%(10) compared with a prevalence of 3-5% in HIV-seronegative men who have sex with men. (11,12) Furthermore, during chronic co-infection, the HBV DNA levels are substantially higher than in HIV-seronegative people and rates of seroconversion from HBeAg to anti-HBe are lower.(7,13-15) Rarely, seroreversion of infection back to HBsAg positivity may occur despite prior seroconversion to anti-HBs, particularly with advanced immunodeficiency.(13)

Despite the high levels of HBV replication seen in people with HIV-HBV co-infection, these patients have significantly lower serum alanine aminotransferase (ALT) levels than people with chronic HBV infection alone,(13-15) and liver biopsies usually demonstrate milder necroinflammatory activity.(13) Despite this, progression to cirrhosis is more common, indicating accelerated fibrosis.(13) Indeed, HIV infection is associated with a 17-fold increase in liver-related mortality compared to HBV mono-infection with the risk being directly related to the degree of immunodeficiency.(16) Partly as a result of this, liver disease is now one of the most common causes of non-AIDS mortality in people with HIV infection.(17) This excess mortality is still present despite the use of HBV-active combined antiretroviral therapy (cART).(18) The reasons for progression are unclear but may relate to factors such as possible direct effects of HIV on liver fibrosis as well as immune activation due to microbial translocation.

Rarely, in severely immunocompromised patients, HBV may exert direct cytopathic effects that are not immune mediated and result in a unique condition called fibrosing cholestatic hepatitis. This condition is associated with very high levels of HBV DNA and has been described in people with HIV infection.(19) The condition has a high mortality rate, although recent treatment approaches have resulted in successful outcomes.

A case control study described a higher rate of hepatocellular carcinoma in patients with HIV-HBV co-infection who had a CD4+ T cell counts of < 500/uL, although this was not correlated with the presence of cirrhosis (Clifford et.al. AIDS 2008; 22:2135). Some authorities therefore recommend HCC screening in this setting in addition to other indications for HCC screening, such as cirrhosis.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Effect of HBV infection on HIV disease progression

In contrast to the effect of HIV on HBV infection, most studies have not detected a significant effect of HBV infection on the clinical course of HIV infection.(20,21)

Effect of cART on HBV disease

Antiretroviral hepatotoxicity

Severe hepatotoxicity occurs in up to 10% of all patients commenced on cART.(22,23) HIV-HBV co-infection is an independent risk factor for the development of cART-related hepatotoxicity.(22-24) Although all antiretroviral drugs have been associated with abnormal liver function tests, ritonavir, nevirapine and tipranavir(25,26) are especially implicated in severe hepatotoxicity(22,23) and thus should be used cautiously in the patient with HIV-HBV co-infection. Most modern ART regimens, however, use integrase inhibitors where this risk seems to be much lower. Patients who have co-infection with HBV or hepatitis C virus (HCV) should have their liver function initially checked every 2 weeks after commencing cART. Mild elevations (less than 5 X ULN (upper limit of normal)) can be observed if asymptomatic and usually resolve. More severe elevations or those associated with systemic symptoms should be managed by cART discontinuation.(27)

Immune restoration disease

In patients with HIV-HBV co-infection, immune restoration following cART has been associated with acute rises in levels of serum, known as hepatitis flares. They occur in approximately a quarter of patients starting cART and, although most cases are asymptomatic and resolve spontaneously, they occasionally result in hepatic decompensation and may even be fatal.(28-30) Risk factors include high pretreatment HBV viral loads and alanine aminotransferase (ALT) levels.(22,24,28,31) Hepatitis flares related to cART have also been reported in other circumstances, including re-activation of HBV infection,(28,32) development of lamivudine resistance(33) and following withdrawal of lamivudine.(34) This highlights the need to test all patients for chronic HBV infection before initiation of cART. Patients with cirrhosis are particularly at risk of hepatic decompensation and require careful observation after the initiation of cART. The role of corticosteroid therapy in this situation is unproven and cannot be recommended outside of a clinical trial.

Assessment of fibrosis

Fibrosis assessment is an important component of the evaluation of patients with chronic HBV infection. In particular, the detection of cirrhosis is an indication to institute regular HCC surveillance and to screen for oesophageal varices.

The traditional, and still the gold standard, method of assessment of fibrosis is liver biopsy. However, the role of liver biopsy is controversial and the technique is associated with significant rates of complications, as well as sampling and interobserver error. Current guidelines base treatment decisions on HBV DNA and ALT levels and do not recommend liver biopsy routinely.(35) More recently, a number of non-invasive methods for assessing liver fibrosis have been developed as alternatives to liver biopsy. These methods include serum biomarker algorithms such as aspartate aminotransferase (AST) to platelet ratio index (APRI), Fibrotest and Hepascore, as well as scanning techniques such as transient elastography (also known as FibroScan). FibroScan in particular has been validated in HIV-HBV populations and has largely replaced liver biopsy.(36)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Management

General principles

Sustained suppression of serum HBV DNA to below the level of detection by the most sensitive available assay method should be the goal of therapy and, at present, treatment of HBV in HIV- HBV co-infection is life-long. Current Australian and US guidelines recommend the consideration of cART in all people with HIV infection regardless of CD4+ T cell count in order to reduce the risk of disease progression. This recommendation is especially important in patients with HIV-HBV co-infection regardless of CD4+ T cell count where liver disease progression is faster and drugs with combined HIV and HBV activity are available. Because emtricitabine (FTC), lamivudine (3TC), tenofovir (TDF) and Tenofovir Alafenemide (TAF) have activity against both HIV and HBV, antiretroviral therapy should be initiated with a combination which includes TDF or TAF in the nucleoside reverse transcriptase inhibitor (NRTI) backbone of a fully suppressive antiretroviral regimen.(37)

If for any reason antiretroviral therapy is not used, and HBV therapy is indicated then the treatment chosen should have no anti-HIV activity. Current therapeutic options in this setting are pegylated interferon and adefovir. Of particular note, although entecavir had previously been thought to have no anti-HIV activity, more recent studies have shown that it does and can result in resistance of HIV to antiretroviral drugs.(38) It should therefore not be used without a concomitant fully suppressive cART regimen.

Anti-HBV therapy

There are six currently licensed treatments available for the management of HBV infection. These include interferons, nucleoside reverse transcriptase inhibitors (lamivudine, emtricitabine, entecavir and telbivudine) and nucleotide reverse transcriptase inhibitors (tenofovir, tenofovir alafenamide and adefovir).

Interferons

In immunocompetent people, interferon-alfa (alfa-IFN) therapy may result in HBeAg seroconversion and induce a clinical remission in 20-40% of patients with chronic HBV infection.(39) Treatment of people with HIV-HBV co-infection is significantly less effective.(40-42) In particular, patients with advanced immunodeficiency usually have poorer responses to therapy.(43) It may therefore be reasonable to occasionally consider interferon-based therapy in people with preserved CD4+ T cell counts (> 500/μL) who are not candidates for cART. There are currently no data on pegylated interferon in the setting of co-infection although it would be reasonable to use it given its proven track record in HBV monoinfection and improved pharmacokinetics with once weekly dosing.

Lamivudine / emtricitabine

Lamivudine and emtricitabine are both nucleoside analogue reverse transcriptase inhibitors that suppress both HIV and HBV replication by inhibition of viral RNA-dependent DNA polymerases.(44,45) In HIV-negative people, the reduction in plasma HBV DNA secondary to lamivudine therapy is associated with HBeAg seroconversion, normalisation of liver function and improved histological activity. Efficacy of lamivudine against HBV has also been demonstrated in people with HIV-HBV co-infection.(28,46,47,48) Unfortunately, the long-term effectiveness of lamivudine is diminished by the development of high rates of HBV resistance mutations.(49) Resistance to lamivudine develops because of mutations in the tyrosine-methionine- aspartate-aspartate (YMDD) motif of the catalytic domain of the HBV polymerase gene. Approximately 20% of patients with HIV-HBV co-infection develop HBV resistance to lamivudine annually, with projected rates of resistance after 4

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

years of lamivudine therapy of approximately 90%.^(50,51) This frequency of lamivudine resistance is higher than that seen in patients with HBV monoinfection.⁽⁵⁰⁾ Prolonged lamivudine therapy has been identified as the major risk factor for the development of drug-resistant HBV. Given that lamivudine, when used as a component of cART, is administered lifelong in patients with co-infection, it is inevitable that HBV monotherapy in this population will result in resistance.⁽⁵⁰⁾ Accordingly, lamivudine or emtricitabine should not be used without a concomitant drug with a high barrier to resistance, such as tenofovir or TAF.

Adefovir dipivoxil

Adefovir dipivoxil is a nucleotide analogue which, at a dose of 10 mg daily, has demonstrated efficacy against both wild-type and lamivudine-resistant HBV. Higher doses of 30 mg or greater have been associated with nephrotoxicity, which has been rarely observed with the 10-mg dose. Adefovir, like alfa-IFN, may also be an alternative option for patients with high CD4+ T cell counts who are not candidates for cART.⁽⁵²⁾ It may also be an option for lamivudine-resistant HBV, although better drugs such as tenofovir or TAF should be the drug of choice (see below). Studies to date have been performed on small numbers of patients and the structural similarity of adefovir to tenofovir may theoretically lead to the possibility of HIV cross resistance to tenofovir although this has not yet been reported.⁽⁹⁾

Tenofovir disoproxil

Tenofovir (TDF) is a nucleotide analogue with the ability to inhibit both HIV and HBV DNA polymerases. It has been demonstrated to exert a profound suppression of HBV DNA which is superior to adefovir.⁽⁵³⁾ It also demonstrates activity against viral strains that contain multiple polymerase gene mutations, including common lamivudine-resistant mutations⁽⁵⁴⁾ and has an extremely high barrier to resistance with no signature resistance mutations reported to date.⁽⁵⁾

One small randomised control study has demonstrated its efficacy in patients with HIV-HBV co-infection with superior virological suppression compared to lamivudine.^(51,55) Tenofovir is now commonly used as combination therapy in conjunction with lamivudine or emtricitabine for the treatment of HBV in patients with co-infection. In addition, the coformulation of tenofovir and emtricitabine allows convenient single-daily dosing and this combination should be the regimen of choice for the vast majority of people with HIV-HBV co-infection.

Tenofovir alafanemide

Tenofovir alafanemide or TAF is a novel prodrug of Tenofovir with a more targeted effect on lymphocytes and hepatocytes resulting in 91% less systemic exposure compared to TDF. As such, it has been shown to have excellent HIV activity with reduced renal and bone toxicity and has now become the nucleotide backbone of choice for HIV regimens. Like TDF, TAF also has excellent HBV activity which is comparable to TDF but at doses of 25 mg unboosted and 10 mg boosted compared to 300 mg for TDF. Large studies in HBV monoinfection have also demonstrated the comparable efficacy of TAF to TDF.⁽⁵⁶⁾ In addition, switch studies of TAF have shown its efficacy in HIV-HBV coinfection.⁽⁵⁷⁾ Like TDF, TAF has been incorporated into multiple single tablet regimens and is now regarded as the treatment of choice for HIV-HBV coinfection.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Entecavir

Entecavir is a guanosine analogue which has well documented, potent anti-HBV activity both in vitro and clinically and has a high barrier to HBV antiviral resistance.(58-60) Although entecavir was initially reported to have no anti-HIV activity, a recent report of three patients with HIV-HBV co-infection who were treated with entecavir monotherapy demonstrated significant reductions of HIV RNA despite no concomitant HIV therapy. Furthermore, one of these patients was shown to develop an M184V mutation, the signature HIV-resistance mutation for lamivudine.(61) In a larger cohort of 17 patients with HIV-HBV co-infection treated with entecavir monotherapy, a significant reduction in HIV RNA was observed in 13 of them (76%), including treatment-naïve patients. The M184V mutation was also identified in six people including three who were antiretroviral-naïve(62) Therefore, entecavir should no longer be used as monotherapy for the treatment of HBV in the setting of HIV co-infection.

Occasionally, entecavir needs to be used when issues of tenofovir toxicity (especially renal) arise. In this setting it should be used with fully suppressive cART. Although entecavir has a high barrier to resistance in wild type HBV infection, it has a very low barrier in the setting of pre-existing lamivudine or emtricitabine resistance.(63)

Telbivudine

There have been no studies to date of telbivudine in HIV-HBV co-infection, however like lamivudine, HBV resistance develops rapidly when telbivudine is used as monotherapy and should therefore not be used in the setting of HIV-HBV co-infection.(64)

Conclusions

HBV infection in people with HIV infection may result in significant morbidity and mortality. People with HIV-HBV co-infection have higher rates of chronic HBV infection and accelerated hepatic fibrosis and cirrhosis compared with those with HBV infection who do not have HIV infection. Management of each viral infection is complicated by the presence of the other virus. Sustained suppression of serum HBV DNA to below the level of detection by the most sensitive available assay should be the goal of therapy, and, at present, treatment of HBV in HIV-HBV co-infection is life-long, with tenofovir or TAF-based regimens preferred. Close monitoring is necessary to detect treatment failure or hepatitis flares, particularly following initiation of cART.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

References

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Hepatitis E virus infection

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Last reviewed: November 2019

Introduction

Hepatitis E virus (HEV) infection is an important cause of acute hepatitis, predominantly in residents of, and returned travellers from, countries where HEV infection is endemic. It has a high mortality rate in pregnant women. It is also rarely a cause of chronic infection in immunocompromised hosts.

Virology

HEV is a small non-enveloped, single-stranded RNA virus approximately 27-34 nm in diameter with a genome that is approximately 7.2 kb in length. It is the only member in the Hepeviridae family and is closely related to members of the Calicivirus family.(1) HEV was previously known as enterically-transmitted non-A, non-B hepatitis.(2) There are four recognised genotypes, which fall into two groups. Genotypes 1 and 2 are confined to humans and cause epidemic hepatitis associated with faecal-oral transmission while genotypes 3 and 4 are swine viruses which are common in domestic and wild pigs and infect humans as an accidental host and therefore are considered as zoonoses.(3)

Epidemiology and pathogenesis

HEV is the most common cause of acute hepatitis and jaundice in the world, although it is uncommon in the developed world. It has been estimated to cause at least 3.3 million cases of hepatitis per year and result in approximately 70,000 deaths.(4) In endemic areas, seroprevalence rates of HEV infection range between 30-80%, usually due to genotypes 1 and 2.(5) In these areas HEV infection occurs both sporadically and in epidemics and is predominantly spread by faecally-contaminated water while person-to-person spread is uncommon. HEV can also be transmitted by blood transfusion, particularly in endemic areas.(6)(7) The highest incidence of HEV infection occurs in Asia, Africa, the Middle East, and Central America. HEV is the second most common cause of sporadic hepatitis in North Africa and the Middle East.(8) High attack rates are found in adults between 15 and 40 years of age.(9) Secondary attack rates from person-to-person transmission in susceptible households are uncommon but have been documented.(10)

Seroprevalence rates of HEV infection in resource-rich areas of the world, such as Europe and the United States of America (USA), are lower than in countries where HEV infection is endemic, with the USA reporting rates of 21%.(11) However, this rate is surprisingly high and suggests a high rate of subclinical HEV infection. In these regions, cases are sporadic and have been predominantly described in people who have travelled to areas of the world where HEV infection is endemic.(12) However, sporadic cases that were not associated with travel have also been reported.(13) HEV can infect pigs, suggesting that some cases of human transmission may be due to transmission across species.(13)(14) This assumption is further supported by the identification of HEV RNA in a high percentage of pig liver and sausage in commercial settings.(15) Zoonotic transmission is also supported by the observation of high seroprevalence rate for HEV infection among people with occupational contact with animals.(16) There is also evidence that infection can be associated with exposure to other animals such as game(17) as well as shellfish.(18)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

There is also some limited information that vertical transmission of HEV from mothers with HEV infection to their infants can occur. In one report, eight babies were born to mothers with HEV in the third trimester of pregnancy. Six infants had clinical, serological, or virological evidence of HEV infection. Two infants died within 24 hours of birth, one of whom had massive hepatic necrosis at autopsy.⁽¹¹⁾ This finding suggests that HEV infection can be transmitted from mother to newborn with significant perinatal morbidity and mortality.

Diagnosis

The diagnosis of HEV infection is based upon the direct detection HEV RNA in serum or stool by polymerase chain reaction (PCR) or by the detection of antibodies to HEV. Serological and nucleic acid tests (qualitative and quantitative HEV RNA) currently form the basis of HEV testing and have been used for both epidemiological and diagnostic purposes. HEV can be detected in stool during the incubation period before symptomatic illness, during the illness, and persists for as long as 2 weeks thereafter. Because HEV is enterically transmitted, patients are infectious during faecal shedding. Both IgG and IgM antibodies appear at the time of clinical onset of hepatitis, just before symptoms and elevations of liver function tests (Figure 1). Following clinical recovery, serum levels of IgG antibodies to HEV increase and usually persist lifelong while IgM antibodies wane and disappear over 3-12 months.⁽¹⁹⁾ Real-time PCR is the assay of choice to detect HEV RNA and can detect all known genotypes, and is suitable for testing faecal as well as tissue samples.⁽²⁰⁾ PCR assays are still largely experimental and not widely available for routine diagnostic use.

Tests for anti-HEV antibody are commercially available but the sensitivity and specificity vary widely between assays, which probably explains the wide variation in the seroprevalence of HEV infection in different populations and the differing sensitivities between different assays in the diagnosis of PCR-proven acute HEV infection.⁽²¹⁾ This mandates that physicians know the performance characteristics of the local assays available to them.

Figure 1. The course of acute hepatitis E infection showing the timeframes for the detection of HEV RNA, the rise of transaminases and the evolution of IgM and IgG antibodies. Adapted from Hoofnagle et al. *N Engl J Med* 2012; 367:1237-44.⁽¹⁾

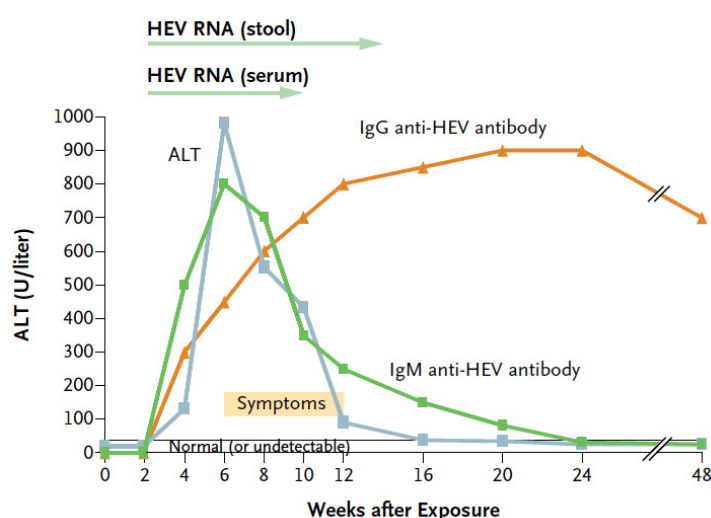


Figure 2. Course of Acute HEV Infection.

HEV RNA becomes detectable in stool and serum during the incubation period, with the subsequent appearance of the IgM and IgG anti-HEV antibodies. The level of IgM antibody peaks early and becomes undetectable during recovery, whereas the level of the IgG antibody continues to increase and persists in the long term. Clinical symptoms (fatigue, nausea, and jaundice) begin shortly after elevations in serum alanine aminotransferase (ALT) levels. HEV RNA disappears from serum with recovery, whereas detectable virus usually persists longer in stool (arrows).

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Clinical manifestations

The incubation period of HEV infection ranges from 3-8 weeks. It generally has a short prodromal phase and a symptomatic period, which is usually associated with jaundice, lasting several days to weeks. Acute HEV infection is usually self-limited, although fulminant hepatitis can develop. Case fatality averages 5% but ranges between 0-10%.⁽¹⁾ Chronic HEV infection does not usually develop after acute HEV infection, except rarely in immunosuppressed individuals (see below). The clinical signs and symptoms in patients with typical HEV infection are similar to those seen with other forms of acute viral hepatitis and jaundice is usually accompanied by malaise, anorexia, nausea, vomiting, abdominal pain, fever and hepatomegaly. Laboratory findings include elevated serum concentrations of bilirubin, as well as alanine aminotransferase (ALT), and aspartate aminotransferase (AST). Resolution of the abnormal biochemical tests generally occurs within 1 to 6 weeks after the onset of the illness.

HEV infection tends to be more severe than hepatitis A virus infection and prolonged cholestasis has been described in up to 60% of patients.⁽²²⁾ An association between HEV infection and Guillain-Barré syndrome has also been reported⁽²³⁾ as well as a number of other neurological manifestations including Bell's palsy, peripheral neuropathy, ataxia and confusion.⁽²⁴⁾

A striking feature of HEV infection is that, for reasons that are not fully understood, fulminant hepatic failure occurs more frequently during pregnancy, resulting in a mortality rate of 15-25%, primarily in women in the third trimester.⁽²⁵⁾ This high rate may be at least partly due to increased viral replication.⁽²⁶⁾ Pregnant women with jaundice and acute viral hepatitis caused by HEV infection also appear to have worse obstetric and foetal outcomes compared to pregnant women who have jaundice and acute viral hepatitis due to other causes.⁽²⁷⁾

Infection with HEV can also lead to hepatic decompensation in patients with pre-existing liver disease and those who are malnourished, a phenomenon called 'acute-on-chronic liver failure'.⁽²⁸⁾

The differential diagnosis of acute HEV infection mainly includes other forms of acute hepatitis including viral hepatitis due to other hepatitis viruses as well as herpesviruses such as herpes simplex virus, cytomegalovirus and Epstein-Barr virus; drug induced liver disease; ischaemic hepatitis; autoimmune hepatitis and other infectious diseases, such as leptospirosis, dengue, malaria and typhoid.

The basis of acute HEV infection management is supportive, as the disease appears to be self-limiting in non-immunocompromised patients. The exception is chronic HEV in immunocompromised individuals as detailed below.

Chronic HEV infection

A subset of patients who undergo solid organ transplantation develop chronic HEV infection as evidenced by the presence of persistently elevated transaminase levels, detectable serum HEV RNA, histologic findings compatible with chronic viral hepatitis and absence of other viral causes.⁽²⁹⁾ In one study of solid organ transplant recipients, 5% acquired HEV infection of whom half developed chronic infection.⁽³⁰⁾ Chronic infection has also been reported in patients undergoing cancer chemotherapy as well as HIV patients.⁽³¹⁾⁽³²⁾

The natural history of transplant recipients with chronic infection is incompletely understood but progressive disease with the development of cirrhosis has been reported.⁽³³⁾ Therapy consists of a reduction in immunosuppression which leads to spontaneous clearance in a third of individuals. In addition interferon-alpha and ribavirin or a combination of both have been reported to clear HEV infection in a majority of patients.⁽¹⁾

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Prevention of HEV infection

Basic sanitation is the cornerstone of HEV prevention in resource-poor countries; however standard interventions in recent outbreaks have not been successful, highlighting the need for more specific preventative measures such as vaccination.⁽³⁴⁾ Travellers to endemic areas should practise preventive measures, such as avoiding drinking water of unknown purity, eating uncooked shellfish and uncooked fruits or vegetables. In developed countries an approach to contain infection in animals, especially pigs, would seem logical but has not yet gained acceptance.

HEV vaccines

Two HEV vaccines are in development. A recombinant vaccine developed in China has proven to be 87% protective over 4.5 years of follow-up. It uses a 30 µg dose in a 3 dose schedule administered at 0, 1 and 6 months and was also found to be safe.⁽³⁵⁾ A second recombinant vaccine, evaluated in the Nepalese army and given at a dose of 20 µg at 0, 1 and 6 months, showed a vaccine efficacy of 96% over a shorter period of time.⁽³⁶⁾

Little information exists regarding the efficacy of pre- or post-exposure immune globulin prophylaxis for the prevention of HEV infection. There is at present no proof that immune globulin, including lots produced in countries where HEV infection is endemic, confers protection against HEV infection.⁽³⁷⁾

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

References

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

HTLV/HIV-1 Co-infection

Australian Clinical Guidelines on HTLV-1 Now Available

The Australian Clinical Guidelines on HTLV-1 for Aboriginal Primary Health Care Settings provide a comprehensive, culturally safe, and evidence-based approach to the prevention, testing, diagnosis, management, and care of Human T-lymphotropic virus subtype 1 (HTLV-1).

[Read the guidelines](#)

HTLV-1 and -2 infection have been described in people with HIV-1, Hepatitis B virus (HBV) and Hepatitis C virus (HCV) infection. (73) HTLV co-infections are more common than assumed, since HTLV infection is not routinely tested for in people who are diagnosed with other blood-borne/sexually transmissible infections. (74, 75) It is estimated that rates of HTLV-1 or HTLV-2 co-infection in HIV-1-infected individuals are significantly higher than in the general population, especially in people who inject drugs and/or have condom-less sex. (13, 76) In some geographic regions, 5–74% of people who inject drugs and are infected with HIV-1 may be coinfecting with HTLV-1 or HTLV-2; in a recent study about 27% of people with syphilis also tested positive for HTLV-1. (13, 18, 77-80)

While there are only a few studies of HTLV/HIV-1 co-infection, and no definitive studies, the general consensus is that the natural history of HIV-1 infection in people co-infected with HTLV-1 differs from that in patients with HTLV-2 co-infection. HTLV-2 co-infection seems to have no adverse, and a possibly beneficial, effects on immunological and survival outcomes in people with HIV-1 infection independently of the effects of antiretroviral therapy (ART). (81-83) However, this is disputed and other investigators have reported higher HIV viral loads and faster progression to AIDS with HTLV-2 co-infection. (84, 85)

HTLV-1 co-infection carries no benefit and may be detrimental to the health of people with HIV-1 infection, even if taking ART. Due to HTLV-1 driven cellular proliferation, CD4+ T cell counts may be misleadingly normal or higher than expected compared to the observed HIV-1 clinical stage of patients with only HIV-1 infection. This increase in CD4+ T cell count occurs without immunological benefit. Co-infected patients may experience a faster clinical progression and a shorter survival time, especially in the absence of ART. (86-88) Due to HIV-1-induced immunosuppression, patients with HIV-1/HTLV-1 co-infection may have an increased risk of developing HTLV-1 diseases, such as HAM/TSP and ATL. (89, 90)

Acknowledgements

I am indebted to Dr Graham Nielsen for commenting on and proof reading the manuscript.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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8. ARV Drugs & other Therapies

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Antiretroviral drugs

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Last reviewed: November 2019

More recent Australian clinical guidelines on ARV are available.

Read the Adult ARV guidelines: <https://hiv.guidelines.org.au/arv-adult/home/>

Read the Paediatric ARV guidelines: <https://hiv.guidelines.org.au/arv-pediatric/home/>

Antiretroviral drug classes

The six classes of antiretroviral drugs currently licensed for use in Australia are:

- Nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs);
- Non-nucleoside reverse transcriptase inhibitors (NNRTIs);
- Protease inhibitors (PIs);
- Integrase strand transfer inhibitors (INSTIs);
- Entry inhibitors: Fusion inhibitors;
- Attachment inhibitors: CCR5 inhibitors.

Since 2015, antiretroviral therapy (ART) in Australia has been recommended for all patients diagnosed with HIV infection irrespective of clinical stage, HIV viral load and CD4+ T cell count. (1, 2) This is based on large randomised controlled trials with clinical endpoints which demonstrated that all HIV-infected individuals benefit from ART. (3, 4) In addition to clinical benefit to the HIV-infected individual, ART also prevents HIV transmission. (5-7) Australia does not have antiretroviral guidelines but ASHM has maintained a commentary on the US DHHS Guidelines, on which this chapter is based, except where stated otherwise.

In ART-naïve patients initiating ART, several factors are relevant to achieving sustained virological suppression of HIV infection. These include maximising adherence to the antiretroviral drug regimen and the use of baseline drug resistance testing to detect transmitted HIV drug resistance, where appropriate. A patient's ability to adhere to a regimen is critical for successful treatment, as poor adherence can lead to virological failure, the development of HIV drug resistance mutations, and decreased patient survival.(8)(9)(10)(11) It is therefore important to consider factors such as toxicity, pill burden and dietary restrictions which may affect the ability of a patient to adhere to a given regimen. Other important factors include co-infection with hepatitis B virus (HBV) or hepatitis C virus (HCV) and use of illicit substances and alcohol.(12)(13) The former is included because the toxicity of some antiretroviral drugs is worse in the setting of hepatitis virus co-infection.(14) and the latter because of greater risk of non-adherence and the potential for drug-drug interactions.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Recommended regimens for treatment of HIV infection

The four regimens currently recommended for the initial treatment of most people with HIV infection combine a two-drug NRTI backbone with a third antiretroviral drug from the INSTI class, as follows:

Dolutegravir/abacavir/lamivudine (if HLA-B*5701 negative)

Dolutegravir + emtricitabine/tenofovir alafenamide (tenofovir AF) or tenofovir disoproxil fumarate (tenofovir DF)

Raltegravir + emtricitabine/tenofovir AF or tenofovir DF

Bictegravir/emtricitabine/tenofovir AF

Integrase inhibitor-based therapy has become the preferred option for ART based on the results of randomised clinical trials involving raltegravir or dolutegravir, which showed superiority over other third agents, such as efavirenz or darunavir. (15,16) Elvitegravir has been shown to be non-inferior to either efavirenz or atazanavir boosted with ritonavir in clinical trials. (17) Bictegravir has been shown to be non-inferior to dolutegravir-based ART. (18,19) Notably, there have been no reported cases of dolutegravir or bictegravir resistance recorded in virologically failing subjects in clinical trials involving ART-naïve individuals. In addition to the above three drug combinations, two drug combinations of dolutegravir and lamivudine and dolutegravir and rilpivirine are also approved for use.

Other antiretroviral drugs are largely reserved for the treatment of drug-resistant strains of HIV, including maraviroc, etravirine and enfuvirtide. New regimens that include these types of antiretroviral drugs in treatment-experienced patients with virological failure should include at least two, and preferably three, fully active drugs. In this context, the expected activity of an antiretroviral drug should be based on the patient's prior treatment history and drug-resistance testing results.

Nucleoside and nucleotide reverse transcriptase inhibitors

NRTIs inhibit HIV RNA-dependent DNA polymerase (reverse transcriptase) by acting as structural analogues for thymidine or adenosine when DNA is reverse transcribed inside cells leading to premature DNA chain termination and inhibition of viral replication. All NRTIs also have the potential to inhibit human intracellular DNA polymerases, including those necessary for mitochondria to replicate. Mitochondrial dysfunction is the source of many of the potential toxicities of this class of drug, particularly with older agents. Currently available nucleoside analogues are lamivudine (3TC), emtricitabine (FTC), abacavir (ABC) and zidovudine (AZT). Tenofovir is the only nucleotide analogue currently in use. Tenofovir DF and tenofovir TAF are orally bioavailable prodrugs of tenofovir, that are metabolised intracellularly into the active metabolite tenofovir diphosphate. Tenofovir DF is actively transported into proximal renal tubular cells, which is an important cause of its renal toxicity. Tenofovir AF is an alternative prodrug to tenofovir DF that is preferentially metabolised into the active metabolite in lymphocytes, allowing lower systemic doses to be administered that minimise renal toxicity without compromising virological efficacy. Both tenofovir AF and tenofovir DF achieve higher levels of drug absorption when co-administered with cobicistat or ritonavir. This results in the different recommended dosages for tenofovir AF. Emtricitabine, lamivudine, tenofovir DF and tenofovir AF also display activity against hepatitis B virus (HBV) and are recommended in HIV/HBV co-infected patients.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Importantly, many drugs in this class are available as fixed-dose combination (FDC) tablets. These tablets include earlier FDCs such as zidovudine/lamivudine (Combivir™) and zidovudine/lamivudine/abacavir (Trizivir™), and the currently recommended FDC tablets: tenofovir AF/emtricitabine (Descovy™), tenofovir DF/emtricitabine (Truvada™) and abacavir/lamivudine (Kivexa™). Moreover, tenofovir DF/emtricitabine has been coformulated with efavirenz (Atripla™), rilpivirine (Eviplexa™) and with elvitegravir/cobicistat (Stribild™). More recently, tenofovir AF based combinations have become available: bictegravir /tenofovir AF/emtricitabine (Biktarvy™), elvitegravir/cobicistat/tenofovir AF/emtricitabine (Genvoya™), and tenofovir AF/emtricitabine/rilpivirine (Odefsey™). Alternative FDC tablets to the tenofovir-based tablets are abacavir/lamivudine coformulated with dolutegravir (Triumeq™) or dolutegravir/rilpivirine (Juluca™).

Importantly, the only NRTIs currently recommended for initial therapy in the US and European guidelines are the combinations of abacavir plus lamivudine and tenofovir (tenofovir DF or tenofovir AF) plus emtricitabine, plus a third agent. Abacavir should only be prescribed to people who test negative for HLA-B*5701, which accurately predicts the development of abacavir hypersensitivity syndrome and is carried by 5-8% of the Australian population.⁽²¹⁾ Other NRTIs, including thymidine analogues, are no longer recommended, even as an alternative, largely because of unacceptable toxicity including, peripheral neuropathy, lipodystrophy, pancreatitis and lactic acidosis.

Guidelines for the dosing of NRTIs are shown in Table 1.

Table 1. Guidelines for NRTI dosing

Drug (dose per tablet)	Dosing	Food requirements	Dose adjustment for renal impairment	Dose adjustment for hepatic impairment
Abacavir (300 mg)	600 mg qd	No	No	Yes, for people with mild hepatic impairment (Child-Pugh Class A), the dose recommended is 200mg BD (use Ziagen™ solution). Contraindicated if Child-Pugh Class B or C.
Emtricitabine (200 mg)	200 mg qd	No	Yes*	No
Lamivudine (300 mg or 150 mg)	300 mg qd 150 mg bd	No	Yes*	No
Tenofovir (300 mg)	300 mg qd	No	Yes*	No
Zidovudine (250 mg)	250 mg bd	No	Yes, for very severe impairment *	No, but AZT may accumulate due to a reduction in glucuronidation. Precise dosage recommendations are available,
Co-formulated preparations				
Kivexa™ (ABC 600 mg/ 3TC 300 mg)	One tablet qd	No	Yes – do not use if CrCl < 50 mL/min	

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Truvada™ (TDF 300 mg/ FTC 200 mg)	One tablet qd	No	Yes. If CrCl is 30-49 L/ min use 1 tablet every 48h. Do not use if CrCl <30 mL/min	No
Descovy™ (TAF 10 mg/ FTC 200 mg) Descovy™ (TAF 25 mg/ FTC 200 mg)	One tablet qd If prescribed with ritonavir or cobicistat boosted PI, use 10mg formulation	No	Yes. Do not use if CrCl < 30 mL/min	No
Combivir™ (AZT 300 mg / 3TC150 mg)	One tablet bd	No	Yes. Do not use if CrCl < 50 mL/min	No, but AZT may accumulate due to a reduction in glucuronidation. Precise dosage recommendations are available.
Atripla™ (TDF 300 mg/ FTC 200 mg/ EFV 600 mg)	One tablet qd nocte	Take at night or before bedtime on an empty stomach to reduce side effects	Yes. Do not use if CrCl < 50 mL/min	Use with caution
Eviplera™ (TDF 300 mg/ FTC 200 mg/ RPV 25 mg)	One tablet qd	Take with a meal. Contraindicated with proton pump inhibitors. Caution with any antacid use.	Yes. Do not use if CrCl < 50 mL/min	No
Odefsey™ (TAF 25 mg/ FTC 200 mg/ RPV 25 mg)	One tablet qd	Take with a meal. Contraindicated with proton pump inhibitors. Caution with any antacid use.	Yes. Do not use if CrCl < 30 mL/min	No
Stribild™ (TDF 300 mg/ FTC 200 mg/ EVG 150 mg/ cobicistat 150 mg)	One tablet qd	Take with food	Yes. Do not use if CrCl < 70 mL/min. Discontinue if CrCl decreases below 50ml/min.	Do not use in severe impairment
Genvoya™ (TAF 10 mg/ FTC 200 mg/ EVG 150 mg/ cobicistat 150 mg)	One tablet qd	Take with food	Yes. Do not use if CrCl < 30 mL/min	Do not use in severe impairment

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Triumeq™ (Dolutegravir 50mg, ABC 600mg, lamivudine 300mg)	One tablet qd	No. Do not coadminister with calcium or magnesium supplements	Yes. Do not use if CrCl < 50 mL/min (use individual drugs)	Yes, may need to use individual drugs in mild hepatic impairment (Child-Pugh Class A). Not recommended for people with mod-severe hepatic impairment (Child-Pugh Class B-C)
Biktarvy™ (Bictegravir 50mg, TAF 25mg, FTC 200mg)	One tablet qd	No	Yes. Do not use if CrCl < 30 mL/min	<i>Child-Pugh Class A or B:</i> No dose adjustment <i>Child-Pugh Class C:</i> Not recommended
Juluca DTG 50mg, RPV 25mg	One tablet qd	Take with a meal Contraindicated with PPI therapy. Do not coadminister with calcium or magnesium supplements	No dose adjustment necessary. In patients with CrCl <30 mL/min, monitor closely for adverse effects.	<i>Child-Pugh Class A or B:</i> No dose adjustment <i>Child-Pugh Class C:</i> No dose recommendation

* check product information for change in dosing according to creatinine clearance

qd: once daily; bd: twice daily; nocte: at night; CrCl: creatinine clearance; EFV: efavirenz; RPV: rilpivirine; EVG: elvitegravir; TAF: tenofovir alafenamide fumarate

Non-nucleoside reverse transcriptase inhibitors

The NNRTI class includes nevirapine (NVP), efavirenz (EFV), rilpivirine (RPV), etravirine (ETR) and doravirine (DOR). NNRTIs bind directly to the reverse transcriptase enzyme and block the RNA-dependent and DNA-dependent polymerase activities by causing a disruption of the enzyme's catalytic site. This reduces enzyme activity and diminishes viral replication. Importantly NNRTIs are not active against HIV-2 as the reverse transcriptase binding site has a different structure. Also, NNRTIs do not inhibit human DNA polymerases. Furthermore, as a class, NNRTIs are considered to have a low genetic barrier to the development of antiretroviral drug resistance with suboptimal adherence and treatment interruptions of as little as 48 hours leading to selection of single mutations that confer high-level resistance to these agents.⁽²²⁾

Nevirapine was the first NNRTI developed for use in people with HIV infection and while it remains an effective antiretroviral drug, it is currently not recommended for initial therapy due to the risk of hepatotoxicity, especially in women with a CD4+ T cell count >250/μL and men with a CD4+ T cell count >400/μL. Efavirenz was the next NNRTI available and from the late 1990s until 2015 was a recommended third agent to add to an NRTI backbone in all major guidelines and was the recommended third agent in the World Health Organization (WHO) guidelines targeted for use in low-middle income countries.⁽²³⁾ It was removed from the recommended category of the 2015 DHHS guidelines as a result of the availability of equipotent and better tolerated agents available as single dose FDC tablets. The main reason for the removal of efavirenz was an association with neuropsychiatric adverse effects, including depression and suicidality.

Etravirine and rilpivirine are second-generation NNRTIs that have efficacy in the presence of the classic NNRTI resistance mutation K103N. The virological impact of these drugs diminishes in the presence of other NNRTI

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

mutations (of which 15 have been identified) that each confer variable impact on virological efficacy.⁽²⁴⁾ Rilpivirine is also available in a once-daily coformulated tablet. Despite a lower side effect profile than efavirenz, US and European guideline panels recommend initiation of rilpivirine only if baseline HIV viral load is < 100,000 copies/mL because increased numbers of virological failures have been observed in subjects with high HIV viral loads.⁽²⁵⁾ Because etravirine has been principally studied in people with previous virological failure and HIV drug resistance, it is not recommended for ART-naïve people but rather be used in conjunction with a boosted protease inhibitor for treatment of ART-experienced people infected with HIV exhibiting resistance to multiple classes of antiretroviral drugs.⁽²⁶⁾⁽²⁷⁾

Doravirine is a newer NNRTI, which has been shown to be virologically non-inferior to efavirenz or darunavir for treatment ART-naïve patients. It retains activity against the commonest efavirenz resistance mutation (K103N) and does not have the neuropsychiatric toxicities associated with efavirenz. There are also no food requirements with doravirine. The drug is metabolised through CYP3A4 but is not an inducer or inhibitor of this system. It is a substrate for P-GP and as such will be affected by ritonavir or cobisistat co-administration. It has not yet been compared with integrase inhibitor-based therapy and as such its role as initial therapy remains unclear.

Guidelines for NNRTI dosing are presented in Table 2 and adverse effects listed in Table 3.

Table 2. Guidelines for NNRTI dosing

Drug (dose per tablet)	Dosing	Food requirements	Dose adjustment for renal impairment	Dose adjustment for hepatic impairment
Efavirenz (600 mg or 200mg) Also available in a FDC tablet	600 mg qd nocte	Take at night or before bedtime on an empty stomach to reduce side-effects.	No	Use with caution
Etravirine (100 mg)	200 mg bd	Yes	No	No
Rilpivirine (25 mg) Also available in a FDC tablet	25 mg qd	Take with a meal Contraindicated with PPI therapy	No	No
Nevirapine (200 mg) or Nevirapine XR (400 mg)	200 mg bd or 400 mg qd (XR) after initiation with 200 mg qd for 14 days	No	No	Contraindicated in Child-Pugh class B or C
Doravirine (DOR)	100mg qd	No	No	No

qd: once daily; bd: twice daily; nocte: at night; tds: three times daily; XR: extended release;

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Table 3. Adverse effects of NNRTIs

Drug	Adverse effects	Potentially life-threatening adverse effect
Efavirenz Also available as part of a FDC tablet	Skin rash Neuropsychiatric symptoms (dizziness, somnolence, insomnia, abnormal dreams, suicidality, confusion, abnormal thinking, impaired concentration) Increased transaminase levels Hyperlipidaemia	2% of subjects report severe depression Potentially teratogenic in humans
Etravirine	Rash (SJS very rare) Nausea	HSR: skin rash, constitutional symptoms and sometimes organ dysfunction, including hepatic failure, are reported
Rilpivirine Also available as part of a FDC tablet	Rash (SJS very rare) Depression, insomnia, headache Hepatotoxicity	None
Nevirapine	Rash Fever Nausea Headache Hepatotoxicity (esp. higher CD4+ T cell counts)	SJS (rare) Hepatitis, including fatal hepatic necrosis
Doravirine (DOR)	Nausea, dizziness, insomnia	None

FDC: fixed dose combination; SJS: Stevens-Johnson syndrome; HSR: hypersensitivity reaction

HIV protease inhibitors

HIV protease inhibitors (PIs) inhibit HIV-1 and HIV-2 proteases and prevent cleavage of the gag-pol polyprotein during maturation of the newly formed viral particle. This results in the production of immature, non-infectious virus. There are currently seven licensed PIs: atazanavir (ATV), darunavir (DRV), fosamprenavir (FOS), lopinavir (coformulated with ritonavir [LPV/r]), ritonavir (RTV), saquinavir (SQV) and tipranavir (TPV). Whilst ritonavir is a protease inhibitor, it is not used for its antiretroviral activity; rather, it is used as a pharmaco-enhancer by exploiting its activity as an inhibitor of the cytochrome p-450 (3A4) enzyme to boost levels of concomitantly administered PIs. Similarly, cobicistat, a newer non-PI pharmaco-enhancer, is used to boost INSTIs and PIs. These actions of ritonavir and cobicistat may also lead to interactions with other medications that are metabolised by the cytochrome p-450 (3A4) system.

Guidelines on the dosing of PIs can be found in Table 4 and adverse effects are presented in Table 5. The usual dose of ritonavir for boosting protease inhibitors is 100 mg once daily or 100-200 mg twice daily, depending on the PI being boosted (referred to as PI/r). Furthermore, ritonavir boosting increases plasma levels of PIs to levels greatly above those required to inhibit viral replication, even in the setting of one or two PI mutations. This means that the development of PI resistance is much less likely to occur for a given level of adherence.⁽²⁹⁾ Third generation PIs include ritonavir-boosted darunavir and tipranavir, which are licensed for use in patients with multidrug resistant HIV.⁽³⁰⁾⁽³¹⁾ Boosted darunavir is also licensed for use as once daily

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

dosing in ART-naïve patients and treatment-experienced patients infected with a HIV that has no darunavir resistance mutations. (32) Of this antiretroviral class, only darunavir is recommended for treatment initiation, largely because of different adverse effects seen with other agents in this class, including: hyperlipidaemia, hyperglycaemia, fat maldistribution, diarrhoea and hepatotoxicity.

Table 4. Guidelines on PI dosing

Drug	Dosing	Food requirement	Dose adjustment for renal impairment	Dose adjustment for hepatic impairment
Atazanavir (300 mg or 400 mg)	<u>ARV-naïve people:</u> • ATV 300 mg + RTV 100 mg once daily; or • ATV 400 mg once daily <u>With TDF or in ARV-experienced people:</u> • ATV 300 mg + RTV 100 mg once daily Co-formulated with cobicistat (ATV/c): • (ATV 300 mg + COBI 150mg) once daily	Take with food; avoid antacids, H2 antagonists and proton pump inhibitors. Seek expert advice if unsure	No, ATV/c not recommended for use with TDF if baseline CrCl < 70 mL/min.	Not recommended if Child-Pugh class C. If Child-Pugh class B use ATV 300 mg qd (without ritonavir)
Darunavir (600 mg or 800 mg)	800 mg qd with RTV 100 mg qd or 600 mg bd with RTV 100 mg bd if DRV-associated mutations Co-formulated with cobicistat (DRV/c): DRV 800 mg + COBI 150 mg once daily. DRV/c is not recommended for patients with DRV-associated mutations.	Take with food	No. DRV/c not recommended for use with TDF if baseline CrCl < 70 mL/min.	Not recommended if severe hepatic impairment
Fosamprenavir (700 mg)	1400 mg qd with RTV 100 mg qd for ART-naïve people 700 mg bd with RTV 100 mg bd for treatment experienced people	Without RTV, take without regard to meals. With RTV, take with meals.	No	Complex. Seek expert advice. Dose reduction as Child-Pugh score increases
Lopinavir/ ritonavir (200 mg/50 mg)	400 mg/100 mg bd or 800 mg/ 200 mg qd (if < 3 lopinavir-associated drug resistance mutations)	No	No	Use with caution

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

saquinavir (500 mg)	1g bd with RTV 100 mg bd	Take within 2 hours of food	No	Use with caution: mild-mod impairment. Contraindicated in severe impairment
Tipranavir (TPV) (250 mg)	500 mg bd with RTV 200 mg bd	Take with meals	No	Use with caution Contraindicated with Child-Pugh class B and C
qd: once daily; bd: twice daily; ART: antiretroviral treatment; RTV: ritonavir; tenofovir DF: tenofovir disoproxil fumarate				

Table 5. Adverse effects of PIs

Drug	Adverse effect	Potentially life-threatening adverse effect
All PIs	• Hyperglycaemia • Hyperlipidaemia • Fat maldistribution • Transaminase elevations / hepatotoxicity	
Atazanavir	• Indirect hyperbilirubinaemia • Cholelithiasis • Nephrolithiasis • Renal insufficiency • Skin rash • Increase in serum creatinine (with COBI)	Prolonged PR interval -1st degree symptomatic AV block in some patients; use with caution in patients with conduction defects or on medications that cause PR prolongation
Darunavir *	• Skin rash (10%) – due to sulfonamide moiety • Diarrhoea, • Nausea • Headache • Increase in serum creatinine (with COBI)	SJS, toxic epidermal necrolysis, acute generalised exanthematous pustulosis and erythema multiforme have been reported (rare)
Fosamprenavir *	• Skin rash (12-19%) – due to sulfonamide moiety • Diarrhoea • Nausea • Vomiting • Headache • Nephrolithiasis	Possible increased bleeding episodes in patients with haemophilia

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Lopinavir/ritonavir	- GI intolerance: nausea, vomiting, diarrhoea - Asthenia	PR interval prolongation QT interval prolongation and torsades de pointes reported Pancreatitis Possible increased bleeding episodes in patients with haemophilia
Ritonavir (boosting)	- GI intolerance – nausea, vomiting, diarrhoea - Paresthesias -circumoral and extremities - Asthenia - Taste perversion	Caution with drug-drug interactions for drugs with a narrow therapeutic index Possible increased bleeding episodes in patients with haemophilia
Saquinavir *	- GI intolerance – nausea, diarrhoea - Headache	PR interval prolongation QT interval prolongation and torsades de pointes reported Pancreatitis Possible increased bleeding episodes in patients with haemophilia
Tipranavir *	Skin rash (2–21%) – due to sulfonamide moiety	Clinical hepatitis including hepatic decompensation has been reported, especially in patients with underlying liver disease Rare cases of fatal and non-fatal intracranial haemorrhages have been reported but most patients had underlying comorbidity including brain lesions, head trauma, recent neurosurgery, coagulopathy, hypertension, alcoholism or medication with risk for bleeding Possible increased bleeding episodes in patients with haemophilia

*can only be administered with boosting doses of ritonavir; SJS=Stevens-Johnson syndrome; AV: atrioventricular

HIV integrase inhibitors

Integrase strand transfer inhibitors (INSTIs) prevent the integration of HIV DNA into the nucleus of the host cell. Elvitegravir is only available as part of an FDC tablet with tenofovir or emtricitabine and cobicistat, unlike raltegravir and dolutegravir which are available as individual medications. Dolutegravir is also available co-formulated with abacavir and lamivudine or rilpivirine in a FDC tablet. Bictegravir is only available coformulated with tenofovir AF and emtricitabine. All four INSTIs are metabolised by glucuronidation via the enzyme UDP-glucuronosyltransferases (UGT1A1) to varying degrees, influencing their potential for drug-drug interactions with medications metabolised by cytochrome p450 enzymes. Raltegravir is exclusively metabolised by UGT1A1 whereas dolutegravir also has some elimination by CYP3A4 and elvitegravir is primarily metabolised by cytochrome p450 with a minor contribution from UGT1A1. Bictegravir is metabolised by both UGT1A1 and CYP3A. Dolutegravir inhibits OCT-2 in renal tubule cells, which is important for the excretion of creatinine and

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

metformin. This inhibition results in an increase of the serum creatinine level by about 10 $\mu\text{mol/L}$ that does not indicate a true renal impairment. Bictegravir also does this to a lesser degree. No dose adjustment is needed for metformin when co-administrated. The potential for drug-drug interactions is greater when metabolised by cytochrome p450 enzymes, except for some circumstances when coadministered with potent UGT1A1 inducers, such as rifampicin. A long acting injectable version of a dolutegravir analogue (cabotegravir) is currently in development as a 2 monthly injectable therapy (Phase III).

Guidelines for INSTI dosing can be found in Table 6 and adverse effects are listed in Table 7.

Table 6. Guidelines on INSTI dosing

Drug (dose per tablet)	Dosing	Food requirement	Dose adjustment for renal impairment	Dose adjustment for hepatic impairment
Dolutegravir (50 mg)	50 mg qd or 50 mg bd if proven/suspected INSTI resistance	No	No	No dose adjustment if Child-Pugh class A-B. Not recommended if Child-Pugh class C
Elvitegravir (only available in a FDC tablet)	150mg qd	No	Yes. Do not use if CrCl < 30 mL/min due to coformulated agents. See Table 2.	Do not use in severe impairment
Raltegravir (400mg)	400mg bd	No	No	No
Raltegravir HD (600mg)	2x600mg qd for ART-naïve people and for patients with suppressed HIV replication on 400 mg BD.	No	No	No
Bictegravir (Only available in a FDC tablet)	50mg od	No	Yes. Do not use if CrCl < 30 mL/min due to coformulated agents. See Table 2.	<i>Child-Pugh Class A or B:</i> No dose adjustment <i>Child-Pugh Class C:</i> Not recommended

Qd: once daily; bd: twice daily; FDC: fixed dose combination

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Table 7. Adverse effects of INSTIs

Drug	Adverse effect	Potentially life-threatening adverse effect
Dolutegravir	Insomnia Headache	HSRs including rash, constitutional symptoms and organ dysfunction (including liver injury) reported. Possible increased risk of congenital neural tube defects when taken at time of conception.
Elvitegravir * Only available in a FDC tablet	Nausea Diarrhoea	
Raltegravir	• Nausea • Headache • Diarrhoea • Pyrexia • Creatine phosphokinase elevation • Myalgia	• Rash, including SJS, HSR and toxic epidermal necrolysis reported • Rhabdomyolysis
Bictegravir Only available in a FDC tablet	• Headache	

SJS: Stevens-Johnson syndrome; HSR: hypersensitivity reaction; FDC: fixed dose combination

*These adverse effects are not specific to elvitegravir but a consequence of other agents in the fixed dose combination

HIV entry inhibitors

Two antiretroviral drugs have been developed that act as entry inhibitors, forming two separate classes; the fusion inhibitor enfuvirtide and the CCR5-receptor antagonist maraviroc.

Fusion inhibitors

Enfuvirtide (also known as T-20) is a synthetic 36-amino acid peptide analogue. It binds to HIV-1 gp41, interrupting the fusion reaction and preventing the virus from infecting the host cell. Enfuvirtide, is an injectable agent licensed for use in patients with multidrug resistant HIV based on two key trials. (33)(34) The main disadvantage of enfuvirtide is the universal development of injection site reactions, which are unpleasant for the patient, and appear to be associated with skin sclerosis with long-term use. Enfuvirtide is administered at a dose of 90mg bd by subcutaneous injection. Dose adjustments are not required for food or renal or hepatic impairment. Reported adverse effects include injection site reactions (pain, erythema, induration, nodules and cysts, pruritus, ecchymosis) in almost 100% of patients and an increased rate of bacterial pneumonia. A potentially life-threatening hypersensitivity reaction occurs uncommonly (< 1% of patients) and may include rash, fever, nausea, vomiting, chills, rigors, hypotension, or elevated serum transaminases. Rechallenge is not recommended.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

CCR5 inhibitors

The development of CCR5 inhibitors arose from the recognition that CCR5 is a key cell-surface receptor for HIV.(35) at least early in the disease, and that absence of CCR5 expression resulting from a homozygous 32 base pair deletion in the CCR5 gene (delta 32 homozygosity) was associated with protection against HIV infection.(36) Moreover, people with reduced levels of CCR5 expression (delta 32 heterozygotes) have an attenuated disease course with lower HIV viral loads.(36)

CCR5 inhibitors lock CCR5 into a conformation that render it incapable of binding HIV envelope proteins. Maraviroc is the only CCR5 inhibitor available in Australia. It is effective in patients whose virus utilises CCR5 for cell entry (R5 tropic) and testing of the patient's HIV for tropism for CCR5 is essential before the use of this drug.(37)(38) There is no virological efficacy in patients with CXCR4 (X4) or dual tropic HIV. A guide to dosing of maraviroc can be found in Table 7. Reported adverse effects of maraviroc are abdominal pain, cough, dizziness, musculoskeletal symptoms, pyrexia, skin rash, upper respiratory tract infections, hepatotoxicity and orthostatic hypotension, especially in patients with severe renal insufficiency.

Table 7. Guidelines on dosing of CCR5 inhibitors

Drug (dose per tablet)	Dosing	Food requirement	Dose adjustment for renal impairment	Dose adjustment for hepatic impairment
Maraviroc (150mg and 300mg)	150 mg bd when given with all PI/r except tipranavir/r 300 mg bd when given with NRTIs, enfuvirtide, NVP, tipranavir/r, raltegravir and other non-potent CYP3A inhibitors or inducers 600 mg bd when given with CYP3A inducers including efavirenz and etravirine	No	Complex. If CrCL < 30mL/min: - Without potent CYP3A inhibitors or inducers, > 300 mg bd; reduce to 150 mg bd if postural hypotension occurs - With potent CYP3A inducers or inhibitors – not recommended	Concentration likely to be increased in hepatic impairment

bd: twice daily; CrCL: creatinine clearance; CYP3A: hepatic cytochrome p450 enzyme 3A; PI/r: protease inhibitor boosted with ritonavir; NRTI: nucleoside reverse transcriptase inhibitor

New antiretroviral agents

New antiretroviral agents in the existing classes are being developed with the aim of producing drugs with more favourable toxicity profiles and activity against drug-resistant HIV. These include a new CCR5 inhibitor cenicriviroc (Phase III) that also has activity blocking CCR2, thereby dampening inflammation. There is also a monoclonal antibody directed against CCR5 (PRO 140) currently under development in Phase II trials that is administered subcutaneously. New classes of antiretroviral agents currently in phase II stage of development are the attachment inhibitor fostemsavir that binds to the gp120 protein on HIV-1, interfering with its ability to bind to the CD4 cell receptor, and the maturation inhibitor BMS-9551. Maturation inhibitors block a step in the processing of the group-specific antigen (Gag) polyprotein, necessary for virion maturation, leading to the

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

release of immature non-infectious virions. In addition to new antiretroviral agents in current classes, or in new classes, there are multiple compounds based on currently available antiretroviral drugs. These include long acting injectable versions of rilpivirine (Phase I) and a dolutegravir analogue (cabotegravir) that is being developed in long-acting injectable and oral forms (Phase II).

Contraindicated antiretroviral drug regimens

Antiretroviral drug regimens that should not be offered at any time are shown in Table 8.

Table 8. Antiretroviral drug regimens that should not be offered at any time
(See [ASHM HIV Guidelines Adult Antiretroviral Guidelines](#))

Antiretroviral drug regimen	Rationale
Monotherapy with NRTIs	Inferior virological activity plus rapid development of resistance
Dual-NRTI regimens	Inferior virological activity plus rapid development of resistance.
Triple-NRTI regimens	High rate of early virological nonresponse. The only exceptions are abacavir/zidovudine/lamivudine and possibly tenofovir DF + zidovudine/lamivudine (Evidence: BII) in patients in whom other combinations are not desirable
Nevirapine in ART-naïve women and men with CD4+ T cell counts $\geq$ 250 cells/μL and 400 cells/μL, respectively	Greater risk of severe, life-threatening hepatotoxicity
Unboosted saquinavir, darunavir or tipranavir	Inadequate bioavailability
Nevirapine + efavirenz, or nevirapine/ efavirenz/ etravirine	Higher incidence of toxicity and similar resistance profiles
Emtricitabine + lamivudine	Similar resistance profiles, no potential benefit
Etravirine + unboosted PI	ETR may induce metabolism of PIs; appropriate doses not yet established
Etravirine + ritonavir-boosted atazanavir or fosamprenavir	ETR may alter the concentrations of these PIs; appropriate doses not yet established
Etravirine + ritonavir-boosted tipranavir	ETR concentration may be significantly reduced by ritonavir -boosted TPV

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Initiation of antiretroviral therapy in the treatment-naïve patient

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Last reviewed: March 2016

Next review due: December 2019

More recent Australian clinical guidelines on ARV are available.

Read the Adult ARV guidelines: <https://hiv.guidelines.org.au/arv-adult/home/>

Read the Paediatric ARV guidelines: <https://hiv.guidelines.org.au/arv-pediatric/home/>

Initiation of antiretroviral therapy (ART) for human immunodeficiency virus (HIV) in the naïve patient centres around two main questions: When to start therapy and what to therapy to start. Data from recently published studies have provided evidence supporting starting therapy as soon after diagnosis as possible.⁽¹⁾⁽²⁾ The standard use of a three-drug regimen consisting of an anchor drug with a backbone of two nucleoside analogue drugs remains the recommendation for therapy. The addition of newer drugs, particularly from the integrase strand transfer inhibitor (INSTI) class, with beneficial efficacy and tolerability, has changed the choice of the anchor drug used to commence therapy.⁽³⁾⁽⁴⁾⁽⁵⁾ Because the key determinant of treatment success involves a commitment by the patient to ongoing treatment adherence, the critical decision to initiate ART is the patient's readiness and willingness to commence treatment.⁽⁶⁾

The current gold standard of triple combination antiretroviral therapy (cART, previously referred to as highly active antiretroviral therapy or HAART) has evolved in the context of significant advances in the understanding of viral dynamics⁽⁷⁾ and HIV drug resistance. Early trials of monotherapy with zidovudine demonstrated limited clinical benefit and virological and immunological failure, now known to be due in part to the development of drug resistance. Studies of dual nucleoside reverse transcriptase inhibitors or nucleoside analogues (NRTIs) published in 1996-1997 showed improved survival in asymptomatic individuals.⁽⁸⁾⁽⁹⁾ Shortly after, the early studies of triple therapy with two NRTIs and a protease inhibitor (PI) demonstrated a reduction in morbidity and mortality in individuals with advanced HIV.⁽¹⁰⁾

Due to the existence of a latently infected pool of long-living CD4 cells (established early in HIV infection),⁽¹¹⁾ currently available ART is unable to achieve eradication of HIV infection. The current goals of therapy are:

- attaining maximal and durable suppression of HIV replication (as measured by a viral load below the limit of detection) with a well tolerated and simplified cART regimen
- restoring and preserving immune function
- reducing HIV-related morbidity
- reducing non-acquired immune deficiency syndrome (AIDS) comorbidities
- improving both quality of life and survival
- preventing HIV transmission.

As newer agents with simpler dosing schedules (including fixed-dose combinations) and more favourable toxicity profiles have become available, there has been a shift in emphasis towards early recognition and minimisation of treatment-related toxicities and early intervention with strategies to improve adherence, in order to achieve a durable treatment response.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

In addressing the questions faced by individuals living with HIV and their clinicians – when to start therapy and which regimen to choose – the discussion below outlines the current consensus approach in Australia which is based on a mix of available clinical trial data and expert opinion.⁽¹²⁾ The Australian commentary⁽¹³⁾ on the US Department of Health and Human Services (DHHS) antiretroviral guidelines⁽¹⁴⁾ are reviewed regularly in parallel with the review of the DHHS guidelines, and the most recent iteration may be found on the Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine (ASHM) website.

When to start therapy in the individual with HIV

In the Australian context, ASHM Sub-Committee for Guidance on HIV Management recommends that antiretroviral therapy should be initiated in all people with HIV, irrespective of CD4 count, taking into account the following principles:⁽¹⁵⁾

1. ART is recommended for all individuals with HIV infection, irrespective of CD4 count, to reduce the risk of disease progression.
2. The decision to start ART should take into account both personal health benefits and risks, and reduction in transmission risk.
3. Clinicians should regularly discuss the current state of knowledge regarding when to start ART with all individuals with HIV who are not yet on treatment.
4. All decisions to start ART should be made by the individual with HIV, in consultation with their health-care providers and on the basis that they are fully informed and supported in their decision making.

This recommendation is consistent with guidance from the US DHHS Panel, which has recently been upgraded to an A1 Recommendation (strong recommendation based on data from randomised controlled trials) following the publication of the results of the START⁽¹⁶⁾ and TEMPRANO⁽¹⁷⁾ trials, which showed benefit in initiating therapy in patients with normal immunity.

Treatment as prevention

Apart from the personal benefit in initiating ART to the individual, there is a benefit in prevention of transmission of HIV to partners without the infection where the person initiating ART achieves and maintains virological suppression on therapy.

Recent data from interim analyses of two cohort studies presented at Conference on Retroviruses and Opportunistic Infections (CROI) in 2014 and 2015 reported no transmissions in serodiscordant homosexual male couples with undetectable viral load. This result included data from the European PARTNER study⁽¹⁸⁾ which reported no HIV transmissions in 308 couple-years of follow-up when condomless anal intercourse was reported, and the HIV-positive partner had undetectable viral load⁽¹⁹⁾ and data from the Australian-Thai-Brazilian Opposites Attract study, which reported no transmissions when condomless anal intercourse was reported in 89 person-years of follow-up in couples with viral load less than 200 copies/mL.⁽²⁰⁾ Data from these two studies strongly suggest that ART greatly reduces HIV transmission in serodiscordant homosexual couples. A very low rate of transmission cannot be ruled out. Follow-up continues in both studies and final study results are expected in 2016-17.

Cohort and randomised clinical studies in the pre-cART era⁽²¹⁾ and cART era⁽²²⁾ suggested an enormous benefit in terms of reduction in both mortality and progression to AIDS as a result of cART. These studies have been pivotal in the development of the HIV treatment guidelines.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

The clear benefit to the individual of commencing cART irrespective of CD4 count has been demonstrated through the results of two major randomised studies, START and TEMPRANO. The benefit of early cART initiation in reducing HIV transmission has been demonstrated in the randomised HPTN 052 study.(23)

Patients with CD4 counts > 500 cells/μL

Results for two pivotal randomised controlled trials (START(24) and TEMPRANO(25)) were recently published, both demonstrating that the clinical benefits of ART are greater when ART is started early, with pre-treatment CD4 T-lymphocyte (CD4) counts > 500 cells/μL, than when initiated at a lower CD4 cell count threshold.

With the availability of the START and TEMPRANO trial results, the DHHS Panel's overall recommendation remains the same: ART is recommended for all patients with HIV infection regardless of pre-treatment CD4 count. However, the strength of the recommendation will be changed to *Ala* (strong recommendation based on data from randomised controlled trials) for all patients.

The additional benefit of ART in reducing the risk of HIV transmission further underscores the potential public health value of this recommendation. The Panel continues to emphasise that patients starting ART should be willing and able to commit to treatment and to understand the benefits and risks of therapy and the importance of adherence. On a case-by-case basis, ART may be deferred because of clinical and psychosocial factors, but therapy should be initiated as soon as is feasible.

It should be noted that neither of these trials included adolescents. However, our recommendations have been extrapolated to adolescents based on the expectation that they will derive benefits from early ART similar to those observed in adults.

Below are summaries of the results from these two randomised controlled trials:

START (Strategic Timing of AntiRetroviral Treatment) trial (26)

The START trial is a large, multinational, randomised controlled clinical trial designed to evaluate the role of early ART in asymptomatic patients with HIV infection in reducing a composite clinical endpoint of AIDS-defining illnesses, serious non-AIDS events or death. In this study, ART-naïve adults (aged >18 years) with HIV infection with CD4 counts > 500 cells/μL were randomised to either initiate ART immediately (early arm) or wait until CD4 counts declined to < 350 cells/μL or until the development of a clinical indication for therapy (deferred arm).

A total of 4,685 participants were enrolled in this study, with a mean follow-up of 3 years. In May 2015, interim study data reviewed by the study's independent Data and Safety Monitoring Board (DSMB) showed a significantly greater number of clinical events in the deferred therapy arm than in the early therapy arm. On the basis of these interim results, the DSMB concluded that the data provided significant evidence of the benefit of early ART and recommended that the study sponsor make the results available to the public and offer treatment to any study participants in the deferred therapy arm not yet on ART. The study participants will continue to be followed in this study until the end of 2016.

When the randomised arms of the study were closed, the primary endpoint of serious AIDS or non-AIDS events was reported in 42 participants (1.8%, or 0.60 events/100 person-years) in the early ART arm and 96 participants (4.1%, or 1.38 events/100 person-years) in the deferred ART arm (hazard ratio, 0.43, favouring early ART [95% confidence interval (CI), 0.30–0.62, $p < 0.001$]). The most common clinical events reported were tuberculosis and AIDS and non-AIDS malignancies.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

TEMPRANO ANRS 12136 study (27)

The TEMPRANO study is a randomised controlled trial conducted in Cote d'Ivoire. Using a two-by-two (2 X 2) factorial design, participants with HIV infection with CD4 counts < 800 cells/μL were randomised to either immediate ART or deferred ART (based on the national guidelines criteria for starting treatment) and with or without isoniazid for prevention of tuberculosis for 6 months. The primary study endpoint was a combination of all-cause deaths, AIDS diseases, non-AIDS malignancies, and non-AIDS invasive bacterial diseases. More than 2,000 participants enrolled in the trial, with a median follow-up of 30 months. Among the participants, 849 had baseline CD4 counts > 500 cells/μL. In the analysis of this high CD4 count subgroup, 68 primary outcome events were reported in 61 patients. The risk of primary events was lower with immediate ART than with deferred ART, with a hazard ratio of 0.56 in favour of early ART (CI, 0.33–0.94). On the basis of these results, the study team concluded that early ART is beneficial in reducing the number of these clinical events.

Prevention of sexual transmission

A number of investigations, including biological, ecological and epidemiological studies and one randomised clinical trial, provides strong support for the premise that treatment of the individual with HIV can significantly reduce sexual transmission of HIV. Lower plasma HIV RNA levels are associated with decreases in the concentration of the virus in genital secretions.(28)(29) Studies of HIV-serodiscordant heterosexual couples have demonstrated a relationship between level of plasma viraemia and risk of transmission of HIV—when plasma HIV RNA levels are lower, transmission events are less common.(30)(31)(32) A study conducted in KwaZulu-Natal, South Africa, used geospatial techniques to assess the relationship between ART use and HIV incidence in an observational cohort of more than 16,000 study participants living in many different communities.(33) After adjustment for sexual behaviour and prevalent HIV cases, each percentage point increase in ART coverage of people with HIV infection lowered the HIV infection risk in a community by 1.7%.

Most significantly, the multi-continental HPTN 052 trial enrolled 1,763 HIV-serodiscordant couples in which the partner with HIV was ART naïve with a CD4 count of 350 to 550 cells/μL at enrolment to compare the effect of immediate ART versus delayed therapy (not started until CD4 count < 250 cells/μL) on HIV transmission to the partner with HIV infection.(34) At study entry, 97% of the participants were in heterosexual monogamous relationships. All study participants were counselled on behavioural modification and condom use. Twenty-eight linked HIV transmission events were identified during the study period, but only one event occurred in the early therapy arm. This 96% reduction in transmission associated with early ART was statistically significant (HR 0.04; 95% CI, 0.01–0.27; $p < 0.001$). These results show that early ART is more effective at preventing transmission of HIV than all other behavioural and biomedical prevention interventions studied. This study, as well as other observational studies and modelling analyses showing a decreased rate of HIV transmission among serodiscordant heterosexual couples following the introduction of ART, demonstrate that suppression of viraemia in ART-adherent patients with no concomitant sexually transmitted infections (STIs) substantially reduces the risk of transmission of HIV. HPTN 052 was conducted in heterosexual couples and not in populations at risk of transmission via homosexual exposure or needle sharing. In addition, in this clinical trial, adherence to ART was well supported and near complete. However, the prevention benefits of effective ART observed in HPTN 052 can reasonably be presumed to apply broadly. Therefore, the Panel recommends that ART be offered to patients who are at risk of transmitting HIV to sexual partners (the strength of this recommendation varies according to mode of sexual transmission: AI for heterosexual transmission and AIII for male-to-male transmission and other modes of sexual transmission). Clinicians should discuss with patients the potential individual and public health benefits of therapy and the need for adherence to the prescribed regimen and counsel patients that ART is not a substitute for condom use and behavioural modification and that ART does not protect against other STIs (see Preventing Secondary Transmission of HIV).

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Which regimen to use in the individual with HIV infection

When selecting a regimen for an individual patient, a number of patient- and regimen-specific characteristics should be considered, with the goal of providing a potent, safe, tolerable and easy to adhere to regimen for the patient in order to achieve sustained virological control. Some of the factors can be grouped into the following categories:

Initial characteristics of the patient

- Pre-treatment HIV RNA level (viral load) – there are some regimens which are not recommended if RNA is > 100,000 copies/mL
- Pre-treatment CD4 cell count
- HIV genotypic drug resistance testing results will determine if any specific drugs should be avoided in the regimen
- HLA-B*5701 status – HLA B*5701 positive patients should not receive abacavir-containing regimens
- Patient preferences
- Patient's anticipated adherence – patients with potential adherence difficulties should be commenced on a ritonavir-boosted protease inhibitor (PI/r)-based regimen.

Specific comorbidities or other conditions

- Cardiovascular disease, hyperlipidaemia, renal disease, osteoporosis, psychiatric illness, neurological disease, drug abuse or dependency requiring narcotic replacement therapy
- Pregnancy or pregnancy potential
- Co-infections: hepatitis C virus (HCV), hepatitis B virus (HBV), tuberculosis (TB).

Regimen-specific considerations

- Regimen's genetic barrier to resistance
- Potential adverse drug effects
- Known or potential drug interactions with other medications
- Convenience (e.g., pill burden, dosing frequency, availability of fixed-dose combination products, food requirements)
- Choice of a regimen that is known to be potent i.e. one which includes at least three drugs from at least two classes, generally two drugs (backbone drugs) from the nucleoside/nucleotide reverse transcriptase inhibitors (NRTI/NtRTI) class (backbone) and a third (anchor drug) from either the integrase strand transfer inhibitor (INSTI), non-nucleoside reverse transcriptase inhibitor (NNRTI) or PI/r class
- Choice of a regimen that is currently recommended by the Australian Antiretroviral Guidelines Panel: alternatives to currently recommended therapy should generally only be used in the context of a specific clinical indication.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Panel's recommendations

An antiretroviral regimen for a treatment-naïve patient generally consists of two nucleoside reverse transcriptase inhibitors in combination with a third active antiretroviral drug from one of three drug classes: an integrase strand transfer inhibitor, a non-nucleoside reverse transcriptase inhibitor, or a protease inhibitor with a pharmacokinetic enhancer (cobicistat or ritonavir).

The Panel classifies the following regimens as recommended regimens for antiretroviral-naïve patients: Integrase strand transfer inhibitor-based regimens

- Dolutegravir/abacavir/lamivudine—only for patients who are HLA-B*5701 negative (AI)
- Dolutegravir plus tenofovir disoproxil fumarate (tenofovir)/emtricitabine (AI)
- Elvitegravir/cobicistat/tenofovir/emtricitabine—only for patients with pre-antiretroviral therapy creatinine clearance > 70 mL/min (AI)
- Raltegravir plus tenofovir/emtricitabine (AI)

Protease inhibitor-based regimen

- Darunavir/ritonavir plus tenofovir/emtricitabine (AI)

On the basis of individual patient characteristics and needs, an Alternative regimen or, less frequently, an other regimen; may in some instances be the optimal regimen for a patient.(35)

Given the large number of excellent options for initial therapy, selection of a regimen for a particular patient should be guided by factors such as virologic efficacy, toxicity, pill burden, dosing frequency, drug-drug interaction potential, resistance testing results, comorbid conditions, and cost. Table 1 provides guidance on choosing an antiretroviral regimen based on selected clinical case scenarios.(36)

Rating of Recommendations: A: Strong; B: Moderate; C: Optional

Rating of Evidence: I: Data from randomised controlled trials; II: Data from well-designed nonrandomised trials or observational cohort studies with long-term clinical outcomes; III: Expert opinion

Note: Lamivudine may substitute for emtricitabine or vice versa in above regimens

The INSTI-based regimens were selected because of their high virologic efficacy, excellent safety and tolerability profiles, and (with RAL and dolutegravir [DTG]) low number of drug-drug interactions (see the INSTI section of the guidelines for discussion regarding the special characteristics and clinical trial results for each of the three recommended INSTIs). For patients who are at high risk for intermittent therapy because of poor adherence or have transmitted NRTI drug resistance, a PI/r-based treatment is preferred given the PIs high genetic barrier to resistance. In some situations, an NNRTI-based regimen may be a better choice for a particular patient.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Table 1 provides guidance on regimen selection based on various patient- and regimen-specific characteristics.

Table 1. Antiretroviral regimen considerations as initial therapy based on specific clinical scenarios(37):

Patient or regimen characteristics	Clinical scenario	Consideration(s)	Rationale/comments
Pre-ART characteristics	CD4 count < 200 cells/ μ L	Do not use the following regimens: • RPV-based regimens • DRV/r plus RAL	Higher rate of virological failure observed in those with low pre-treatment CD4 cell count
	HIV RNA >100,000 copies/mL	Do not use the following regimens: • RPV-based regimens • ABC/3TC with EFV or ATV/r • DRV/r plus RAL	Higher rates of virological failure observed in those with high pre-treatment HIV RNA
	HLA-B*5701 positive Do not use ABC-containing regimen.	Do not use ABC-containing regimen	ABC hypersensitivity, a potentially fatal reaction, is highly associated with positivity for the HLA-B*5701 allele
	Must treat before HIV drug resistance results available	Avoid NNRTI-based regimen	Transmitted mutations conferring NNRTI resistance are more likely than mutations associated with PI or INSTI resistance Some experts avoid using INSTI-containing regimens in this setting because of concern regarding their ability to fully suppress viral replication if transmitted NRTI mutations are present
ART-specific characteristics	One pill once daily regimen desired	ART options include: • DTG/ABC/3TC • EFV/TDF/FTC • EVG/c/TDF/FTC • RPV/TDF/FTC (if HIV RNA <100,000 copies/mL and CD4 count >200/μL)	Available as fixed-dose combination tablets
	Food effects	Regimens that should be taken with food: • ATV/r or ATV/c-based regimens • DRV/r or DRV/c-based regimens • EVG/c/TDF/FTC • RPV/TDF/FTC Regimens that should be taken on an empty stomach: • EFV-based regimens	Food improves absorption of the listed regimens Taking EFV-based regimens with food increases EFV absorption and may increase CNS side effect

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Presence of other conditions	Chronic kidney disease (defined as eGFR < 60 mL/min)	Consider avoiding TDF If eGFR is < 70 mL/min, do not use: • EVG/c/TDF/FTC, or • ATV/c with TDF, or • DRV/c with TDF Options for CKD patients Use ABC/3TC if HLA-B*5701 Negative: • If HIV RNA > 100,000 copies/mL, do not use ABC/3TC with EFV or ATV/r. • If CrCl < 50 mL/min, do not use coformulated ABC/3TC because 3TC requires dose adjustment Other options (See text for discussion): • DRV/r plus RAL (if HIV < 100,000/mL and CD4 count > 200/μL), or • LPV/r plus 3TC, or • Modify TDF dose	TDF has been associated with renal tubulopathy See Appendix B, Table 7 (in Guidelines) (38) for recommendations on ARV dose modification
	Osteoporosis	Consider avoiding TDF. ABC/3TC if HLA-B*5701 negative If HIV RNA > 100,000 copies/mL, do not use ABC/3TC plus (EFV or ATV/r)	TDF is associated with greater decrease in bone mineral density along with renal tubulopathy, urine phosphate wasting, and osteomalacia
	Psychiatric illness	Consider avoiding EFV-based regimens	EFV can exacerbate psychiatric symptoms and may be associated with suicidality
	HIV-associated dementia (HAD)	Avoid EFV-based regimens if possible Favour DRV-based or DTG-based regimen	EFV neuropsychiatric effects may confound assessment of the effect of ART on improvement of symptoms associated with HAD Theoretical CNS penetration advantage
	Narcotic replacement therapy required	If patient receiving methadone, consider avoiding EFV-based regimen. If EFV is used, an increase in methadone dose may be necessary	EFV reduces methadone concentrations and may lead to withdrawal symptoms
	High cardiac risk	Consider avoiding ABC- and LPV/r – based regimens	Increased cardiovascular risk in some studies (see ABC discussion in the guidelines)
	Hyperlipidaemia	The following ARV drug classes or drugs have been associated with deleterious effects on lipids: • PI/r • ABC • EFV • EVG/c	TDF has been associated with beneficial lipid effects, thus it may be preferable to ABC
	Pregnancy	Refer to the <u>Perinatal Antiretroviral Treatment Guidelines</u> .	

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Presence of co- Infections	HBV infection	Use TDF/FTC (or TDF plus 3TC) whenever possible If TDF is contraindicated: • For treatment of HBV, use FTC or 3TC with entecavir or another drug active against HBV	TDF, FTC, and 3TC are active against both HIV and HBV. 3TC- or FTC-associated HBV mutations can emerge rapidly when these drugs are used without another HBV-active agent
	HCV treatment required	Refer to recommendations in the HIV/HCV co-infection section of the guidelines	
	Tuberculosis infection	If rifampin is used: • EFV-based regimens have the least drug- drug interactions • If RAL is used, increase RAL dose to 800 mg twice daily • Use DTG at 50 mg twice daily dose only in patients without selected INSTI mutations (refer to product label) If using a PI-based regimen, rifabutin should be used in place of rifampin in the tuberculosis regimen	• Rifampin is a strong inducer of CYP3A4 and UGT1A1 enzymes, causing significant decrease in concentrations of PI, INSTI, and RPV • Rifampin has a less significant effect on EFV concentration than on other NNRTIs, PIs, and INSTIs • Rifabutin is a less potent inducer and is a good option for patients receiving non- EFV-based regimens Refer to Tables 19a, b, d and e for dosing recommendations for rifamycins used with different ARV agents in the guidelines

3TC: lamivudine; ABC: abacavir; ATV/r: ritonavir-boosted atazanavir; ART: antiretroviral therapy; ARV: antiretroviral; c: cobicistat; CKD: chronic kidney disease; CrCl: creatinine clearance; DRV/r: ritonavir- boosted darunavir; DTG: dolutegravir; eGFR: estimated glomerular filtration rate; EFV: efavirenz; EVG/c/TDF/FTC: elvitegravir/cobicistat/tenofovir/emtricitabine; FDA: Food and Drug Administration; FTC: emtricitabine; HBV: hepatitis B virus; HCV: hepatitis C virus; INSTI: integrase strand transfer inhibitor; LPV/r: ritonavir-boosted lopinavir; NNRTI: non-nucleoside reverse transcriptase inhibitor; NRTI: nucleoside reverse transcriptase inhibitor; PI: protease inhibitor; r/PI: ritonavir-boosted protease inhibitor; RAL: raltegravir; RPV: rilpivirine; RTV: ritonavir; TDF: tenofovir disoproxil fumarate

Antiretroviral treatment strategies

Acute or primary HIV infection

Improved recognition of the clinical syndrome suggestive of acute HIV or primary HIV infection combined with use of newer diagnostic tests enables early identification of this group of individuals and thus consideration of antiretroviral therapy.

The SPARTAC study randomised patients with primary HIV infection to 48 weeks vs 12 weeks vs standard of care (no treatment) with follow-up to measure end point of CD4 count < 350 cells/μL. The 48-week treatment arm had significantly fewer patients reaching CD4 < 350 cells/μL average follow up 42 months.(39) There are potential benefits from treating patients with primary HIV infection including clinically reducing the flu-like symptoms characteristic of primary infection which can be severe, reduced seeding of the viral reservoirs, alteration of virological set point, reduced immunological damage and rapid immunological recovery, and finally, less opportunity for the development of viral resistance mutations.(40)(41) The potential disadvantages

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

of initiating cART in primary infection include patient readiness to commence ART at the time of managing the psychological and physical effects of a new HIV diagnosis, particularly since cART requires ongoing life-long adherence. There can be a delay in obtaining a baseline resistance result before commencement of cART.

ART is recommended for all people with HIV infection and should be offered to those with acute HIV infection (BII), although definitive data are lacking as to whether this approach will result in long-term virologic, immunologic, or clinical benefits.(42) For patients with early HIV infection in whom therapy is initiated, testing for plasma HIV RNA levels, CD4 count, and toxicity monitoring should be performed as described for patients with chronic HIV infection.

Genotypic drug resistance testing should be performed before initiation of ART to guide the selection of the regimen (AII). If therapy is deferred, genotypic resistance testing should still be performed because the results will be useful in selecting a regimen with the greatest potential for achieving optimal virological response when therapy is ultimately initiated. ART can be initiated before drug resistance test results are available. Since resistance to ritonavir (RTV)-boosted PIs emerges slowly and since clinically significant transmitted resistance to PIs is uncommon, these drugs combined with NRTIs should be used in this setting (AIII).

Patients starting ART should be willing and able to commit to treatment and should understand the possible benefits and risks of therapy and the importance of adherence (AIII). Patients may choose to postpone therapy, and providers, on a case-by-case basis, may elect to defer therapy because of clinical or psychosocial factors.

Treatment interruption

Treatment interruption following initiation of ART is not recommended apart from specific short-time situations. The SMART study, which examined ART interruption as a potential method of reducing ART exposure and thus ART toxicity, resulted in significantly higher rates of AIDS, severe non-AIDS events and death in the treatment interruption arm.(43)(44)

Antiretroviral treatment in specific clinical scenarios

HIV and hepatitis C co-infection

HIV-hepatitis C virus (HCV) co-infection is increasingly prevalent in Australia, affecting approximately 10% of those with HIV, and with clinical consequences for both diseases. The rate of progression of liver disease from hepatitis C has long been known to be accelerated in the setting of co-infection and a recent meta-analysis demonstrated the risk of cirrhosis to be three-fold higher when compared with an HIV-negative control population.(45)(46) Standard-of-care therapy for individuals with HCV mono-infection up to recently consisted of pegylated interferon plus ribavirin (IFN/RBV). In patients with HIV-HCV co-infection, sustained virological response rates of approximately 60-70% for genotype 2/3 and 25% for genotype 133,(47) (the most common genotype in Australia) have been shown. Response rates in genotype 1 have been increased with the addition of an NS3A inhibitor to IFN/RBV, (previously bocepravir or telapravir were used,(48)(49) although at the cost of greater toxicities), and more recently simepravir has provided beneficial responses with lower toxicity and lower pill load.(50)

There has been a revolutionary advance in treatment of HCV infection with the advent of direct-acting antiviral (DAA) agents which in some cases can be coformulated, but can provide oral-only therapy, (depending on HCV genotype, stage of liver disease and prior treatment, DAA therapy is given with or without ribavirin, for 12-24 weeks) with sustained virological response 12 weeks after cessation of therapy (SVR12) which is cure, in over 90-95% of patients treated. Not only do DAAs provide excellent efficacy and tolerability, the results seen in patients with HIV co-infection are the same as those seen in patients with mono HCV infection.(51)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

A number of DAAs such as sofosbuvir-ledipasvir and daclatasvir, have been approved by the Therapeutic Goods Administration (TGA) in Australia, while the Pharmaceutical Benefits Scheme (PBS) reimbursement is pending and expected in the near future. It is expected that the prescribing of DAAs will be broadly permitted for all patients with chronic HCV, regardless of stage of disease.

Low-grade abnormalities of liver function tests are common in HCV and HIV infection, regardless of treatment status. A common practical problem facing the clinician following the initiation of ART in the person with HIV-HCV co-infection is worsening liver function tests. All classes of antiretroviral drugs have been associated with hepatotoxicity.(52)(53) The NNRTI, nevirapine, is associated with the greatest estimated hepatotoxicity, with two-thirds of the episodes of clinical hepatitis occurring within 3 months of starting nevirapine.(54) This risk however can be significantly reduced by following the guidelines regarding CD4 cell criteria discussed above. As a general rule nevirapine should be used with caution in individuals with co-infection with cirrhosis. In some instances following commencement of ART, elevation of liver enzymes has been associated with a transient rise in HCV RNA,(55) attributed by some to immune restoration disease (IRIS). IRIS is particularly a risk where patients initiate cART at low CD4 cell levels. At present the relative contributions of hepatitis C and antiretrovirals to hepatic toxicity remain uncertain. A practical approach to this problem includes avoidance of antiretroviral agents with a known association with significant hepatotoxicity and further evaluation of hepatitis C disease (see Hepatitis C co-infection section). Mild abnormalities in liver function in the setting of HIV infection can be observed, but in cases of severe hepatotoxicity (elevation of enzymes greater than five times normal)(56) antiretroviral therapy should be withdrawn. Another potential cause of liver toxicity relates to mitochondrial damage due to NRTIs. This effect has markedly reduced in the context of waning use of stavudine and didanosine.

In the past, decisions were required by the clinician on which virus to treat first in patients with HIV-HCV co-infection. However, in the rapidly changing landscape of HIV and HCV therapy, all patients with HIV should be commenced on cART unless specific reasons preclude this procedure; all patients with HIV-HCV co-infection will be offered oral DAA anti-HCV regimens associated with > 90% HCV cure. There are specific drug-drug interaction between some DAAs or ribavirin and specific antiretrovirals, as well as between DAAs and some other therapies patients may be taking. It is recommended to consult a current drug-drug interaction website with up-to-date information prior to commencing a patient on HCV therapy e.g. the site provided by the University of Liverpool, UK: <http://www.hep-druginteractions.org>

HIV and hepatitis B co-infection

Morbidity and mortality related to liver disease secondary to chronic hepatitis B virus (HBV) infection in the context of HIV infection are increasing. The diagnosis of HIV-HBV co-infection has implications for the treatment of both infections. The two viruses, although classified in different families, have a number of similarities in replication pathways including a reverse transcription step (with the reverse transcriptase enzyme being virally encoded) and a number of analogous gene products. As a result, some reverse transcriptase inhibitors are active against both viruses. In addition, as is seen in HCV-HIV co-infection, progression of liver disease from chronic hepatitis B is accelerated with HIV co-infection.(57) Unlike HCV, which can potentially be cured, HBV treatment at this stage needs to be continued indefinitely.

Treatment decisions in individuals with HIV-HBV co-infection are predicated upon whether neither or both viruses require treatment, or if only one of the viruses require treatment. In addition to the usual HIV parameters used in guiding therapy, severity of liver disease, likelihood of response and risk of adverse events should be considered. Detailed treatment algorithms may be found in a review of the topic.(58) To date the US

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Food and Drug Administration (FDA) have approved seven agents for the treatment of chronic hepatitis B,(59)(60)(61)(62)(63) including interferon alpha-2b, pegylated interferon alpha-2a, lamivudine, tenofovir, adefovir, entecavir, telbivudine and emtricitabine. In Australia, pegylated interferon alpha-2a, lamivudine, tenofovir, adefovir, telbivudine and entecavir are available under the Australian Government's Highly Specialised Drugs Program as Section 100 (S100) items for the treatment of hepatitis B.

Case Study 1. A man with a rash attends his local clinic

A 44-year-old man from Indonesia, previously known to have HIV infection, presented to his local medical officer with an unusual rash. He had no follow-up for HIV since diagnosis and was antiretroviral naïve. His CD4 cell count was 50 cells/μL and plasma HIV RNA was over 100,000 copies/mL. Investigation revealed elevated hepatic transaminase levels of twice normal. Hepatitis B surface antigen (HBsAg), hepatitis B envelope antibody (HBeAg) and anti-hepatitis B core antibody (anti-HBcAb) and hepatitis A IgG were detected. Delta antigen and antibody were not detected; HCV antibody was not detected and HCV polymerase chain reaction (PCR) was negative.

His doctor started prednisolone 50 mg daily for the rash, with rapid dose reduction, and 2 weeks later started combivir, efavirenz and cotrimoxazole. Fourteen days later, the man developed pain in the right upper quadrant and jaundice. Examination revealed tender hepatomegaly, but no splenomegaly or signs of chronic liver disease. He had oropharyngeal candidiasis. Liver function tests revealed an alanine aminotransferase of 3900U/L, gamma-GT of 390 U/L, alkaline phosphatase of 97 U/L and bilirubin of 297μmol/L. His albumin was 28 g/L and platelet count was 57 x 109/L. Coagulation was abnormal. A diagnosis of acute exacerbation of chronic hepatitis B was made. The patient's hepatitis B virus (HBV) DNA was 266 IU/L. His course was complicated by haematemesis and melaena from severe ulcerative oesophagitis, development of hepatic encephalopathy, persistent coagulopathy, and acute renal failure. He died 6 weeks after commencing antiretroviral therapy.

This man did not have an assessment of the severity of the chronic HBV before starting antiretroviral therapy (which included only a single agent with activity against hepatitis B: lamivudine). In addition, empirical use of prednisolone in this situation should be undertaken with great caution. The course in this man was complicated by the prednisolone withdrawal, which is known to cause a hepatitis flare in patients with HBV infection.

Consideration of antiretroviral therapy in patients with HIV and HBV co-infection should include:

- Assessment of other potential causes of liver disease including non-infectious causes, serology for HCV, hepatitis A virus and hepatitis D virus, and HCV PCR, and assessment of level of HBV replication by quantitative HBV DNA PCR assay. Additionally consider other tropical infections, particularly if this patient is not from an urban Indonesian area.
- Liver imaging and coagulation parameters and consideration of liver biopsy to determine degree of necroinflammatory and fibrotic changes present.
- Counselling regarding alcohol intake and other hepatotoxic agents.
- Advice regarding vaccination for hepatitis A if not immune, safer sexual behaviour and travel advice.
- Choice of antiretroviral regimen directed against both HIV and hepatitis B, with avoidance of ritonavir and nevirapine;
- Advice about avoidance of treatment interruption: removal of anti-HBV agents may cause a severe flare in liver disease.
- Regular monitoring of markers of liver disease in response to anti-HBV and antiretroviral therapy.

In situations where therapy for hepatitis B alone is indicated, consideration may be given to treatment with pegylated interferon alpha-2a, which is more effective than standard interferon.(64) Adefovir is generally avoided due to concerns regarding potential development of HIV resistance (this agent is closely related to tenofovir), nephrotoxicity and data showing its inferiority to tenofovir.(65) If lamivudine, emtricitabine or tenofovir is chosen it should only be administered in the context of a fully suppressive cART regimen that

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

includes both tenofovir and either lamivudine or emtricitabine. Use of lamivudine alone is well documented to be associated with the rapid development of resistance mutations to HIV while use of lamivudine in a cART regimen without another agent active against hepatitis B e.g. lamivudine/emtricitabine (3TC/FTC) will lead to HBV resistance mutations in 94% of individuals by 4 years. While entecavir was initially believed not to have activity against HIV, a recent report showed that its use was associated with a 1 log drop in HIV viral load and selection of the M184V resistance mutation of HIV, thus conferring lamivudine resistance. In light of these data, entecavir should only be used in the context of a fully suppressive cART regimen.(66) Telbivudine in HIV-HBV co-infection is safe and efficacious although there is cross resistance with M204 lamivudine hepatitis B resistance mutation.(67)

In situations where therapy for both viruses or HIV alone is indicated, a fully suppressive cART regimen should be commenced, with the NRTI backbone including either lamivudine or emtricitabine and tenofovir.

All patients commencing therapy should be counselled regarding the risks of cessation of HBV active agents as a severe flare of liver disease may result. Liver function should be monitored carefully as immune reconstitution flares may occur. Development of abnormal liver function tests may indicate impending HBeAg seroconversion,(68) which is readily confirmed by checking HBeAg and eAb.

HIV infection in women

Women tend to be under-represented in clinical trials examining HIV therapies. The indications for initiation of ART and the goals of treatment are the same for women with HIV infection as for other adults and adolescents with HIV (AI).(69)(70) Nevertheless, some large scale studies in women such as GRACE and WAVES that examined ART initiation, showed similar efficacy and safety as in men.(71)(72)

It is generally recommended that NVP not be prescribed to antiretroviral- naïve women who have CD4 counts > 250 cells/μL unless there is no other alternative and the benefit from NVP outweighs the risk of hepatotoxicity (AI).

There is a female predominance in the increased incidence of symptomatic and even fatal lactic acidosis associated with prolonged exposure to NRTIs, particularly with stavudine (d4T), didanosine (ddI) and zidovudine (ZDV).(73)

Women with HIV infection are more likely to experience increases in central fat with ART and are less likely to have triglyceride elevations on treatment.(74) Women have an increased risk of osteopenia/ and osteoporosis, particularly after menopause, and this risk is exacerbated by HIV and ART.(75)

For women taking oral contraceptives, consideration should be given for potential drug-drug interactions with ART, and choice of therapy or alternative forms of contraception may need to be considered.

For women considering pregnancy and for women of childbearing age not taking adequate contraception, efavirenz should be avoided. Efavirenz has a risk during the first 4-6 weeks of pregnancy of neural tube defects found with this drug in animal studies. Women taking an efavirenz-containing regimen and realised to be pregnant, who have virological suppression, may continue with this therapy if they have passed the initial 6 weeks.(76)

The goals of management of pregnancy include maternal virological suppression that will be beneficial to the mother and reduce the risk of HIV perinatal transmission.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

When designing a regimen for a pregnant woman, clinicians should consult the most current [Health and Human Services \(HHS\) Perinatal Guidelines](#) (AIII).

Women of childbearing potential

All women of childbearing potential should be offered pre-conception counselling and care as a component of routine primary medical care.

Hormonal contraception

See [HIV and Pregnancy](#) chapter

Safe and effective reproductive health and family planning services to reduce unintended pregnancy and perinatal transmission of HIV are an essential component of care for women with HIV of childbearing age. Counselling about reproductive issues should be provided on an ongoing basis.

Providers should be aware of potential interactions between antiretroviral drugs and hormonal contraceptives that could lower contraceptive efficacy. Several PIs and NNRTIs have drug interactions with combined oral contraceptives. Interactions include either a decrease or an increase in blood levels of ethinyl estradiol, norethindrone or norgestimate which potentially decreases contraceptive efficacy or increases estrogen- or progestin-related adverse effects (e.g., thromboembolism). Small studies of women with HIV infection receiving injectable depot-medroxyprogesterone acetate (DMPA) while on ART showed no significant interactions between DMPA and EFV, NVP, nelfinavir (NFV), or NRTI drugs.(77) Contraceptive failure of the etonogestrel implant in two patients on EFV-based therapy has been reported and a study has shown EFV may decrease plasma progestin concentrations of combined oral contraceptives containing ethinyl estradiol and norgestimate.(78) Several RTV-boosted PIs decrease oral contraceptive estradiol levels.(79) A small study from Malawi showed that NVP use did not significantly affect estradiol or progestin levels in women with HIV.(80) Overall, data are relatively limited and the clinical implications of these findings are unclear. The magnitudes of change in drug levels that may reduce contraceptive efficacy or increase adverse effects are unknown. Concerns about pharmacokinetic interactions between oral and implant hormonal contraceptives and antiretroviral agents should not prevent clinicians from prescribing hormonal contraceptives for women on ART if that is their preferred contraceptive method. However, when women wish to use hormonal contraceptives and drug interactions with antiretroviral agents are known, additional or alternative contraceptive methods may be recommended. (Consistent use of male or female condoms to prevent transmission of HIV and protect against other sexually transmitted infections [STIs] is recommended for all women with HIV infection and their partners, regardless of contraceptive use).

Intrauterine devices (IUDs) appear to be a safe and effective contraceptive option for women with HIV infection.(81) Although studies have focused primarily on non-hormone-containing IUDs (e.g., copper IUD), several small studies have also found levonorgestrel-releasing IUDs to be safe and not associated with increased genital tract shedding of HIV.(82)

Approach to pregnancy in women with HIV infection

See [HIV and Pregnancy](#) chapter

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

HIV infection in children

Most HIV-specialist clinicians in Australia will rarely, if ever, face the multiple challenges of managing an infant or young child with HIV infection. Ideally management should be directed by a clinician with experience in this area. The recognition of a number of differences in HIV infection between adults and children has led to some specific recommendations in paediatric practice. The US guidelines for the use of antiretroviral agents in paediatric HIV infection provide a comprehensive summary of management issues.⁽⁸³⁾ Specific considerations in the management of the child with HIV infection include:

- Perinatal transmission (i.e. known time of infection and immature immune system)
- In utero, intrapartum and postpartum exposure to zidovudine and other antiretroviral drugs
- Use of virological assays for diagnosis in infants aged under 18 months
- Differences in monitoring infection and threshold for therapy due to differences in CD4 cell counts, virological responses and clinical progression
- Changes in drug metabolism and clearance with age
- Issues of adherence to therapy, especially in adolescents.

Clinical progression in children

HIV infection in children is markedly more aggressive. One quarter of children who acquire HIV infection by vertical transmission progress to AIDS within the first year (rapid progressors), and the remainder progress to AIDS over 5 years (slow progressors). Typical early signs include candidiasis, lymphadenopathy, hepatomegaly, splenomegaly and growth impairment. Common opportunistic infections include *Pneumocystis jirovecii* pneumonia, fungal infections, bacterial infections (particularly with encapsulated bacteria), mycobacterial infection and recurrent herpes zoster. The progression risk at given CD4 cell count levels in children over 5 years of age equate to that of adults. Due to the risk of rapid clinical progression, ART is recommended for all infants with HIV infection aged less than 12 months.⁽⁸⁴⁾

CD4 cell count in children

Children naturally have considerably higher and more variable CD4 cell counts than adults. As a result, the CD4 cell thresholds used to gauge the risk of opportunistic infection and progression have been adapted to the immunological development of infants and children with HIV infection. In addition, in children under the age of 6 years, CD4 cell percentage is more reliable than CD4 cell count.

Plasma HIV RNA in children

In infants who acquire HIV perinatally, the mean plasma HIV RNA level in the first year of life is 185,000 copies/mL, while rapid progression and death has been predicted by plasma HIV RNA > 299,000 copies/mL. There may be overlap in levels between those who progress rapidly versus slowly. Regardless of plasma HIV RNA level, a CD4 cell count of less than 15% is highly predictive of disease progression and death.

Antiretroviral drug treatment recommendations in children

Specific recommendations regarding therapy initiation in children are summarised in Table 2. Regardless of the manufacturers recommendations, the current US guidelines state that all antiretroviral agents approved for use in adults may be considered in children.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Table 2. Indications for initiation of antiretroviral therapy in children with HIV infection (85)

Age	Criteria	Recommendation
<12 months	Regardless of clinical symptoms, immune status, or viral load	Urgent treatment (AI for <12 weeks of age; AII for ≥ 12 weeks)
1 to <6 years	CDC Stage 3-defining opportunistic illnesses ^b	Urgent treatment (AI*)
	CDC Stage 3 immunodeficiency: ^d CD4 <500 cells/mm ³	Urgent treatment (AI*)
	Moderate HIV-related symptoms ^b	Treat (AII)
	HIV RNA > 100,000 copies/mL ^c	Treat (AII)
	CD4 cell count ^d 500-999 cells/mm ³	Treat (AII)
	Asymptomatic or mild symptoms and CD4 cell count ^d ≥ 1000 cells/mm ³	Consider treatment (BIII)
≥ 6 years	CDC Stage 3-defining opportunistic illnesses ^b	Urgent treatment (AI*)
	CDC Stage 3 immunodeficiency: ^d CD4 <200 cells/mm ³	Urgent treatment (AI*)
	Moderate HIV-related symptoms ^b	Treat (AII)
	HIV RNA > 100,000 copies/mL ^c	Treat (AII)
	CD4 cell count 200-499 cells/mm ³	Treat (AI* for CD4 cell count <350 cells/mm ³ and AII* for CD4 cell count 350-499 cells/mm ³)
	Asymptomatic or mild symptoms ^b and CD4 cell count ≥ 500 cells/mm ³	Consider treatment (BIII)

Rating of recommendations: a=Strong; B=moderate; C=Optional

Rating of Evidence: I= data from randomised controlled trials in children; I*=data from randomised trials in adults with accompanying data in children from nonrandomised trials or observational cohort studies with long-term clinical outcomes; II*=data from well-designed non randomised trials or observational cohort studies in adults with long-term clinical outcomes with accompanying data in children from smaller non-randomised trials or cohort studies with clinical outcomes data; III=Expert opinion

1. Children in whom cART is deferred need close follow-up. Factors to consider in deciding when to initiate therapy in children whom treatment was deferred include: CD4 cell count or percentage values approaching the age-related threshold for treatment; Development of clinical symptoms; and The ability of caregiver and child to adhere to the prescribed regimen.
2. To avoid overinterpretation of temporary blips in viral load (which can occur during intercurrent illnesses, for example), plasma HIV RNA level > 100,000 copies/mL should be confirmed by a second level before initiating cART.
3. Laboratory data should be confirmed with a second test to meet the treatment criteria before initiation of cART.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

HIV-associated neurocognitive disorders

In the cART era, HIV-associated neurocognitive disorders (HAND) have not diminished in prevalence which ranges from 25-40% of individuals with HIV. However, the more severe forms of HIV-associated dementia (HAD) are seen less frequently, in contrast to the more frequent milder forms of mild neurocognitive disorder (MND) and asymptomatic neurocognitive impairment (ANI). Some key points to consider:

- Currently there are no optimally available screening tools in the clinic to detect HAND
- Dementia may be seen in individuals on cART as well as those who are treatment naïve or have ceased cART
- Late commencement of cART and failure to recognise dementia are likely to be significant factors
- Thorough evaluation (neuroimaging, neuropsychological testing and cerebrospinal fluid (CSF) examination) is indicated to exclude other causes and confirm the diagnosis
- CART improves the cognitive impairment due to HIV- associated dementia⁽⁸⁶⁾⁽⁸⁷⁾
- Consideration should be given to the use of antiretroviral agents, which penetrate the central nervous system⁽⁸⁸⁾
- Rarely, differential patterns of resistance mutations may be seen in plasma versus CSF⁽⁸⁹⁾
- Individuals with HIV-associated dementia often have a very slow response to therapy over months rather than weeks
- During this time it may be necessary to institute directly observed therapy in a supported environment
- Cognitive impairment is frequently associated with poor medication adherence.

Case Study 2. Patient with short-term memory loss

A 56-year-old man presents with short-term memory loss and a generalised epileptic fit. HIV is diagnosed and no opportunistic infection or other contributing factor is identified on brain-imaging studies. He lives alone, is dishevelled in appearance, and has lost weight recently.

Management of this man includes:

- Baseline screening for dementia, and assessment of the severity of dementia, using formal neuropsychological testing
- Assessment of cerebrospinal fluid HIV RNA, MRI and surrogate markers (CD4 cell count, plasma HIV RNA)
- Specialist neurological review
- Commencing ART, (possibly with CNS penetrating ART) if diagnosed with HIV-associated neurocognitive disorder (HAND)
- Consideration of directly observed therapy with agents which may be dosed once-daily
- Monitoring of clinical, radiological and cerebrospinal fluid response to therapy, including HIV RNA in both plasma and cerebrospinal fluid and consideration of compartmentalisation of resistant virus in the central nervous system if response is suboptimal.

HIV and drugs of dependence

The prevalence of HIV infection in people who inject drugs (PWID) in Australia, assuming no other risk factors for acquisition, is approximately 2%.⁽⁹⁰⁾ The prevalence of HIV in Australian male homosexual PWID is much higher however, at 32%.⁽⁹¹⁾ Despite the relatively low numbers involved, the management of HIV infection in this group presents unique challenges. Poorer outcomes in PWID with HIV infection are related to a variety of factors including increased rates of non-HIV related deaths, hepatitis C, delayed access to effective treatment, lower adherence to treatment regimens, continuation of illicit drug use, depression and negative life events.⁽⁹²⁾

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Clinical implications

CD4 cell count and plasma HIV RNA provide prognostic information⁽⁹³⁾ and progression does not appear to be influenced by means of acquisition of HIV infection.⁽⁹⁴⁾ A range of infections occurs more commonly in PWID with HIV infection,⁽⁹⁵⁾ including:

- bacterial infections (e.g. septicaemia, infectious endocarditis and pneumonia)
- sexually transmissible infections (especially in sex workers)
- tuberculosis
- co-infection with HBV or HCV In addition, regular or intermittent use of illicit drugs may complicate assessment of psychiatric symptoms or confusional states.

Treatment implications

Social disadvantage, psychiatric comorbidity, previous incarceration, and a history of sex work are common associations of HIV infection in PWID. These circumstances impact on interactions with health-care professionals, health-care delivery and adherence to antiretroviral therapy. It is important to approach these people in a non-judgmental manner, in order to develop a relationship based on trust and mutual respect. Studies have demonstrated decreased uptake of ART and higher use of non-cART regimens in PWID. Initiation of cART has been associated with decreased use of injecting drugs and concurrent methadone.⁽⁹⁶⁾

Drug interactions in methadone- and buprenorphine-treated individuals receiving cART are an important consideration. (Tables 3 and 4) As methadone is metabolised by the cytochrome p-450 system there are significant interactions with NNRTIs and some PIs, in particular. Concomitant efavirenz or nevirapine and methadone administration has precipitated opioid withdrawal symptoms. Stabilisation necessitates a substantial increase in methadone dosage.⁽⁹⁷⁾ There are significantly less drug interactions with buprenorphine; however, attention to potential drug interactions and education of the individual regarding the possible outcomes are required.

Table 3. Antiretroviral-methadone interactions

Antiretroviral	Interaction	Recommendations
Non-nucleoside reverse transcriptase inhibitors		
Efavirenz	Efavirenz decreases methadone C _{max} and AUC by mean 60% in PK study of patients on methadone maintenance Symptoms of opioid withdrawal have been reported from 4 days to 4 weeks after the introduction of efavirenz	Monitor for symptoms of opioid withdrawal and increase methadone dose as required PK study: increase methadone dose in increments of 5-10 mg until symptoms resolved (22 – 55% increase in methadone dose reported)
Nevirapine	Nevirapine decreases methadone AUC by 50-70% in PK study of patients on stable methadone dose. 30% of 45 patients in a prospective study of PWID on methadone maintenance required increase in methadone dose	As for efavirenz (above). In PK study 16% mean increase in methadone dose required. Other case reports have required increase of 33% and 100% in methadone dose
Etravirine	No significant effects	No dosage adjustment necessary
Rilpivirine	R-methadone AUC decreased by 16%	No dosage adjustment necessary but monitor for opioid withdrawal

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Protease inhibitors		
Atazanavir	Small PK study showed no effect and no symptoms of opioid withdrawal observed Decreased atazanavir levels have been observed	Can be used safely in combination without dose adjustment Monitor atazanavir levels
Darunavir/ ritonavir	R-methadone decreased by 16%	No dosage adjustment necessary but monitor for opioid withdrawal
Lopinavir/ ritonavir	Lopinavir/ritonavir decreases methadone AUC and Cmax ~50% in PK study of healthy volunteers on methadone	Monitor for symptoms of opioid withdrawal and increase dose if necessary
Fosamprenavir/ ritonavir	PK study showed decrease AUC and Cmax by 20% for active methadone and 40% for inactive methadone. No change in fosamprenavir or opioid withdrawal	Combination appears safe without modification
Indinavir	No significant effect of indinavir on methadone AUC when compared with historical controls in PK study No significant effect of methadone on indinavir AUC, but increase indinavir Cmin 50-100% and decrease indinavir Cmax 16-36% (All historical controls)	Combination appears safe
Ritonavir/ saquinavir	PK studies have demonstrated a clinically insignificant decrease in unbound methadone levels, and there was no evidence of opiate withdrawal There has been one case report of opioid withdrawal requiring an increase in methadone dose	Monitor for symptoms of opioid withdrawal and increase dose if necessary
Tipranavir/ ritonavir	PK study showed large (50%) decrease in methadone levels	Dosage of methadone may need to be increase
Amprenavir	Preliminary data from PK study: decreases AUC methadone 12-24%	Combination appears safe based on preliminary data
Nucleoside reverse transcriptase inhibitors		
Abacavir	No significant change in Cmax, half-life or renal clearance of methadone despite slight increase in methadone clearance by abacavir. Slight delay in rate but not extent of abacavir absorption by methadone	Combination appears safe
Didanosine, stavudine	PK study demonstrated d4T AUC decreased by 23% and ddI AUC decreased by 57%. Effect predominantly related to reduced bioavailability	No data to guide dose adjustments. Monitor for virological failure
Zidovudine	Two PK studies have demonstrated zidovudine AUC increase 29-43%	Monitor for zidovudine related toxicities
Tenofovir	PK study showed no change in kinetics of methadone	Combination appears safe
Integrase inhibitors		
Dolutegravir	No significant effect	No dosage adjustment necessary

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Elvitegravir / cobicistat / tenofovir / emtricitabine	No significant effect	No dosage adjustment necessary
Raltegravir	No significant effect	No dosage adjustment necessary
Other		
Maraviroc	No data; potentially safe in combination	Monitor clinically

AUC: area under the curve; PK: pharmacokinetics; Cmax: maximum concentration achieved; Cmin: trough concentration; PWID: people who inject drugs

Source: Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents. Department of Health and Human Services. With Australian commentary.(98) Available at: <http://arv.ashm.org.au/arv-guidelines/drug-interactions> McCance-Katz EF, Sullivan LE, Nallani S. Am J Addict 2010;19:4-16.74

Table 4. Interactions between buprenorphine and antiretroviral agents

Mild-moderate enzyme inhibitors	Potent enzyme inhibitors	Enzyme inducers
Atazanavir Darunavir Efavirenz Elvitegravir Fosamprenavir Indinavir Nelfinavir Saquinavir	Lopinavir/ritonavir Ritonavir	Efavirenz Nevirapine Tipranavir Ralpivirine
Potential increase in opioid concentration	Potential increase in opioid concentration	Potential decrease in opioid concentration
Atazanavir: reports of opioid excess when used in combination due to increased BUP levels, no significant change in ATV levels. If on boosted ATZ (with ritonavir) may initiate BUP slowly and at reduced dose; if on BUP consider dose reduction when initiating ATV Do not co-administer BUP with unboosted ATZ Darunavir: norbuprenorphine AUC increased by 46% and Cmin increased by 71%. No dosage adjustment necessary but clinical monitoring is recommended Efavirenz: BUP AUC decreased by 50% and norbuprenorphine AUC by 71%. Monitor for opioid withdrawal symptoms Elvitegravir: BUP AUC increased by 35% and norbuprenorphine by 42%. No dosage adjustment necessary but clinical monitoring recommended Raltegravir – no significant interactions Dolutegravir- no significant interactions	Lopinavir/ritonavir: addition not associated with significant change in AUC for BUP and clinical status unchanged	Efavirenz: addition associated with 50% decrease in AUC of BUP, but no clinical evidence of opioid withdrawal. No effect on efavirenz No dose adjustment necessary for nevirapine or rilpivirine but monitor for opioid withdrawal

Source: Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents. Department of Health and Human Services. With Australian commentary.(99) Available at <http://arv.ashm.org.au/arv-guidelines/drug-interactions> McCance-Katz EF, Sullivan LE, Nallani S. Am J Addict 2010;19:4-16.(100)
University of Liverpool, drug interactions tables available at <http://www.hiv-druginteractions.org/>

BUP: buprenorphine; ATV: atazanavir; AUC: area under the curve.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Harm minimisation strategies

Minimisation of risk to the individual and the community is the basis of the public health approach to HIV infection. Rates of transmission of HIV infection among PWID can be reduced through needle-exchange programs, access to drug-dependence treatment options such as opioid substitution therapy and education regarding sexual transmission.

Thus, optimal management of PWID with HIV infection includes a combination of specialist HIV care and expertise, and facilities for drug-dependence treatment.

Interactions between recreational drugs and antiretroviral therapy

The clinician at baseline and at regular intervals thereafter should seek information regarding current use of recreational drugs. It is important for patients to have an understanding of the (potentially dangerous) interactions between recreational drugs that are intermittently used and the antiretroviral drugs that are taken regularly. Table 5 summarises demonstrated and theoretical interactions between recreational drugs and antiretroviral agents. The recent increase in use of crystal methamphetamine in men who have sex with men in Australia is worth particular mention as is the fact that methamphetamine was the most commonly reported drug last injected among HIV antibody positive respondents in the Australian NSP survey in all survey years between 2009-13).⁽¹⁰¹⁾ Associated phenomena and complications of use of this drug are well summarised elsewhere.⁽¹⁰²⁾ Although formal data regarding drug interactions are not available, methamphetamine is likely to be potentiated by ritonavir in a similar manner to mythylenedioxymethamphetamine (MDMA). Patients should be advised to reduce the dose of crystal methamphetamine to one-quarter to one-half of normal. There is one report in the literature of an individual in Melbourne whose death was suspected to be due to the combination of methamphetamine use with concurrent antiretroviral therapy that included ritonavir.⁽¹⁰³⁾

Table 5 Interactions between antiretroviral and recreational drugs

Drug	Interactions	Recommendations
Amphetamines	Possible increased levels with ritonavir	Avoid combination with RTV if possible. If not, start with 1/4 – 1/2 of initial amount of amphetamine taken
Codeine	Due to different pathways of metabolism may increase or decrease morphine levels	Monitor for signs of opiate toxicity or withdrawal
Gamma hydroxybutyrate (GHB) (Fantasy)	Possible increased levels/prolonged effect with antiretrovirals, especially RTV	Use cautiously with inhibitors of cytochrome P-450 (PIs, efavirenz). Users should be aware of signs/symptoms of GHB toxicity (e.g. seizures, respiratory depression)
Ketamine	Possible increased levels with antiretrovirals, especially RTV, NFV and EFV	Use cautiously with cytochrome P-450 inhibitors. Users should be aware of signs/symptoms of ketamine toxicity (e.g. hallucinations, respiratory depression)
Lysergic acid diethylamide (LSD)	Unknown	Use cautiously with cytochrome P-450 inhibitors. Users should be aware of signs/symptoms of LSD toxicity (e.g. hallucinations, psychosis, agitation)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Methylenedioxy-methamphetamine (MDMA) (Ecstasy)	Possible increase levels with RTV. Two deaths have been reported	Avoid combining with ritonavir if possible. If not, reduce MDMA dose by about 1/4 – 1/2 of usual amount used, and watch for signs of MDMA toxicity. Other precautions include staying well hydrated, avoiding alcohol and taking breaks from dancing
Oxycodone	Due to different pathways of metabolism may increase or decrease levels of active metabolite oxymorphone, resulting in possible opiate withdrawal or toxicity	Monitor for signs of opiate withdrawal or toxicity
Phencyclidine (PCP)	Possible increase levels with antiretrovirals	Use cautiously with cytochrome P-450 inhibitors. Ensure patient aware of signs/symptoms of phencyclidine toxicity (e.g. seizures, rhabdomyolysis, hypertension, hyperthermia)
Tetrahydro-cannabinol (THC), active moiety of marijuana, hashish and hash oil	Drugs which inhibit CYP3A4 or 2C9 (PIs) may increase THC concentrations. Drugs which induce CYP3A4 (EFV, NVP) may decrease THC concentrations. A randomised trial of the effects of cannabinoids on the pharmacokinetics of IDV and NFV: smoked THC decrease NFV AUC by 17%, and decrease IDV Cmax 21%	There have been no reports documenting adverse events secondary to the combination of THC and protease inhibitors despite the wide use of THC derivatives as antiemetics and appetite stimulants

AUC: area under the curve; EFV: efavirenz; IDV: indinavir; NFV: nelfinavir; NVP: nevirapine; RTV = ritonavir.

Source: Adapted from Antoniou T, Tseng A. Ann Pharmacother 2002;36:1598-613. (104)

Case Study 3. Man on methadone therapy

A 43-year-old man with a history of injecting drug use and heroin dependence currently maintained on methadone maintenance therapy presents for initiation of anti-HIV therapy. His HIV infection was diagnosed 8 years previously. He has monitored his surrogate markers infrequently. In recent months he has noted increasing lethargy, weight loss and cough. He currently lives in a boarding house however he has been attacked on a number of occasions and has resolved to move out. His plasma HIV RNA is above 100,000 copies/mL and CD4 cell count 210 cells/μL (14%).

Considerations when initiating therapy include:

- assessment for occult infection (e.g. endocarditis, pneumonia, tuberculosis)
- status of hepatitis infections and vaccination
- address housing issue – referral to social worker or housing agency
- formal adherence assessment and plan to support adherence when commences therapy
- resistance testing if possible
- consideration of drug-drug interactions with methadone (e.g. nevirapine in the cART regimen will require an increase in methadone dose)
- consider daily regimen that may be dispensed with opioid replacement therapy assessment of social supports, and access to harm minimisation strategies.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Long-term management of antiretroviral therapy

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Last reviewed: June 2021

Introduction

Long term management of HIV infection encompasses the following broad objectives:

- Prevention of HIV disease progression and associated mortality and morbidity;
- Restoration and preservation of immunologic function;
- Prevention of antiretroviral drug resistance;
- Prevention of HIV transmission to others (Treatment as prevention);
- Minimisation of antiretroviral drug-related adverse effects, intolerances and drug-drug interactions (DDIs) with concurrent medications;
- Monitoring and prevention of long-term antiretroviral drug-related toxicity;
- Maintenance and improvement of quality of life of people with HIV infection (PWH).

HIV infection is now a chronic manageable condition with antiretroviral therapy (ART). However, eradication of HIV infection cannot be achieved with current ART regimens, so treatment is life-long, with the main goal of achieving and maintaining plasma HIV RNA levels that are below the lower limits of detection (LLOD) of currently used laboratory assays i.e. "undetectable viral load".

ART has reduced HIV-related morbidity and mortality at all stages of HIV infection and has reduced HIV transmission. A high level of adherence to prescribed treatment is essential for optimal outcomes. This level of adherence is beyond that generally necessary for the effective management of many chronic medical conditions. As HIV replication is error-prone, mutations that confer resistance to particular antiretroviral drugs or classes of drugs arise unless viral replication is maximally suppressed. Medication adherence has been demonstrated to be the most important prognostic factor in treatment success. Therefore, patient engagement and commitment to his or her treatment plan is fundamental to the successful long-term management of HIV infection. (Refer to later discussion on Retention in care)

The foundations of the relationship between health professionals and PWH built in the early days and months following a new diagnosis of HIV infection is crucial, and includes a number of principles: having the person with HIV infection feel supported and reassured about their long-term prognosis and other concerns about how HIV may impact their life; developing an understanding of what HIV is and how it causes disease; how antiretroviral drugs work and the goals of treatment, including an understanding of fundamental goals such as establishing and maintaining control of viral replication and recovery of immune function. Before treatment starts, we recommend that clinicians engage in specific discussions about how HIV medication will fit into the person's daily routine. For instance, it is useful to help PWH identify the most suitable time to ingest medications and discuss strategies to aid adherence. In the case of adherence to treatment, prevention is better than cure, as once established, patterns of non-adherence and disengagement may be difficult to change.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Routine monitoring of PWH receiving ART

The main objective of monitoring PWH receiving ART is to optimise the efficacy of ART while minimising ART-related adverse drug reactions and toxicities. HIV RNA (viral load) and CD4+ T cell (CD4) count are the two surrogate markers of ART response and HIV disease progression. In addition to the CD4 count and viral load, a number of other laboratory monitoring tests and investigations are recommended to aid in assessing the efficacy and tolerability of ART.

The table below summarises the main monitoring recommendations. (Adapted from BHIVA guidelines on the routine investigation and monitoring of HIV-1-positive adults⁽¹⁾ and other international guidelines^(2,3)).

Main HIV Laboratory Tests	
HIV serology	At entry into care
HIV plasma viral load	At entry into care
	2 to 8 weeks after ART initiation or modification
	During first 2 years on ART every 3 to 6 months
	After 2 years of ART with consistently suppressed VL every 6 months
	Treatment failure or otherwise clinically indicated
CD4+ T cell count (and percentage of lymphocytes)	At entry into care
	During first 2 years of ART: every 3 to 6 months, or if viremia develops while on ART, or CD4 count <300/mL
	After 2 years on ART with consistently suppressed VL: CD4 Count 300–500/mL: every 12 months CD4 Count >500/mL: CD4 monitoring is optional
	Virological failure or otherwise clinically indicated
HIV genotypic resistance test	At entry into care /before ART initiation, according to local guidelines and if test is available
	Repeat in treatment failures or as otherwise clinically indicated
HLA-B*5701 testing	At ART initiation or modification if considering use of abacavir therapy (one test only)
Tests for co-infections	
Hepatitis B virus serology	HBsAg, HBsAb, HBcAb
	At entry into care. Vaccination if not immune (refer to subsection on Vaccines in people with HIV infection) and repeat HBsAb to confirm seroconversion
Hepatitis A virus (HAV)	HAV IgG or total Ab
	At entry into care. Vaccination if not immune (refer to subsection on Vaccines in people with HIV infection) and repeat test to confirm seroconversion
Hepatitis C virus (HCV)	HCAb or plasma HCV RNA (qualitative) if past infection
	At entry into care. Repeat annually as clinically indicated
TB risk assessment	In addition to a clinical assessment of risk factors for <i>Mycobacterium tuberculosis</i> infection, investigations pre-ART might include chest X-ray, interferon-γ release assay (IGRA), such as the QuantiTiter (QIFN) TB-Gold assay, or Tuberculin skin test (TST), as per local guidelines.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

STIs testing	As per national guidelines https://sti.guidelines.org.au/
Medical History	
Review all prescribed and over the counter medications and other supplements.	Up to date medication history At every visit; at minimum every 12 months
Document allergies	At entry to care and update as necessary
Review treatment adherence, adverse effects and DDIs	At every visit; at minimum every 12 months
Check the need for antiretroviral drug dose adjustment as a consequence of change in kidney and liver function	At every visit; at minimum every 12 months
Recreational drug use and MSM "Chem Sex"	Assessment of alcohol, tobacco and other recreational drug use as per local guidelines e.g. https://yourroom.health.nsw.gov.au/ MSM "Chem Sex" assessment as per guidelines e.g. https://ashm.org.au/global-projects/chemsex-toolkit-for-clinical-service-providers-in-the-asia-pacific-region/
Other laboratory test monitoring	
Full blood count	At entry into care /before ART initiation 2 to 8 weeks after ART Initiation or modification Every 6 months More frequent monitoring as clinically indicated
Kidney and liver function tests	At entry into care /before ART initiation 2 to 8 weeks after ART Initiation or modification Every 6 months
Random or Fasting Glucose	More frequent monitoring may be indicated for patients with evidence of kidney disease or at increased risk of kidney disease
Urine analysis	Urine dipsticks, urine Pr /Cr ratio, urine Alb/Cr ratio At entry into care Every 12 months for those receiving TDF version of tenofovir or those who have risk factors for CKD4
Pregnancy test for women	At entry into care and during long-term care, as clinically indicated and with consent
Chronic Disease Risk Assessment	
CVD risk over next 5 years	All PWH older than 45 years (or >35 years for Aboriginal people) without existing cardiovascular disease or not already known to be at increased risk of cardiovascular disease: Australian absolute CVD risk calculator https://www.cvdcheck.org.au/
Osteoporosis risk calculation for next 5 and 10 years	Assess for risk factors every 12 months in women older than 45 years, men >50 years; consider BMD measurement Australian Bone Fracture Risk Calculator https://www.garvan.org.au/promotions/bone-fracture-risk/calculator/

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Virological failure

The goal of ART is to suppress HIV replication to a level below which drug-resistance mutations do not emerge within the HIV genome. Although not conclusive, most evidence suggests that selection of drug-resistance mutations does not occur in patients with plasma HIV RNA levels persistently suppressed to below 200 copies/mL, although virological suppression to below the lower limit of detection (LLOD), (<20-50 copies/ml with currently available assays) is preferable.(5)

Assessing and managing PWH who are experiencing failure of ART is complex and expert advice is recommended, especially in PWH in whom there is a history of multiple previous ART exposures. The following definitions are used to describe the different levels of virological response to ART.

Virological Response Definitions	
(Adopted from Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. US Department of Health and Human Services ⁶)	
Virological suppression	A confirmed HIV RNA level below the LLOD of available assays.
Virological failure	The inability to achieve or maintain suppression of viral replication to an HIV RNA level <200 copies/mL
Incomplete virological response	Two consecutive plasma HIV RNA levels ≥ 200 copies/mL after 24 weeks on an ART regimen in a patient who has not yet had documented virological suppression on this regimen.
Virological rebound	Confirmed HIV RNA level ≥ 200 copies/mL after virological suppression
Virological blip	After virological suppression, an isolated detectable HIV RNA level that is followed by a return to virological suppression
Low-level viremia	Confirmed detectable HIV RNA level <200 copies/mL

Persistent HIV RNA levels ≥ 200 copies/mL are often associated with evidence of accumulation of antiretroviral drug-resistance mutations with the viral genome. This association is particularly common when HIV RNA levels are >500 copies/mL³. Therefore, patients who have persistent plasma HIV RNA levels ≥ 200 copies/mL are considered to be experiencing virological failure.

Causes of virological failure	
(Adopted from Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. US Department of Health and Human Services ⁶)	
Patient/ adherence related factors	Mental health related comorbidities (e.g. drug addiction, psychotic illness, learning disability, cognitive impairment) Homelessness and unstable housing Difficulty in ART access and affordability (e.g., cost, limited access to relevant health services) ART adverse effects (e.g. GI side effects) High pill burden and cumbersome dosing regimens

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

HIV-related factors	Presence of transmitted or acquired drug-resistant virus documented by current or past drug resistance test results Prior treatment failure Innate HIV resistance to antiretroviral drugs due to naturally-occurring mutations in HIV genes encoding enzymes targeted by the drugs Higher pre-treatment HIV RNA level
ART regimen related factors	Suboptimal pharmacokinetics (PKs) (e.g., variable absorption, metabolism) Suboptimal virological potency Low genetic barrier to resistance Reduced efficacy due to prior exposure to suboptimal regimens (e.g., monotherapy) Food requirements Adverse drug-drug interactions with concomitant medications Prescription errors

Principles of managing antiretroviral drug resistance

The possibility of antiretroviral drug resistance should be considered before commencing any antiretroviral drug regimen, whether initial treatment or subsequent changes in regimen, and if virological suppression is sub-optimal.

When a person is newly infected with HIV, he or she may be infected with a strain that already carries drug-resistance mutations; this is known as transmitted resistance. If available, a baseline drug resistance assay should be done prior to commencing ART, as close as possible to the time of seroconversion, in order to detect transmitted resistance. Over time, mutations that confer drug resistance may not remain detectable in blood cells as wild-type virus becomes the dominant strain. However, these mutations persist in viruses within the viral reservoir and may be selected by subsequently used antiretroviral drugs and re-emerge, leading to virological failure. Drug resistance mutations that are present in low numbers of viruses and not detected by drug resistance assays are said to be “archived”. Testing early in the course of infection is not possible unless infection is detected at seroconversion or shortly afterwards. The possibility of “archived” transmitted and/or selected resistance should be kept in mind, and monitored by validated surrogate markers of treatment response, particularly viral load. If viral load is slow to decrease or does not fall to <200 copies/mL within 6 months of initiating ART, drug resistance should be considered as a possible cause. Ideally, a repeat drug resistance assay will detect resistance at this stage, as long as the viral load is high enough for the assay to be successful (generally $\geq 1,000$ copies/mL). Other possible causes of virological failure should also be considered.

Some patients with long-standing HIV infection may have unrecognised drug-resistant strains, as HIV viral load and drug resistance assays were not available until the 1990s. Treatment history and results of previous viral load testing can identify probable resistance. For example, if a regimen was failing, or if a person with HIV infection was treated with suboptimal ART in the early treatment years.

In the case of a failing regimen, where resistance testing cannot identify the specific resistance mutation/s and other causes have been ruled out, particularly non-adherence, a change of antiretroviral drug regimen should be considered.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

The most common indications for genotypic antiretroviral drug resistance tests are:

- Primary HIV infection
- Baseline: ART-naïve with established infection
- Virological failure
 - Collect sample while on failing regimen or add-on testing of stored sample
- Pregnancy – not on ART
- ART-treated patient who has ceased therapy (usually due to non-adherence)
 - Restart last effective regimen and assess virological response
 - If the re-initiated ART suppresses viral replication, continue the regimen
 - Repeat resistance testing if the re-initiated ART fails to suppress viral replication.

A common scenario is when the patient lapses from treatment and re-presents months or even years later. Prior to treatment interruption, intermittent adherence or different pharmacokinetic properties of individual drugs in the regimen could lead to the selection of drug-resistant HIV. However, once the patient has stopped drugs for a period of time, the wild-type virus will usually become dominant and drug resistance mutations may not be detected in blood cells, though are archived. Consider whether the components of the regimen have differing durations of action and whether resistance is likely to have emerged, and in that case, consider using an alternative regimen. In these cases, expert advice could reasonably be sought.

Immunological failure: persistent CD4+ T cell deficiency

Recovery of immune function after ART is started is variable but generally not related to the ART regimen used. Duration of the HIV infection and degree of immunodeficiency when ART is commenced (nadir CD4+ T cell count) are much more important factors. Age is another very important factor, with a slower and often blunted immune recovery as age increases. Immune recovery may also be delayed because of other factors, such as concomitant disease, including kidney disease or sarcoidosis; persistent infections by other viruses, such as cytomegalovirus and HCV; and development of malignancy and the use of chemotherapy and/or radiotherapy to treat it.

Medications that can cause cytopenias represent one potential factor in delayed immune recovery that can be modified. Prophylaxis for *Pneumocystis jirovecii* infection is used when the CD4 count is <200/μL (~15%). First-line prophylaxis with trimethoprim/sulfamethoxazole may be associated with leucopenia. Interventions to consider include reducing the dose if a relatively high dose is being used, for example, switching from cotrimoxazole DS (160/800 mg) 1 tablet daily to cotrimoxazole single strength (80/400 mg) 1 tablet daily or cotrimoxazole DS 1 tablet on three days per week. (7)

In assessing slow immune recovery, both the total CD4 count and CD4% should be considered. The possibility of a laboratory error should be considered in the case of an unexpectedly low or high result.

Illustrative case examples:

- A 65 year-old man with a late diagnosis of HIV infection had concomitant chronic kidney disease and diabetes. Despite consistently undetectable HIV RNA levels, the CD4 count increased from 100 to only 180/μL after 10 years of ART. *Late diagnosis, older age and chronic kidney disease likely contributed to the suboptimal CD4+ T cell recovery.*

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

- A 52-year-old man commenced ART when the CD4 count was 30/μL (3%). Three years later, his CD4 count was only 204/μL (12%). The ART regimen remained unchanged and by two years later, he had a more robust immune recovery, with a CD4 count of 670/μL (24%). *Slow recovery of CD4+ T cell count likely reflected the very low nadir CD4+ T cell count and older age but recovery eventually did occur indicating that the ART regimen was not relevant.*
- A 40 year-old man with long-term well-controlled HIV infection and a usual CD4 count of ~500/μL came for monitoring when the CD4 count was found to be 210/μL with CD4% unchanged at ~30%, and HIV RNA <20 copies/ml. He had recently developed polyarthrititis and had a previous diagnosis of sarcoid disease. *The fall in CD4 cell count was due to a relapse of sarcoid disease and recovered after treatment. The decline in CD4 count with preservation of CD4% provided evidence that the low CD4+ T cell count was a consequence of lymphopaenia caused by sarcoidosis rather than CD4+ T cell depletion related to HIV infection.*
- An unexpectedly low CD4 count result was received. On checking the calculation of CD4 as percentage of total lymphocyte count, it was found to be due to a laboratory calculation error. An amended report was made after discussion with the laboratory staff.

Principles of managing antiretroviral drug toxicity and drug-drug interactions

Antiretroviral drug toxicity and DDIs are both reasons for revising an antiretroviral drug regimen but thankfully are encountered much less frequently than they were in the first two decades of ART. Detailed consideration of renal, bone, endocrine, cardiovascular disease and drug hypersensitivity reactions are covered in specific subsections of the “Co-morbidities” and “ARV drugs and other Therapies” sections of these guidelines.

Managing antiretroviral drug toxicity starts with preventative measures by taking into account the patient's age, sex, lifestyle, concomitant medical conditions and medications, including potential DDIs, genetic risk factors and family history in the choice of antiretroviral drug regimen. These precautions will help to avoid ART toxicity in the majority of patients given the superior tolerability of modern antiretroviral drugs.

Evaluation of the cause of reported treatment side-effects involves detailed history taking including a time-line of symptoms, review of concomitant medications (prescribed and non-prescribed), and consideration of alternative causes of symptoms. Symptoms may be due to a new or existing co-morbidity or medicine. Some antiretroviral drug adverse effects may occur for a short period of time after commencement of a new treatment and subsequently resolve. Warning the patient about possible side effects, and early review following change of treatment, may help the patient to manage them without treatment disruption. In some cases, when no other cause is likely, change of antiretroviral drug may be necessary.

People with HIV infection are more likely to develop hypersensitivity reactions to drugs than people without HIV, particularly those with a low CD4 count. Baseline HLA B5701 testing identifies those susceptible to abacavir hypersensitivity. Hypersensitivity reactions to most antiretrovirals are possible, but are:

- rarely reported with rilpivirine, though much more common with other NNRTIs;
- rarely reported with integrase inhibitors;
- reported with all individual protease inhibitors but are not class-wide.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Adverse interactions between antiretroviral drugs and other drugs

Potential drug-drug interactions with prescribed and other drugs need to be considered at the time of choosing a suitable antiretroviral drug regimen and actively monitored at each follow-up visit. Potential interactions can occur with concomitant medicines, nutritional supplements, complementary therapies and recreational drugs, and frequently have the potential to cause toxicity or reduce the efficacy of either the antiretroviral or other drug. As patients age, they may develop new co-morbidities and commence medicines with the potential for interaction with ART. Lifestyle factors may change, including use of recreational drugs or treatments for erectile dysfunction.

Refer to the subsection on “Drug-drug interactions in people with HIV infection” in the “ARV drugs and other Therapies” section of these guidelines for detailed information and links to on-line interaction checkers. The UK HIV drug interaction website provided by the University of Liverpool, Liverpool, UK (available at <https://www.hiv-druginteractions.org/>) and the HIV drug therapy guide of Toronto General Hospital, Toronto, Canada (available at <https://hivclinic.ca/drug-information/drug-interaction-tables/>) are valuable resources.

ART regimen simplification

Patient adherence to medication is the cornerstone of successful long-term treatment. Simpler dosing regimens are associated with improved adherence and virological control. Other reasons to consider regimen simplification may arise in both treatment-naïve and treatment-experienced patients, most commonly due to the presence of comorbidities, and avoidance or management of long-term toxicity and adverse effects. Decisions to use alternative regimens should be evidence-based and made with expert advice.

Strategies to simplify regimens include use of:

- ART formulated as a single tablet, e.g., dolutegravir/lamivudine/abacavir (Triumeq) or bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy);
- once-daily regimens;
- drugs that do not require dosing with food;
- combination drug formulations replacing individual drugs, e.g., darunavir/cobicistat (Prescobix) replacing a separate dose of the pharmacokinetic enhancer ritonavir with co-formulated cobicistat into a single tablet.
- drugs with fewer adverse effects, e.g., replacing ritonavir with cobicistat as a pharmacological booster;
- 2-drug regimens where appropriate (see below);
- drugs with fewer potential DDIs for patients on concomitant potentially interacting drugs, e.g., tenofovir alafenamide/emtricitabine/bictegravir (Biktarvy) replacing tenofovir alafenamide/emtricitabine/elvitegravir/cobicistat (Genvoya);
- nucleoside/nucleotide-sparing regimens to reduce risk of toxicity, particularly for patients with co-morbidities.

2-Drug Regimens (2DR)

To reduce risk of long-term toxicity, consider using an approved and recommended 2DR for initial antiretroviral treatment, or maintenance therapy in virologically suppressed individuals without:

- drug-resistance mutations that would compromise the two-drug option;
- chronic HBV infection;

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

- potential problematic adherence;
- Significant drug-drug interactions that might reduce either drug's plasma concentration

In addition, use caution in the case of a very high HIV viral load (>500,000 copies/mL) and/or low CD4 count (<200/mL) as outcome data is limited in these sub-groups.

The antiretroviral drugs in a 2DR should target a minimum of two different sites of HIV replication and should include a potent N(t)RTI and an integrase inhibitor. Most 2DRs that include a single NRTI have used lamivudine, because of its potency and relatively low toxicity compared with other NRTIs. The improved tolerability and potency of newer integrase inhibitors has made simplification to 2DR more attractive. Bictegravir only comes in a FDC with 2N(t)RTIs so the only single tablet FDC is dolutegravir plus lamivudine.

Dolutegravir plus lamivudine: initial and maintenance therapy

Dolutegravir plus lamivudine has proven to be an effective 2DR in treatment-naïve individuals, with 48-week week data from randomised controlled trials demonstrating virological equivalence, and 96-week data showing fewer drug-related renal and bone adverse effects for the 2DR, although the comparator regimen which included tenofovir DF had lipid profile advantages.⁸

A phase 3 study of maintenance of virological suppression in treatment-experienced adults with fixed-dose dolutegravir plus lamivudine versus a TAF-containing three-drug regimen demonstrated non-inferiority at 48 weeks and 96 weeks.^(9,10)

Boosted protease inhibitors plus lamivudine for initial and maintenance therapy

Darunavir/ritonavir plus lamivudine was non-inferior to darunavir/ritonavir plus TDF/FTC after 48 weeks in a randomised open label study in treatment naïve individuals.⁽¹¹⁾ Previous studies of boosted protease inhibitors plus lamivudine with or without another NRTI in treatment-naïve individuals showed virological equivalence but were either small studies or were impacted by the poor tolerability of lopinavir/ritonavir. In maintenance treatment, a number of studies using boosted protease inhibitors (atazanavir or darunavir) with lamivudine have met non-inferiority criteria without development of drug resistance.⁽¹²⁾

Nucleoside/nucleotide-sparing regimens

Recent maintenance studies using rilpivirine with either ritonavir-boosted darunavir, dolutegravir, or cabotegravir have had excellent results to date.

- Randomised controlled open-label trial data support the use of dolutegravir plus rilpivirine as maintenance therapy in patients on their first or second regimen and without a history of virological failure.⁽¹³⁾
- Several maintenance studies using cabotegravir, a structural analogue of dolutegravir, with rilpivirine or two NRTIs with either oral (LATTE study) or long-acting intramuscular dosing (LATTE-2), have shown virological equivalence.
- Fully powered phase 3 maintenance studies using long-acting cabotegravir plus rilpivirine every four weeks (ATLAS, FLAIR) and comparing 4 versus 8-weekly treatment intervals with long-acting cabotegravir plus rilpivirine (ATLAS-2M) have demonstrated efficacy and safety for the long-acting treatment with a virological failure rate of ~1% across studies.^(14 – 17)
- Virological suppression at week 48 was equivalent for ritonavir-boosted darunavir plus rilpivirine or 2 NRTIs in one small study.⁽¹⁸⁾

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Retention in Care

After the initial diagnosis of HIV infection and establishment of a care plan, ongoing regular engagement with HIV treatment services is known as “retention in care” and has been defined as having at least two monitoring visits with an HIV medical provider spaced at least three months apart within 1 year. Retention in care has been consistently shown to be an important factor influencing outcomes for HIV-infected individuals, including survival, suppression of HIV RNA levels, improved health outcomes, and lower risk of transmitting HIV.

Retention in care rates are higher for high-income compared with low- and middle-income nations, and for nations with universal healthcare. Retention in care in Australia is estimated to be relatively high by international standards. Using active follow-up of cases thought to be lost-to-follow-up, HIV treatment centres in Victoria were able to facilitate re-engagement in care and show that true rates of retention in care were higher than previously estimated.⁽¹⁹⁾

Factors that have been associated with poor retention in care in high-income countries include drug and alcohol use, mental illness, being from an ethnic minority group, younger age, health belief systems and social barriers to care.⁽²⁰⁾ Little specific data on factors associated with disengagement from care are available for Australia. A study of over 5,000 HIV-infected people attending six sites in Victoria found that disengagement with care was associated with being “well and busy”, transport and financial difficulties, psychological stressors or issues around acceptance of HIV diagnosis, active psychiatric illness, being from a non-English-speaking background and lack of access to Medicare services.⁽²¹⁾

In order to facilitate retention in care, it is important to identify risk factors for disengagement and provide appropriate support to mitigate their potential effect on engagement in care. Strategies include developing positive therapeutic relationships, HIV education, including addressing negative health beliefs and providing support for psychosocial issues that could impact on care. Active monitoring of retention in care known as “data to care” can assist with re-linking those who lapse from care.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

References

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Immune reconstitution inflammatory syndrome and other immune reconstitution disorders

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Last reviewed: July 2019

Introduction

The advent of antiretroviral therapy (ART) revolutionised the care of patients with human immunodeficiency virus (HIV) infection. However, from the late 1980s, when zidovudine monotherapy was introduced, through to the late 1990s, when combination ART became standard of care, clinicians began to recognise that some patients experienced an exacerbation of a previously treated opportunistic infection or initial presentation of a new infection despite increased CD4+ T cell counts after commencing ART.^(1, 2) These disease episodes were characterised by exaggerated and/or atypical inflammation and involved a wide variety of opportunistic pathogens, including non-tuberculous mycobacteria (NTM), *Mycobacterium tuberculosis*, Pneumocystis, Cryptococcus, varicella zoster virus (VZV), John Cunningham (JC) virus and cytomegalovirus (CMV). Notably, *Mycobacterium avium* complex (MAC) disease was associated with the restoration of immune responses against mycobacteria. These conditions were therefore referred to as immune restoration disease to differentiate them from immunodeficiency disease, though the term immune reconstitution inflammatory syndrome (IRIS) is now more commonly used.⁽³⁾ IRIS events occur in patients who are very immunodeficient when ART is commenced, mostly in the first 6 months of therapy but may also occur in the setting of ART intensification. Importantly, IRIS is not limited to individuals with HIV infection but also occurs in non-HIV settings, particularly solid organ transplant and haematopoietic stem cell transplant recipients in the setting of immune recovery after withdrawal of immunosuppressant drug therapy,^(4, 5) and in multiple sclerosis patients who experience progressive multifocal leucoencephalopathy (PML) during natalizumab therapy and an exacerbation of PML with inflammatory features after natalizumab withdrawal.⁽⁶⁾

Terminology and classification

An IRIS is best described in relation to the type of provoking pathogen e.g. tuberculosis-associated IRIS (TB-IRIS) or cryptococcosis-associated IRIS (C-IRIS) because the immunopathogenesis may differ for different types of pathogen. Further classification is based on the body locality or organ involved, e.g. cryptococcal meningitis IRIS (CM-IRIS), or MAC-IRIS lymphadenitis. The temporal relationship between recognition of a pathogen causing an IRIS and ART commencement is also important. Unmasking IRIS is the term used when ART unmasks a previously unrecognised infection whereas paradoxical IRIS is the term used when a previously treated opportunistic infection flares post-ART. For example, unmasking TB-IRIS is diagnosed when an ART-naïve patient with no recognisable features of *Mycobacterium tuberculosis* infection, commences ART and soon after develops tuberculosis (TB). The term 'ART-associated TB' is also sometimes used if the TB is not characterised by unusual inflammation. In contrast, paradoxical CM-IRIS is said to occur when an ART-naïve HIV patient presents with cryptococcal meningitis (CM), undergoes and displays improvement on CM treatment, then starts ART, after which an exacerbation of CM develops. This detailed classification system helps the clinician predict outcomes and produce a management algorithm. Furthermore, it assists in research on the immunopathogenesis of the various forms of IRIS and the development of strategies for prevention and treatment.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

IRIS definitions and diagnosis

There are no accepted diagnostic tests for an IRIS. Diagnosis of an IRIS is therefore made clinically on the basis of the temporal relationship between starting ART and disease onset, disease manifestations including exclusion of alternative diagnoses, a fall in plasma HIV viral load (indicating that ART is effective) and direct or indirect evidence of the restoration of cellular immune responses against the triggering pathogen. Diagnostic criteria for an IRIS have been proposed (7-9) but with low consensus, in part because studies have been undertaken in different geographical settings. On the other hand, consensus clinical case definitions for TB-IRIS (10) and C-IRIS (11) have been reported. Clinical case definitions for CMV immune recovery retinitis have also been proposed.(12)

Despite uncertainty about diagnostic criteria for an IRIS, it is possible to provide guiding principles that are, at least, applicable for diagnosing an IRIS in Australasia. Thus, a diagnosis of an IRIS is justifiable when there is an initial presentation or exacerbation of disease associated with an HIV-related infection or cancer following commencement of effective ART, especially when disease manifestations are exaggerated and/or atypical, with exclusion of recurrent or new infections and drug hypersensitivity reactions, associated with a decline in plasma HIV RNA level by >1log10 copies/mL. Direct or indirect evidence of the restoration of a cellular immune response against the triggering pathogen provides additional evidence and is particularly important when information about change in HIV viral load is not available. This evidence includes (a) an atypical inflammatory response in affected tissues, such as granulomas in the context of severe CD4+ T cell depletion, tissue necrosis and suppuration, and CD8+ T cell infiltrates in PML-IRIS lesions of the brain; (b) Spontaneous resolution of disease without specific antimicrobial therapy or tumour chemotherapy with continuation of ART; (c) increase in an immune response specific to the relevant pathogen, eg. delayed-type hypersensitivity skin test response to mycobacterial antigens; (d) increased blood CD4+ T cell count after ART. However, while an increased blood CD4+ T cell count is commonly observed, it is not a prerequisite for a diagnosis of an IRIS.

The major differential diagnosis is relapse of the infection that triggered the IRIS or occurrence of another infection. Clinicians should think broadly for other causes of presenting symptoms and signs. Inflammation that arises from an IRIS is not uncommonly misinterpreted as an opportunistic infection, but the process is one of restoration, rather than loss of pathogen-specific immune responses.(13) Differentiation of these conditions is essential as clinical management differs. The validity of an IRIS diagnosis may vary both in clinical practice and research studies. In research studies, an IRIS is often classified as definite, probable or possible – this approach may also be helpful in routine clinical management.

Immunopathogenesis of an IRIS

An IRIS is an undesirable outcome of restoring immune responses against an active (sometimes unrecognised) HIV-related infection or antigens of non-viable pathogens remaining after treatment of the infection.(7) The strongest risk factors for an IRIS are a low CD4+ T cell count (usually <50/mL) and a high pathogen load.(3, 7, 13) The latter is a consequence of decreased pathogen-specific immune responses associated with severe CD4+ T cell deficiency as well as depletion and/or dysfunction of other immune cells, which include B cells in the case of C-IRIS.(14) The disease-causing inflammatory response in an IRIS is largely determined by the provoking pathogen(3) with mycobacterial and fungal IRIS being associated with granulomatous and/or suppurative inflammation, while tissue inflammation in an IRIS associated with infections by viruses, such as herpes simplex virus (HSV) or JC virus, is usually characterised by CD8+ T-cell infiltration.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

The majority of IRIS research has been undertaken on mycobacterial and cryptococcal IRIS. TB-IRIS and MAC-IRIS are associated with an increase in the frequency of pathogen-specific CD4+ T cells producing multiple cytokines (interferon-gamma, tumour necrosis factor and interleukin-2) and with cytotoxic activity (15, 16) whereas an increase in pathogen-specific T cell responses has not been demonstrated in C-IRIS (17), though the latter was examined using whole blood interferon gamma release assays. There is also convincing evidence that activation of monocytes and neutrophils contributes to the immunopathology of TB-IRIS, particularly through activation of monocyte inflammasome pathways, (18-20) MAC-IRIS, (16) and C-IRIS. (22, 23) It therefore appears that an IRIS associated with mycobacterial and cryptococcal infections reflects the restoration of diverse cellular immune responses with pro-inflammatory activity against pathogens, which generates an exaggerated inflammatory response. Further information about the immunopathogenesis of the various types of IRIS is provided elsewhere. (24, 25)

Clinical presentation of an IRIS

An IRIS mostly occurs between 2 weeks and 3 months after ART commencement or ART intensification but may occur earlier (within days) and as late as a year after treatment. Temporal onset of an IRIS is particularly difficult to attribute in patients with erratic ART adherence. Typically, IRIS patients had a very low CD4+ T cell count when ART was commenced and present with fever and exaggerated or atypical clinical manifestations of an HIV-related infection or cancer. Practically, any chronic viral, mycobacterial, fungal or protozoan infection that is usually controlled by cellular immune responses may be associated with an IRIS (Table 1). Further information on clinical characteristics of different types of IRIS is available elsewhere. (26)

Table 1. The most common types of immune reconstitution inflammatory syndrome that may occur in very immunodeficient HIV patients after commencing ART1

Pathogens associated with an IRIS	Clinical characteristics	Common abbreviations
Mycobacteria		
<i>Mycobacterium avium complex</i>	Initial presentation or exacerbation of MAC disease, eg. fever, lymphadenitis	MAC-IRIS
<i>Mycobacterium tuberculosis</i>	Initial presentation or exacerbation of TB, eg. fever, lymphadenitis, pneumonitis, pleural or pericardial effusions, meningoencephalitis	TB-IRIS or TBM-IRIS when meningitis is the only clinical manifestation
Bacille Calmette-Guerin	Regional lymphadenitis	BCG-IRIS
Fungi		
<i>Cryptococcus neoformans</i>	Initial presentation or exacerbation of cryptococcal meningoencephalitis	C-IRIS or CM-IRIS when meningitis is the only clinical manifestation
<i>Pneumocystis jirovecii</i>	Exacerbation of pneumonitis	PJP-IRIS
Viruses		
Cytomegalovirus	CMV retinitis presenting after commencement of ART	CMV immune recovery retinitis
	Uveitis after previously treated CMV retinitis	IRU (immune recovery uveitis)
Kaposi's sarcoma-associated herpesvirus	Initial presentation or exacerbation of KS	KS-IRIS

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Varicella zoster virus	Dermatomal or multidermatomal zoster	
	Rarely, myelitis or encephalitis	
Herpes simplex virus	Genital or oral herpes with atypical inflammation	
	Rarely, myelitis or encephalitis	
JC virus	Initial presentation or exacerbation of PML with inflammatory characteristics	PML-IRIS
Hepatitis B virus	Hepatitis flare	HBV-IRIS
Hepatitis C virus	Hepatitis flare	HCV-IRIS
Protozoa		
<i>Toxoplasma gondii</i>	Initial presentation or exacerbation of Toxoplasma encephalitis	TE-IRIS
Uncertain pathogens		
	Lymphoma presentation after commencing ART	

1. Many other pathogens have also been associated with the development of an IRIS.

General approach to the management of an IRIS

For patients with a suspected paradoxical IRIS, the initial consideration is exclusion of a recurrence of the associated infection or development of a new infection. For example, when suspecting paradoxical TB-IRIS, considerations should include non-adherence to TB medications, infection with drug-resistant mycobacteria, new community-acquired pneumonia, PJP and viral infections. Investigations should include sputum microscopy and culture for bacterial and mycobacterial infection, chest X-ray or CT scan of chest or both. Similarly, a patient being considered for paradoxical CM-IRIS, should have a CT scan of brain and lumbar puncture to measure the opening pressure and obtain CSF to determine cell counts and to culture for bacteria, mycobacteria and fungi. When evaluating cultures, it is important to note that while cultures are often negative in an IRIS (in keeping with the concept that non-viable organisms may be antigenic and provoke an immune response), the presence of a positive culture does not exclude an IRIS, as viable pathogens are clearly also antigenic.

After the exclusion of alternative diagnoses, symptomatic management of an IRIS is usually sufficient. For example, therapeutic lumbar punctures and non-steroidal anti-inflammatory drugs often relieve symptoms in paradoxical CM-IRIS. Escalation of antimicrobial therapy is only necessary when there is a clear microbiological relapse of the infection. Importantly, ART should not be ceased unless the patient's condition becomes critical. While many clinicians consider the use of corticosteroid therapy for an IRIS, the evidence for use of this therapy is not strong and it should only be considered in cases of severe symptomatic IRIS refractory to simple measures. A randomised placebo-controlled trial in South Africa, used 4 weeks of prednisolone (1.5 mg then 0.75 mg/kg/day) in patients with paradoxical pulmonary TB-IRIS,⁽²⁷⁾ and showed reduction in a combined endpoint of duration of hospitalisation and number of procedures, and improvement in symptoms and wellbeing but increased concurrent infections and glucocorticoid reactions. In PML-IRIS, corticosteroid therapy has been reported to be effective in individual cases⁽²⁸⁾ but overall, there is insufficient evidence to recommend routine use. Results of randomised controlled trials of corticosteroid therapy for the treatment of PML-IRIS are needed.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Some IRIS manifestations notoriously recur in the setting of decreased corticosteroid dosing, resulting in extremely long durations of therapy and its accompanying risks, including immunosuppression. In this setting, blockade of tumour necrosis factor (TNF) activity through the use of monoclonal antibodies to TNF has been shown to be effective in MAC- and TB-IRIS, though only in case reports (29-31). The CCR5 inhibitor Maraviroc has been advocated as adjunctive ART in patients with severe PML-IRIS on the basis that it will decrease the migration of pathogen-specific memory T cells (which express CXCR5) into the brain, but efficacy has only been demonstrated in a case study (32).

Surgical measures are occasionally necessary, such as drainage or excision of large lymph nodes or abscesses in mycobacterial-IRIS.

Prevention of an IRIS

Given that severe CD4+ T cell deficiency when ART is commenced is a risk factor for an IRIS, prevention of CD4+ T cell depletion through early diagnosis and treatment of HIV infection regardless of CD4+ T cell count, as supported by the findings of the START study, (33) is the most effective measure for reducing the risk of developing an IRIS. However, 'late presenters' with advanced immunodeficiency continue to present and they must be assessed carefully for HIV-related infections that might trigger an IRIS when ART is commenced. Those patients without obvious signs or symptoms of an HIV-related infection should be screened for a subclinical infection. At a minimum, a chest x-ray and assay of serum for cryptococcal antigen, HBV surface antigen and core antibodies, and HCV antibodies should be performed.

Decisions about the optimal timing of ART commencement in patients with an established HIV-related infection should take into consideration the CD4+ T cell count and the site of infection. In general, commencement of ART early in the course of therapy for the infection is recommended, particularly when the CD4+ T cell count is <50/mL (34, 35). Several studies examining the timing of ART commencement in the setting of pulmonary TB have also produced results favouring early commencement of ART (36 – 39).

Special consideration must be given to the timing of ART commencement in patients with an opportunistic infection of the CNS because inflammation resulting from an IRIS in this site carries a particularly high risk of morbidity and mortality. Thus, deferment of ART is recommended in HIV patients with TB meningitis (40) and in the setting of CM, randomised studies suggest ART should be deferred until 5-6 weeks post CM diagnosis. (41 – 43) In PML, deferment of ART is usually not an issue because it is the only therapy that may be effective for this condition. There is insufficient evidence to make recommendations about the optimal timing of ART commencement in patients with Toxoplasma encephalitis.

The ART regimen used is not a consideration in preventing the development of an IRIS, though use of an ART regimen that includes nucleos(t)ide analogues with activity against both HIV and HBV in patients with HIV/ HBV co-infection will minimise the risk of a hepatitis flare (HBV-IRIS). Integrase strand inhibitors have been reported to be associated with an increased risk of developing an IRIS in observational studies (44, 45) but this was not confirmed in a randomised controlled trial. (46) Inclusion of maraviroc in the ART regimen of patients commencing ART with a CD4+ T cell count of <100/μL was explored as a means of preventing an IRIS in the CADIRIS study (47) but was ineffective.

Prednisolone therapy during the first 4 weeks of ART decreases the risk of TB-IRIS in HIV patients with CD4+ T cell counts <100/mL. (48)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Autoimmune disease and immune-mediated inflammatory disease in patients receiving ART

Autoimmune diseases and immune-mediated inflammatory diseases may also be encountered in patients receiving ART⁽⁴⁹⁾ and many appear to be immune reconstitution disorders. Pathogenic mechanisms, however, are distinct from those in an IRIS associated with HIV-related infections or cancers. Psoriasis, sarcoidosis, rheumatoid arthritis, ankylosing spondyloarthritis, Graves' disease, autoimmune hemolytic anemia, immune thrombocytopenia and inflammatory bowel disease are most common whereas systemic lupus erythematosus and multiple sclerosis are rarely encountered. Graves' disease is encountered most often in patients who commence ART at very low CD4+ T cell counts and, in contrast to an IRIS, presents at a median time of 21 months after starting ART.⁽¹³⁾ It appears to be a consequence of an acquired disorder of central immune tolerance.⁽⁵⁰⁾ Sarcoidosis may present in HIV patients not receiving ART but is much more common after commencement of ART. It is also more common in patients who have received interferon-alpha or interleukin-2 therapy. Taken together, these characteristics suggest that sarcoidosis in HIV patients is the result of an acquired disorder of immune regulation that leads to a granulomatous inflammatory response against unknown antigens. From a clinical perspective, it is important to differentiate sarcoidosis from an IRIS associated with infection by mycobacteria or fungi, which may also present with granulomatous tissue inflammation. ⁽¹³⁾ Sarcoidosis in HIV patients may affect various body sites including lungs, lymph nodes and skin.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Drug-drug interactions in patients with HIV infection

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Last reviewed: November 2019

Overview

Drug-drug interactions between antiretroviral (ARV) drugs and co-prescribed medication are common and may lead to an increase or decrease in exposure to either drug. These alterations in exposure may result in unexpected change/s in therapeutic response/s or increase the risk of adverse effects/toxicity. Drug-drug interactions may be beneficial, managed by dose adjustment, or may produce toxicity and thus be contraindicated. When prescribing a new drug or switching drug/s in an ARV regimen, it is important to consider the potential for interactions that may affect the ARV drugs *and* those that may affect other medications.

To prevent or minimize potential drug interactions, regular review of all medications, including alternative therapies and over-the-counter preparations, is essential. An easy to use on-line resource for checking drug interaction potential is the University of Liverpool's HIV drug interaction checker tool (www.hiv-interactions.org). There are also helpful interaction tables available in the US Department of Health and Human Services Guidelines see: <https://clinicalinfo.hiv.gov/en/guidelines>

However, sometimes it can be difficult to predict the magnitude and clinical significance of interactions when several drugs with competing metabolic pathways are co-prescribed. Referral to a specialist HIV pharmacist can assist to thoroughly review the medication list and minimize potential problems.

When co-prescription is unavoidable, monitor the patient carefully for loss of efficacy and/or toxicity of ARV drugs and other medications.

Types of drug-drug interactions

Drug-drug interactions can be either pharmacokinetic or pharmacodynamic in nature. Pharmacokinetic interactions are the primary concern with ARV drugs.

Pharmacokinetic interactions occur when one drug alters the absorption, distribution, metabolism or excretion of another drug, possibly increasing or decreasing its plasma concentration. For ARV drugs the interaction types of concern are absorption, metabolism and excretion.

Interactions affecting drug absorption

Drug absorption may be altered by a change in gastric acidity, by chelation, or by alterations in intestinal membrane transport or intestinal cytochrome P450 enzyme activity. Examples are:

- An increase in gastric pH due to proton pump inhibitors, H₂ antagonists or antacids can reduce the absorption of acid-sensitive drugs such as atazanavir or rilpivirine.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

- Polyvalent cations (e.g. magnesium, zinc, calcium, iron) in antacids, vitamin/mineral supplements or iron preparations can bind to integrase inhibitors and reduce their absorption.
- Induction of efflux transporters such as P-glycoprotein, and/or the cytochrome P450 3A4 enzyme (CYP3A4) (e.g. by rifampicin) in the intestinal wall may significantly decrease the absorption of a number of drugs, including some ARVs. In contrast, inhibition of P-glycoprotein (e.g. by ritonavir) and/or CYP3A4 (e.g. by ritonavir) may increase the absorption of some drugs including several ARV drugs.

Interactions affecting drug metabolism

Drug metabolism occurs through enzyme systems located primarily in the liver. The enzymes most commonly associated with drug interactions are those of the cytochrome P450 superfamily and the uridine diphosphate (UDP)-glucuronosyltransferase (UGT) enzymes which are responsible for glucuronidation.

The cytochrome P450 enzyme system is the major mediator of drug metabolism, with CYP3A4 and CYP2D6 enzymes being the most active. Many ARV drugs are metabolised by (i.e. are substrates for) cytochrome P450 enzymes and may also independently induce and/or inhibit a number of other CYPs to varying degrees. The strength of the enzyme inhibition or induction is important with strong inducers and inhibitors more likely to produce a greater clinical effect. Induction of CYP450 enzymes can result in lower exposure of the affected drug, potentially reducing its efficacy, for example, efavirenz can reduce apixaban levels (by CYP3A4 induction). Inhibition of CYP450 enzymes can increase the exposure of the affected drug, potentially increasing the risk of toxicity, for example, protease inhibitors increase midazolam exposure (by CYP3A4 inhibition). When substrates of the same CYP450 enzyme are co-administered, their rates of metabolism can change. This may alter the plasma concentration/s of the drug/s and increase the risk of toxicity, for example, caution is advised when prescribing colchicine and simvastatin (both CYP3A4 substrates), as concomitant use may result in myopathy and rhabdomyolysis.

UGT enzymes metabolise a small number of drugs with UGT1A1 being the most active enzyme. UGT enzymes can be induced or inhibited. Ritonavir induces glucuronidation, (as do some other drugs e.g. rifampicin) and may reduce levels of other drugs (e.g. thyroxine, lamotrigine). Integrase inhibitors are substrates of UGT1A1 and dose adjustment is required when an integrase inhibitor is co-prescribed with rifampicin.

Pharmacokinetic enhancers:

Ritonavir and cobicistat are both potent inhibitors of CYP3A4; when either drug is co-administered with an ARV agent that is metabolised by CYP3A4, such as a protease inhibitor or elvitegravir, the exposure to that ARV drug is increased. This effect is commonly referred to as "boosting".

It is important to note that cobicistat and ritonavir are not selective in their "boosting" action and have different drug-drug interaction effects. Ritonavir has a much more complex interaction profile due to its effects on other CYP450 enzymes such as CYP2D6 (inhibition), CYP2C9 and CYP2C19 (induction), and UGT1A1 (induction) as well as being an inhibitor of various membrane transporters (e.g. P-glycoprotein). Cobicistat also inhibits CYP2D6 plus several membrane transporters including P-glycoprotein. Therefore, when checking for potential drug interactions with pharmacokinetically enhanced drugs it is important to consider the effects of both the drug and the enhancer.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Interactions affecting drug excretion

Transport proteins in the liver, biliary tree and kidney function in drug elimination. Drug transporter interactions may alter transport activity at these sites potentially affecting drug exposure by increasing or decreasing the rate of elimination of the affected drug. Knowledge and understanding of these drug transporter interactions is evolving. Drugs including a number of ARV drugs may be enzyme inducers, enzyme inhibitors, and/or substrates of drug transporters. For example, dolutegravir inhibits the organic cation transporter (OCT-2) in the kidney, so can decrease the clearance of metformin.

Important drug-drug interactions to consider

In general, watch out for the potent enzyme inducers such as rifampicin, rifabutin, phenytoin and carbamazepine

Specific interactions by ARV drug class to be aware of and their management, where appropriate, include:

INSTIs

- Dolutegravir with metformin: adjust metformin dose.
- All INSTIs with cationic chelation (e.g. iron, magnesium, calcium, zinc), including antacids containing these cations: separate drug administration by 2 hours.

NNRTIs

- Rilpivirine with antacids, proton pump inhibitors and H2 antagonists.
- Nevirapine, efavirenz and etravirine with midazolam, direct acting anticoagulants, warfarin, antiplatelet agents, some hormonal products and methadone.

PIs and low-dose ritonavir or cobicistat

- All PIs (to a varying degree) with midazolam, corticosteroids (including by inhalation), some statins, direct acting anticoagulants, warfarin, antiplatelet agents, sildenafil (and other phosphodiesterase inhibitors), some hormonal and chemotherapeutic agents, amphetamines.
- Atazanavir with antacids, proton pump inhibitors, H2 antagonists and some azoles.
- Many counter-intuitive interactions are possible with low dose ritonavir or cobicistat so *best to check every time!*

Table 1 presents an overview of the ARV drugs which may affect/be affected by alterations in these PK mechanisms.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Table 1. Mechanisms of antiretroviral-associated drug interactions

Adapted from DHHS guidelines¹

Drug by drug class	Pharmacokinetic interaction type				
	Absorption	Metabolism			Other mechanisms
		Substrate	Inducer	Inhibitor	
Integrase inhibitors					
Bictegravir	Chelation decreases absorption	CYP3A4 UGT1A1	–	–	Inhibits transporters OCT2, MATE
Dolutegravir	Chelation decreases absorption	UGT1A1 CYP3A4 (minor)	–	–	Inhibits transporters OCT2, MATE
Raltegravir	Chelation decreases absorption	UGT1A1	–	–	–
Elvitegravir	Chelation decreases absorption	CYP3A4	CYP2C9	–	–
NNRTIs					
Doravirine*	P-glycoprotein substrate	CYP3A4	–	–	–
Efavirenz	–	CYP2B6 (major), 3A4	CYP3A4, 2B6	CYP3A4, 2C19, 2C9	–
Etravirine	Inhibits P-glycoprotein	CYP3A4, 2C9, 2C19	CYP3A4	CYP2C9, 2C19	–
Nevirapine	–	CYP3A4, 2B6	CYP3A4, 2B6	–	–
Rilpivirine	Decreased by gastric acid lowering drugs	CYP3A4	–	–	Inhibits transporter OCT2
Pharmacokinetic enhancers					
Cobicistat	Inhibits P-glycoprotein	CYP3A4, 2D6 (minor)	–	CYP3A4, 2D6	Inhibits OAT1B1, OAT1B3, MATE, BRCP
Ritonavir	Substrate and inhibitor of P-glycoprotein	CYP3A4, 2D6 (minor)	UGT1A1, CYP1A2, 2B6, 2C8, 2C9, 2C19	CYP3A4, 2D6,2C9,2C19, 2A6, 1A2, 2E1	Inhibits OAT1B1, OAT1B3, MATE, BRCP
Protease Inhibitors					
Atazanavir	Decreased by gastric acid lowering drugs P-glycoprotein substrate, inhibitor and inducer	CYP3A4	–	CYP3A4, UGT1A1	Inhibits OATP1B1
Darunavir	P-glycoprotein substrate	CYP3A4	CYP2C9	CYP3A4	Inhibits transporter OATP
Fosamprenavir	P-glycoprotein substrate & inhibitor	CYP3A4	3A4 (weak)	CYP3A4	–

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Drug by drug class	Pharmacokinetic interaction type				
	Absorption	Metabolism			Other mechanisms
		Substrate	Inducer	Inhibitor	
Lopinavir	P-glycoprotein substrate	CYP3A4	–	CYP3A4	Inhibits transporter OATP
Saquinavir	P-glycoprotein substrate & inhibitor	CYP3A4	–	CYP3A4	Inhibits transporter OATP
Tipranavir	P-glycoprotein substrate & inducer	CYP3A4	CYP3A4, 1A2, 2C19	CYP2D6	Inhibits transporter OATP
NRTIs					
Abacavir	–	UGT1A1	–	–	Alcohol dehydrogenase substrate
Emtricitabine	–	–	–	–	–
Lamivudine	–	–	–	–	–
Tenofovir DF	P-glycoprotein substrate	–	–	–	Competition of active renal tubular secretion
Tenofovir AF	P-glycoprotein substrate	–	–	–	OATP substrate
Zidovudine	–	UGT enzymes	–	–	–
Entry inhibitors					
Maraviroc	P-glycoprotein substrate	CYP3A4	–	–	–
Enfuvirtide	–	–	–	–	–

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‘–’ indicates no clinically relevant interactions via these mechanisms

* Drug not yet commercially available in australia

Abbreviations: BCRP, breast cancer resistance protein; CYP, cytochrome P450; MATE, multidrug and toxin extrusion protein; OAT, organic anion transporter; OATP, organic-anion-transporting polypeptide; OCT, organic cation transporter; UGT, uridine diphosphate (UDP)-glucuronosyltransferase

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Adverse reactions to antiretroviral and other drugs in people with HIV infection

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Last Reviewed: January 2021

Introduction

Adverse drug reactions (ADRs) caused by antiretroviral drugs are an increasingly uncommon complication of contemporary antiretroviral therapy (ART) but are occasionally encountered in clinical practice. Type A ADRs, which are predictable dose-dependent non-immune-mediated reactions (e.g. nausea, vomiting, headache), and drug-drug interactions are predictable and usually manageable. Type B ADRs, which are typically immune-mediated (IgE antibodies or T-cells) hypersensitivity reactions, are less often recognized events that in the setting of an isolated mild to moderate skin rash may be managed with continued treatment (e.g. efavirenz) but in the severest of cases necessitate permanent drug discontinuation and avoidance of all structurally related drugs.^(1,2)

Modern combination ART for HIV infection, in the single tablet regimens that are commonly used, is well tolerated.⁽³⁾ However, drug hypersensitivity reactions may be encountered because people with HIV infection are more susceptible to this problem than the general population, particularly those with uncontrolled HIV viremia.⁽⁴⁻⁶⁾ Despite ADRs caused by antiretroviral drugs being encountered in clinical practice, there is a poor understanding of the mechanisms underlying the increased incidence of these ADRs and the prevalence of immunological phenotypes that increase the risk of an ADR. Data has primarily been extracted from clinical trial data with "real world" post marketing data less frequently reported.⁽⁷⁾ Determining the true incidence of hypersensitivity reactions to individual antiretroviral drugs is difficult, due to the routine use of combination ART (dual or triple) and the concomitant use of other antimicrobial drugs for prophylaxis or treatment of opportunistic infections in some patients. We will discuss both immune- and non-immune-mediated ADRs associated with commonly employed antiretroviral drugs, as well as immune mediated ADRs to drugs that might be taken concomitantly with antiretroviral drugs.

Non-immune mediated adverse drug reactions

Type A ADRs are most commonly encountered with nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), with hepatic and renal impairment the most commonly reported reactions.⁽⁸⁾ In the modern era, most cases of renal impairment are attributable to the use of tenofovir disoproxil fumarate (TDF). In contrast, gastrointestinal symptoms occur most often in the setting of protease inhibitor (PI) utilization.⁽⁹⁾

Nucleoside/nucleotide reverse-transcriptase inhibitors

Earlier NRTIs were associated with significant toxicities. Zidovudine use was associated with myopathy and bone marrow suppression (especially anaemia)⁽¹⁰⁾, while stavudine use was associated with lactic acidosis and lipodystrophy, due to inhibition of mitochondrial DNA synthesis, which was most prominent in patients receiving stavudine.⁽¹¹⁾ These drugs are therefore rarely used these days. However, lamivudine

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

remains a commonly employed antiretroviral drug with very few significant adverse events reported.

(12) Emtricitabine also demonstrates a good safety profile, with infrequent reporting of adverse events, the most common being skin discoloration and cough.(13,14) TDF use has been associated with renal toxicity due to proximal tubular damage that may be severe enough to cause Fanconi's syndrome (glucosuria, aminoaciduria, tubular proteinuria and proximal renal tubular acidosis) and, on rare occasions, osteomalacia with decreased bone density (<0.1%).(15) The newer formulation of tenofovir (tenofovir alafenamide fumarate [TAF]) has demonstrated a much lower rate of proteinuria and serum creatinine increase compared with TDF.(16,17) Type A ADRs are infrequent with abacavir use but this drug may cause a well-described immune-mediated hypersensitivity reaction (see later, under immune-mediated drug hypersensitivity reactions).(18) All NRTIs carry an FDA Black box warning for lactic acidosis/hepatic steatosis.

Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

Efavirenz is generally well-tolerated but occasionally central nervous system (CNS) symptoms, including psychiatric symptoms, have led to a significant number of drug discontinuations.(19) Rilpivirine has a similar profile to efavirenz with less marked CNS disturbance reported.(20) Etravirine is extremely well-tolerated. Non-immune mediated reactions to nevirapine have primarily been reported as liver function derangement, nausea, vomiting and transient sedation, with some less frequent reports of CNS efavirenz-like symptoms.(21,22)

Protease inhibitors and inhibitors of CYP3A

A range of symptoms have been reported in the post-marketing phase for atazanavir including oedema, heart block, pancreatitis, liver function derangement, biliary pathology, diabetes, renal calculi and pruritis.(23) The most recognized side effect of atazanavir is hyperbilirubinemia, which is reversible upon cessation.(24) Darunavir, the most recently introduced PI, is generally well-tolerated though gastrointestinal upset, headache and increased triglyceride and lipid abnormalities may occur.(25) Many adverse drug reactions associated with protease inhibitors relate to their inhibition of cytochrome P450 enzymes and drug transporters. Cobicistat is an inhibitor of CYP3A without any antiretroviral activity that is co-formulated with many protease inhibitors. Similar to cobicistat, ritonavir is a potent CYP3A inhibitor associated with many drug interactions which, unlike cobicistat, also induces CYP1A2, CYP2B6, CYP2C9, CYP2C19 and UGT1.(26)

Integrase inhibitors

Integrase inhibitors are usually well-tolerated, with rhabdomyolysis and/or an increase in serum creatinine kinase level the most commonly reported adverse effects, with an unclear relationship to the drug.(27) Reports of insomnia, dizziness, headache and weight gain are occurring more frequently with everyday use of dolutegravir, most often in women and people over the age of 60.(28) However, patients receiving dolutegravir, raltegravir or elvitegravir/cobicistat did not show significant differences in the rate of discontinuation because of any toxicity.(29,30)

Immune-mediated drug hypersensitivity reactions

Immune-mediated drug hypersensitivity reactions are most frequently encountered with nevirapine, efavirenz (both NNRTIs), darunavir (a PI) and abacavir (a NRTI). Despite immune-mediated hypersensitivity reactions occurring at a higher rate in HIV-infected patients than in the general population, pathogenic mechanisms remain largely unknown, though are postulated to result from the interaction of HIV-related, patient (genetic) and drug factors. Of these, genetic factors have most clearly been demonstrated for abacavir and nevirapine. Abacavir hypersensitivity syndrome is now rarely seen due to widespread HLA-B*57:01 screening;

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

however, it represented a distinct clinical entity without another drug correlate. For antiretroviral drugs other than abacavir, immune-mediated drug hypersensitivity reactions predominantly present with a delayed maculopapular exanthema (MPE), though greater severity systemic drug hypersensitivity syndromes, such as **Drug Rash** with Eosinophilia and Systemic Symptoms (DRESS), Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) may occur.

The most extensively described drug hypersensitivity reaction in HIV patients is the abacavir hypersensitivity syndrome, which was initially identified in the pre-marketing phase of abacavir development. It was observed most frequently in people of European ancestry and subsequently shown to be strongly associated with carriage of HLA-B*57:01.(31) Rare reports of severe cutaneous adverse drug reactions (i.e. DRESS) have also been reported with raltegravir (an integrase strand inhibitor)(32-35) and some other antiretrovirals.

Antiretroviral drugs that cause a severe cutaneous adverse drug reaction (SCAR) in HIV patients may also do so if given to non-HIV-infected persons, though less frequently than in HIV patients. For nevirapine, severe immunologically-mediated reactions were seen in non-HIV-infected individuals given this drug as post-exposure prophylaxis for HIV infection.(36) In view of this and the correlation of nevirapine-associated SCAR and hepatitis with high CD4+ T-cell counts, its use was subsequently avoided in non-HIV-infected individuals, as well as in HIV-infected individuals with CD4+ T cell counts >400/mL.

Mild-moderate delayed drug hypersensitivity reactions

Cutaneous adverse drug reactions resulting in a MPE are reported to be 100 times higher in HIV-infected people than in the general population.(37) MPE, typically presenting as a delayed onset benign rash between several days and 8 weeks after exposure to the drug, or as a skin rash occurring or intensifying greater than 6 hours from dosing, are not infrequent when commencing combination ART.(38) Drug causality may be difficult to ascertain when antiretroviral drugs and other medication are used in combination. In the absence of severe features (e.g. persistent fever, blistering, mucosal involvement, derangement of internal organ function [liver, kidney]), or moderate to severe rash covering >50% of body surface area (BSA), therapy may be continued with close observation. Efavirenz most commonly induces an MPE and can be apparent in a photosensitivity distribution, showing annular erythema without severe features.(39) This typically does not progress to a SCAR and can occur in 10% or more of individuals and typically treatment can continue uninterrupted with symptomatic therapy as necessary.

Non-antiretroviral drug hypersensitivity reactions in people with HIV infection

It is important to note that there is an increased risk of drug hypersensitivity reactions with drugs that may be used concomitantly with antiretroviral drugs in people with HIV infection, particularly trimethoprim-sulfamethoxazole (TMP-SMX).(40) The mechanism for this is still unknown; however, the reactions to TMP-SMX that occur early in HIV therapy are frequently not durable and are amenable to either direct oral provocation(41,42) or desensitization.(43-47) Although some reports raised concerns about cross-reactivity between TMP-SMX and darunavir, due to the sulphonamide moiety shared between both drugs, this has proven to be unimportant. The licensing trials for darunavir in fact did not exclude individuals with a history of sulfa antimicrobial allergy.(48) Cross-reactivity between TMP-SMX and dapsone has also been reported(49) with early reports suggesting an incidence of up to 40%.(50) However, true immune mediated cross-reactivity is rare when non-immune mediated reactions to dapsone are excluded(51) Dapsone should not be avoided in patients with mild-moderate delayed hypersensitivities to antimicrobial sulfonamides.(41, 52-53) An approach to sulfa antibiotic allergy in people with HIV infection is provided in **Figure 1**.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Penicillin allergy is also reported in people with HIV infection and this has implications for the treatment of infections by commonly encountered pathogens, including *Treponema pallidum* (syphilis), *Streptococcus pneumoniae* and staphylococci, where the preferred therapy is benzathine penicillin, benzylpenicillin and semi-synthetic penicillins, respectively. However, more than 85% of people reporting a penicillin allergy are negative on formal testing(54) and, therefore, active “delabelling” of patients at HIV diagnosis is likely to be beneficial for treatment of sexually transmissible infections and common community-acquired infections that might occur in the future.

The most commonly encountered cutaneous adverse drug reactions requiring treatment or hospitalization are noted below (adapted from Olteanu C et al (55)):

- Efavirenz
 - Phenotypes: MPE, SJS, TEN, DRESS, annular erythema and photoallergic reactions, drug induced liver disease (DILI)
 - Incidence: MPE (up to 20%), SJS/TEN: 0.1%
- Concurrent anti-tuberculosis drugs
 - Phenotypes: MPE, DRESS, SJS, TEN, fixed drug eruption (FDE), lichenoid reactions, DILI, drug induced kidney disease (DIKI)
 - Incidence: 5-20%
- Trimethoprim-sulfamethoxazole
 - Phenotypes: MPE, SJS, TEN, DRESS, FDE, acute generalized exanthematous pustulosis (AGEP), urticaria (delayed or immediate), cytopenias and DILI
 - Incidence: MPE (up to 30-40%), SJS/TEN 8%, DRESS 6%
- Fluconazole
 - Phenotypes: FDE, DRESS, SJS/TEN, DILI
 - Incidence: rare

Pathogenesis of antiretroviral drug hypersensitivity reactions

A significant achievement in the field of HIV medicine has been the discovery of pharmacogenomic predictors of antiretroviral drug hypersensitivity resulting from the interactions between drug and class I and/or class II human leukocyte antigen (HLA) molecules.(38) Of these, the association of HLA-B*57:01 with abacavir hypersensitivity is the best recognised and has resulted in the introduction of testing for HLA-B*57:01 carriage prior to abacavir prescription into routine clinical practice and provided a roadmap for the translation of pharmacogenomics into the clinic. Other described genetic associations with antiretroviral drug hypersensitivity reactions include HLA-C*04:01 with nevirapine-induced SJS and TEN in African people and with DRESS in association with a low nevirapine metabolism status associated with carriage of the CYP2B6 allele of cytochrome P450(56), HLA-DRB1*01 with nevirapine rash associated with hepatitis(57), efavirenz-induced MPE, and HLA-B*53:01 with raltegravir-induced DRESS.(58) Other described associations are outlined in **Table 2**.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Abacavir hypersensitivity syndrome

The use of abacavir has been limited by the occurrence of abacavir hypersensitivity syndrome, a distinct entity constituting fever, malaise, respiratory symptoms and gastrointestinal upset. The rash is a late manifestation of the syndrome and occurs in 70% of cases.(59) Evidence suggests that most cases present within the first 2–3 weeks of therapy, at a median time of 8 to 9 days, and certainly all cases will have occurred within 6 weeks of continuous therapy.(60) The reported incidence of abacavir hypersensitivity syndrome is 2-9%.(8,61,62)

Immunological mechanisms for abacavir hypersensitivity

CD8+ T-cells recognize abacavir, inducing a well-characterized immune response, in both prior-sensitized patients (exposed T-cells)(63) and abacavir naïve individuals (HLA-B*57:01 positive patients).(64) Confirmation of CD8+ T cell involvement following abacavir exposure has been confirmed in biopsies of positive abacavir patch tests taken from affected individuals.(65) Taken together, these findings demonstrate a class I HLA-restricted CD8+ T-cell mechanism for the abacavir hypersensitivity syndrome. In 2012, evidence from three separate groups(66-68) demonstrated that abacavir activates T cells through a new mechanism of drug hypersensitivity called the “altered peptide repertoire model”. In this model, abacavir binds non-covalently to a portion of the antigen binding cleft of HLA-B*57:01. The initial binding and ensuing immune response does not require drug metabolism. Peptide elution studies suggested that the change in the peptide binding groove that follows causes an alteration in the repertoire of self-peptides that bind. These self-peptides were previously not presented during thymic development and the establishment of T cell tolerance/anergy and, therefore, are able to induce T-cell responses by T cells that were not previously tolerized to ‘self’.

The fact that only 55% of patients with HLA-B*57:01 develop abacavir hypersensitivity syndrome identifies a need for future models to explain the ‘positive predictive value (PPV) gap’ and HLA-B*57:01 positive abacavir tolerance.(8) Recently, an HLA-B*57:01-transgenic mouse model provided some insight into a potential mechanism to explain why 45% of HLA-B*57:01-positive individuals tolerate abacavir. The altered peptide model suggests that in all HLA-B*57:01-positive abacavir-exposed patients, abacavir would bind noncovalently to the floor of the peptide-binding groove of HLA-B*57:01 and alter the repertoire of endogenous peptides presented to CD8+ T cells; however, the recent study by Cardone et al suggests that in the absence of CD4+ T-cell depletion, dendritic cells remain in an immature state and there is tolerance to the altered peptide repertoire.(69,70) Factors outside of the MHC such as endoplasmic reticulum aminopeptidase (ERAP1) allotypes that favour peptide trimming may be important drivers of susceptibility in HLA-B*57:01 positive individuals.(71)

Pharmacogenomic screening for susceptibility to abacavir hypersensitivity syndrome

Since 2008, international guidelines have recommended the use of HLA-B*57:01 screening before abacavir prescription and abacavir hypersensitivity syndrome as a clinical entity has disappeared in the developed world, where these guidelines are currently followed. As a result, HLA-B*57:01 is the most widely used genetic screening test in clinical practice today.(72) The PREDICT-1 study was the first double-blind randomized controlled study to test the utility of a genetic marker in reducing a specific drug toxicity. It demonstrated a significant reduction in abacavir hypersensitivity reactions in people randomized to real-time HLA-B*57:01 testing when abacavir was withheld from those carrying HLA-B*57:01.(8) In this study, where patch testing was a co-primary endpoint with clinically diagnosed abacavir hypersensitivity, HLA-B*57:01 testing eliminated patch test positive (immunologically-confirmed) abacavir hypersensitivity syndrome. In the PREDICT-1 study patients naïve to abacavir (n = 1956) were divided into a prospectively screened group, in which those

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

carrying the predictive allele were excluded from abacavir therapy, and a control group who were treated with abacavir without prior screening. Following 6 weeks of observation there was a clear reduction in subjects with immunologically confirmed AHR: 0% in the screening group and 2.7% in the control group. HLA B*57:01 screening for susceptibility to abacavir hypersensitivity demonstrated a positive and negative predictive value of 55% and 100% respectively. Screening for HLA-B*57:01 is recommended prior to commencement of abacavir in any HIV positive individual in the developed world where populations carrying HLA-B*57:01 are represented.

Nevirapine hypersensitivity reactions

Nevirapine has also been associated with immune-mediated hypersensitivity reactions, including DRESS, SJS/TEN and drug-induced liver disease.(73) Immune-mediated hypersensitivity is the commonest cause of drug cessation, which occurs in approximately 5% of patients. The pharmacogenomic associations identified for nevirapine hypersensitivity and the spectrum of hypersensitivity syndromes are outlined in **Table 2**.

Nevirapine pharmacogenomic screening

HLA associations with nevirapine hypersensitivity reactions include skin rash and associated hepatitis in European populations⁷⁴, HLA-B*35:05 in Southeast Asians and HLA-Cw4 in association with skin rash across an array of ethnicities, particularly in association with CYP2B6 516 G>T in negro people (**Table 2**). In a South African population, HLA-B*58:01 and HLA-DRB1*01:02 were associated with grade 3 or 4 hepatitis⁹, and HLA-C*04:01 was associated with SJS/TEN in a Malawian population.(75) Carr *et al.* demonstrated that HLA-C*04:01 predisposes to nevirapine-induced SJS/TEN in a sub-Saharan African population, but no other drug hypersensitivity phenotypes.(76) In a French cohort, HLA-DRB1*01 was associated with cutaneous hypersensitivity reactions associated with nevirapine or efavirenz use, with no hepatic toxicity noted.(73) Another study showed that predisposition to cutaneous nevirapine hypersensitivity reactions that was seen across different ethnicities could be attributed to a cluster of HLA-C alleles sharing a common binding groove F pocket with HLA-C*04:01. Association of rash with class II HLA alleles sharing the same HLA-DRB1-P4 pocket were also observed as predisposing(77)

The contributory role of other antiretroviral drugs in causing drug hypersensitivity reactions when used in combination with nevirapine remains ill-defined. DRESS, SJS and TEN are infrequently reported in the setting of nevirapine therapy, occurring in less than 1% of patients.(78,79) Cornejo Castro *et al.* in a systematic review and meta-analysis of 13 case-control studies investigating nevirapine hypersensitivity demonstrated that HLA-C*04 carriage may be a common risk factor for cutaneous adverse drug reactions to nevirapine in 4 different ethnic populations (OR 2.63 [95% CI: 1.97-3.52]), whereas HLA-B*35 and HLA-DRB1*01 associations are linked with Thai and White populations, respectively.(80) Although a number of class I and II restricted HLA have been associated with nevirapine hypersensitivity and show promise, at present there is no identified strategy that has been implemented into clinical practice.

Raltegravir hypersensitivity reactions

DRESS has been reported with raltegravir therapy and case reports to-date have underscored the pre-disposition of individuals of African ancestry. In keeping with this, an association of HLA-B*53:01, an allele prevalent in those of African ancestry, with raltegravir associated DRESS has been reported by Thomas *et al.* (35), who demonstrated that 5 of the 6 patients who experienced raltegravir-induced DRESS (5 African, 1 Hispanic) carried this HLA-B allele. This association has recently been supported by findings of another group.(81)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Approach to assessing antiretroviral drug hypersensitivity

Diagnosis

Skin prick and intradermal testing with the drug under investigation, followed by a confirmatory oral provocation test, has been the gold standard for identification of drugs associated with immediate hypersensitivity reactions to antibiotics.(82,83) For antiretroviral drug hypersensitivity reactions, the majority of cutaneous reactions are delayed and drugs are primarily available as oral preparations and not available in a sterile intravenous form appropriate for skin prick or intradermal testing.(84,85) Delayed hypersensitivity reactions to drugs are T cell-mediated and, therefore, patch testing with the drug is used to demonstrate drug-reactive T cells. Patch testing in abacavir hypersensitivity has an 87% diagnostic sensitivity(8,65,86,87), with the sensitivity for other drugs ranging from 30-64%.(88,89) Limited data is available regarding cross-reactivity between antiretroviral drugs from the same class.(90) Our recommendations for the management and diagnosis of antiretroviral drug acute hypersensitivity reactions are outlined below:

- Severe immediate hypersensitivity: desensitization
- Non-severe immediate hypersensitivity: Supervised single or graded test dose
- Non-severe delayed hypersensitivity: Treat through reaction, supervised rechallenge or desensitization
- Severe delayed or immediate hypersensitivity: Drug avoidance – patch testing or ex vivo studies where available may be performed by specialist physicians utilizing case report evidence.(91)

Treatment

The treatment paradigm for hypersensitivity reactions to antiretroviral drugs or antimicrobial drugs in people with HIV infection is generally no different to that in non-HIV-infected people. Treatment complexity is added in the setting of coinfection with hepatitis C virus or *Mycobacterium tuberculosis* (Mtb), which can lead to complex drug interactions and difficulty ascribing drug hypersensitivity causality.(92) Select sequential rechallenge and aborting hypersensitivity reactions with immediate high dose steroids has been successfully applied in difficult cases in patients with HIV-Mtb coinfection where there are limited treatment options.(93) Desensitization is primarily indicated in patients with an IgE antibody-mediated hypersensitivity reaction. It should not be attempted for severe delayed drug hypersensitivity reactions: this is performed only in specialized centres and successful in small cohorts/case studies.(94,95) Desensitisation should be avoided in cases of SCARs.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Tables and Figures

Table 1: Most frequent non-immune mediated adverse reactions reported to currently utilized antiretroviral drug

Drug	Gastroin- testinal	Neuro- logical	Renal (biochemical)	Renal (obstructive)	Metabolic	Musculo- skeletal	Hepatic	Respiratory	Cutaneous (non-rash)
Nucleoside reverse transcriptase inhibitors (NRTI)									
Abacavir	+	–	+	–	++ [^]	–	–	–	–
Lamivudine	+	+ [°]	–	–	+ [^]	–	+	–	–
Emtricitabine	++	–	–	–	+ [^]	–	–	+ (cough)	+ (skin discol- ouration)
Tenofovir disoproxil fumarate (TDF)	+	+ [°]	*	–	+ [^]	+++ [‡]	–	–	–
Tenofovir alafenamide fumarate (TAF)	+	+ [°]	–	–	+ [^]	–	–	–	–
Non-nucleotide reverse transcriptase inhibitors (NNRTI)									
Nevirapine	+	+	–	–	–	–	++	–	–
Efavirenz	–	+++	–	–	+ (lipids, lipodys- trophy)	–	+	–	–
Etravirine	–	–	–	–	–	–	–	–	–
Rilpivirine	–	+	–	–	+/-	–	+/-	–	–
Protease inhibitor									
Atazanavir	+	+	–	+/-	+ [*] [‡]	++	++	–	–
Darunavir	++	+	–	–	+ (TG) [*] [‡]	++	–	–	–
Integrase inhibitor									
Raltegravir	+	+	–	–	–	+ (rhabdo- myolysis)	–	–	–
Dolutegravir	+	+	–	–	–	–	–	–	–
Bictegravir	+	+	–	–	–	–	–	–	–
Eltegravir	+	+	–	–	–	–	–	–	–

Only drugs currently recommended by ASHM and initial and continuing regimens are included in the analysis – Tenofovir, emtricitabine, lamivudine, efavirenz, dolutegravir, bictegravir, elvitegravir, raltegravir, darunavir, atazanavir, rilpivirine.

Abbreviations – OP, osteoporosis; TG, hypertriglyceridemia

+ Mild or infrequent reports; ++ Moderate or not uncommon reports; +++ Severe or frequent

[^] hyperlactatemia/lactic acidosis

[†] fat redistribution

[‡] Increased risk of osteoporosis

*Diabetes/hyperglycemia

[°]Headache only

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Table 2: Pharmacogenomic predictors of drug hypersensitivity reactions in people with HIV infection

Drug	Phenotype	HLA	Population	PPV	NNP	NNT
Nevirapine	SJS/TEN	HLA-C*04:01 ? CYP2B6 983 T-C	African (Malawian) Mozambique			ND
	Rash	HLA-B*35:05 HLA-Cw4	Thai, African, Asian, European White, Black, Asian Han, Chinese	16%	97%	ND
	DRESS	HLA-B*14/Cw8 HLA-Cw*8 or HLA -B*35 HLA -B*35:05 HLA -B*35:01 CYP2B6 516 G-T+C*04 CYP2B6 (rs2054675, rs3786547, rs3745274)	Italian Japanese Asian Asian (Thai) European/Australian White, Black, Asian White, Black, Asian			ND
	Delayed rash (non-specific)	B*35:05; RS1576*G CCHR1 status (GWAS)	Thai			
	Hepatitis	HLA-DRB1*01:01 (CD% > 25) and DRB1*01:02	Australian, European, South African	18%	96%	
Abacavir	Hypersensitivity syndrome	HLA-B*57:01	European, African	55%	100%	13
Dapsone	Rash, hepatitis	HLA-B*13:01	Chinese	7.8%	99.8%	84
Efavirenz	Delayed rash (non-specific)	DRB1*01	French			ND
Raltegravir	DRESS	HLA-B*53:01	African/Hispanic			ND
Sulfamethox-azole	SJS/TEN	HLA-B*38	European			ND

INR = international normalised ratio.

* Indications for assessment by a liver transplant centre include Child–Pugh score $\geq$ B7, MELD score $\geq$ 13 or one of the following clinical events: refractory ascites, spontaneous bacterial peritonitis, hepatorenal syndrome, recurrent or chronic hepatic encephalopathy, small hepatocellular carcinoma or severe malnutrition.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Legend: Type A – Non-immune-mediated adverse drug reactions Type B – Immune-mediated adverse drug reaction. For definitions of severe and non-severe immediate and delayed reactions see “Antimicrobial Hypersensitivity” Chapter of Australian Therapeutic Guidelines (v. 16).[\(96\)](#)

- ^a If TMP-SMX-associated rash within last five years, can consider dapsone rather than rechallenge
- ^b Drug fever, acute interstitial nephritis, fixed drug eruption, severe rash with mucosal ulceration or blistering/desquamation.
- ^c Oral single dose challenge and observe for two hours (TMP-SMX 80mg-400mg) for non-severe delayed reactions. For historical non-severe immediate reactions (> 5 years) can consider an observed two-step TMP-SMX challenge (8mg-40mg orally then 72mg-360mg 30mins post initial) and observe 2 hours.
- ^d Prescribe dapsone 100mg orally daily. Ensure G6PD deficiency screen negative prior to use.
- ^e For all patients proceed with TMP-SMX desensitization or alternatively, dapsone therapy may be employed.

Adapted from [\(41,45,52,96\)](#)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Vaccines in people with HIV infection

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Last reviewed: July 2019

Introduction

HIV primarily affects CD4+ T cell numbers and function whilst also impacting other components of the immune system (such as macrophages, B cells and NK cells; summarised in an earlier section). This places people living with HIV at a higher risk of numerous infections, many of which are vaccine preventable. Whilst patients older than 5 years of age with CD4+ T cell counts of <200/mL should not be administered live attenuated vaccines, those with a CD4+ T cell count between 200-350/mL are moderately immunosuppressed and clinical judgement should be used to guide the administration of live vaccines in this cohort. The key considerations this chapter will focus on:

1. The higher predisposition of people living with HIV to specific vaccine preventable disease
2. The efficacy/clinical effectiveness of vaccine administration in preventing disease in people living with HIV
3. The safety of vaccine administration in people living with HIV
4. Specific considerations in children living with HIV

Recommendations for vaccination of adults with HIV infection are outlined in the following subsections and summarised in Table 1 presented in the subsection entitled Summary of vaccination recommendations for HIV-infected adults.

Diphtheria, tetanus and pertussis vaccine

Corynebacterium diphtheriae and *Bordetella pertussis* are bacterial upper respiratory tract pathogens, whilst *Clostridium tetani* is a toxin producing bacteria causing muscle spasm of varied severity. These infections are not considered to be more prevalent or cause more severe disease in HIV affected persons and vaccination should be administered in accordance with routine indications, regardless of immune status, HIV viral load and antiretroviral therapy (ART).

Hepatitis B virus vaccine

HBV is transmitted via exposure to infected blood and body fluids, with infection occurring via vertical (perinatal infection from mother to child), sexual, parental or percutaneous routes. 5-10% of people with HIV infection are co-infected with HBV, with long-term sequelae such as cirrhosis and hepatocellular carcinoma occurring with increased frequency in co-infected patients.⁽⁹⁾ HBV vaccine is recommended for HIV patients with no immunity to HBV (HBsAg negative, HBsAb <10 IU/ml), especially in those with risk factors for acquisition.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

HBV vaccine contains a recombinant virus protein so can be given at any CD4+ T cell count. There is no evidence that people with HIV infection have a higher rate of adverse events following administration of HBV vaccine compared with individuals not infected with HIV. However response rates to vaccination vary widely with reduced response rates (as low as 33%) associated with low CD4+ T cell counts and high HIV viral load at the time of vaccination.(10-12) Given this information, it may be reasonable to delay vaccination in non-immune individuals or delay re-vaccination in non-responders until HIV replication is suppressed by ART and the CD4+ T cell count is >200-350 /m L.

A meta-analysis of 5 studies concluded that high dose HBV vaccine (40mg) provided higher HBV surface antibody (HBsAb) response rates compared with standard dose vaccine (20mg) with a pooled OR of 1.96 (95% CI 1.47-2.61).(13) In a multicentre randomised controlled trial, four doses of high dose (40mg) vaccine at intervals of 0, 1, 2 and 6 months was associated with superior seroconversion (82%) compared with three standard dose (20mg) vaccines at 0, 1 and 6 months (65%).(7) However an alternative strategy of three high dose vaccines at 0, 1 and 6 months with an additional 4th dose of 40mg if seroconversion (HBsAb>10 IU/L) has not occurred is a feasible alternative, with a retrospective study revealing three high dose vaccines efficacious in 83% of patients.(14) Regardless of whether using the 3 or 4 dose strategy, clinicians should check HBsAb 4-8 weeks after the last dose and repeat dosing (1 further dose if 3 initial vaccines given, or repeat full course if 4 initial vaccines given) if HBsAb <10 IU/L.

Hepatitis A virus vaccine

Hepatitis A virus (HAV) is transmitted via faecal-oral spread and causes an acute (rarely fulminant) hepatitis. Risk factors include travel to high-risk countries, men who have sex with men (MSM) and injecting drug use. HAV infection does not appear to be associated with worse clinical outcomes in people with HIV, but has been associated with higher and more prolonged viraemia.(3)

HAV vaccine is recommended for all patients with HIV infection who have additional risk factors mentioned above. The vaccine's immunogenicity, whilst high, is correlated with CD4+ T cell count and suppression of HIV replication on ART.(4, 5) The proportion of responders and titres of HAV antibodies were higher in recipients of three doses (at 0, 1 and 6 months) compared with two doses.(6, 7) A meta-analysis of five studies of people with HIV infection concluded that pooled seroprotection from HAV infection was 92% after two years and 82% after five years.(8) Vaccination can be administered from 12 months of age.

The single antigen vaccine is recommended in 2 doses 6-12 months apart in patients with CD4+ T cell counts >350/mL. In patients with CD4+ T cell counts <350/mL, three doses are recommended at 0, 1 and 6 months. Combination HAV/hepatitis B virus (HBV) vaccines are also available and should be administered in 3 doses at 0, 1 and 6 months, although the HBV component dose is lower than recommended for HIV-infected individuals (see [HBV section](#)).

Human papilloma virus vaccine

Human papilloma virus (HPV) is an oncovirus responsible for causing genital warts, as well as cervical, vulval, vaginal, penile, anal and oropharyngeal cancers. Whilst many HPV serotypes have been identified, HPV-6 and HPV-11 are responsible for the majority of noncancerous genital warts and HPV16 and HPV-18 are associated with 60% of HPV associated cancers.(15) Australian men with HIV infection were almost twice as likely to carry the oncogenic HPV-16 serotype than were HIV negative homosexual men (44.3% vs 25.4%).(16) HIV-infected people have an increased risk of acquiring HPV infection and associated cancers, the risk of which increases in those with low CD4+ T cell counts and in MSM.(16-18)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

The original quadrivalent vaccine (4vHPV) developed in Australia was a virus-like particle (VLP) vaccine containing the major capsid protein (L1) of HPV types 6, 11, 16, 18. The current 9vHPV vaccine contains L1 proteins of five additional serotypes, (31, 33, 45, 52 and 58) which account for an extra 10% of HPV-related malignancies. Studies of the original 4vHPV vaccine have shown it to be safe and immunogenic in HIV positive people across a wide age group.(19-21) Serum levels of antibodies to HPV proteins in the vaccine are superior to those occurring from natural immunity and are higher in patients with a high CD4+ T cell count and low HIV viral load, perhaps supporting deferring vaccination until patients are established on ART.(21)

Current funding for the HPV vaccine is limited to females up to 45 years and males up to 26 years. This is based on cost-effectiveness from clinical trial data in HIV negative individuals. The vaccine is administered at 0, 1 and 6 months and if interrupted the course should be completed rather than restarted.

Influenza virus vaccine

Influenza viruses cause a respiratory illness with highly variable severity, and is a common cause of hospitalization, morbidity and mortality in at-risk groups. HIV infection is associated with increased severity of influenza and greater risk of complications, comparable to that of other high-risk groups.(22-24) Currently in Australia there are 2 available influenza vaccine types, the quadrivalent vaccine (for people <65 years of age) and an enhanced trivalent vaccine (for people >65 years of age). In people >65 years of age, the enhanced trivalent vaccine has been shown to induce higher serotype-specific antibody responses and reduce the likelihood of laboratory-confirmed influenza.(25) Higher rates of mild injection site reactions have been reported in the elderly, without an increase in systemic or serious adverse reactions.(26)

Antibody responses against influenza virus proteins in the vaccine are lower in HIV- infected individuals compared with controls, and appear to be correlated with lower CD4+ T cell counts and unsuppressed HIV viral loads.(27-29) Administration of higher or more frequent doses of vaccine has not been associated with improved immunogenicity.(30) Despite this, a recent meta-analysis of six studies demonstrated a single-dose trivalent (non enhanced) influenza vaccine prevented laboratory confirmed influenza cases with a pooled efficacy of 85% in adults with HIV infection.(31) The influenza vaccine should be offered to all HIV-infected individuals annually regardless of immune status, HIV viral load and ART.

Measles, mumps, rubella (MMR) vaccine

Measles, mumps and rubella viruses cause a variety of febrile presentations, including conjunctivitis, coryza, maculopapular rash (measles, rubella) and salivary gland swelling (mumps). In HIV-infected patients, measles is associated with a higher mortality, with delayed and atypical presentations.(32) The MMR vaccine contains live attenuated virus and is highly immunogenic in healthy subjects, with measles IgG antibodies developing in 90% of individuals after the first dose and 99% after two doses.(33) Side effects include fever and rash in up to 15% of recipients.

The MMR vaccine is contraindicated in immunocompromised people as well as in pregnancy, and should not be administered to HIV patients with a CD4+ T cell count of <200/mL. For measles virus nonimmune HIV patients with a CD4+ T cell count of >200/mL, one or two doses of MMR vaccine are recommended depending on the number of doses received previously. Doses should be administered at least 1 month apart. As is the case with other vaccines, MMR vaccine responses in HIV-infected patients are reduced.(34) and immune reconstitution following ART appears to increase rates of measles IgG antibody seropositivity post vaccination.(35) Deferring vaccination until patients are established on ART should be considered in cases where the likelihood of exposure to measles is low. The MMRV vaccine is not recommended due to the higher doses of attenuated mumps virus used.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Meningococcal vaccines

Neisseria meningitidis causes meningitis and bacteraemia, with a 5-24 fold increased risk for meningococcal disease among HIV-infected persons across multiple settings associated with a higher mortality.(36) Currently in Australia there are increased notifications of disease caused by meningococcal serogroups W and Y across a wide range of age groups. To date there is no data suggesting the risk is increased in patients with HIV infection.

Currently available vaccines include the conjugate MenC and Men ACWY (quadrivalent) vaccines as well as the recombinant MenB vaccine. All vaccines are immunogenic and induce serogroup specific antibody responses. There appears to be a suboptimal response to a single dose of quadrivalent conjugate meningococcal vaccines in HIV-infected adolescents compared with healthy controls(37) and to conjugate meningococcal C vaccine(38). Low CD4+ T cell count and non-suppressed HIV viral load have been reported as predictors of a poorer response(38). No clinical data in HIV-infected individuals are available for MenB vaccine immunogenicity. Therefore, it is recommended that 2 doses of both MenACWY and MenB be administered 8 weeks apart to adults with HIV infection.

Pneumococcal vaccines

Streptococcus pneumoniae causes pneumonia and invasive disease. The rate of invasive pneumococcal disease (IPD) is five to forty-times higher in HIV-infected patients,(39, 40) despite the use of antiretroviral therapy,(41) with mortality rates ranging from 0-33%,(39-41) and up to 57% in those with bacteraemia in the pre-ART era.(42) Risk factors for severe disease include a low CD4+ T cell count, African race, injecting drug use, smoking, chronic disease and alcoholism.(43)

There are currently two pneumococcal vaccines available in Australia: one containing capsular polysaccharides of 23 serotypes of pneumococci (PPV23) and the other containing protein-conjugated polysaccharides of 13 serotypes of pneumococci (PCV13).

13-valent protein-conjugated pneumococcal polysaccharide vaccine (PCV13)

Protein-conjugated pneumococcal vaccines are designed to elicit a T cell-dependent B cell response resulting in superior antibody and memory B cell responses. In a previous study in Malawian adolescents and adults, two doses of a protein-conjugated pneumococcal polysaccharide vaccine (PCV7) resulted in a vaccine efficacy of 74% against recurrent IPD caused by vaccine serotypes.(44) Multiple serological studies have confirmed significant increases in serum serotype-specific IgG antibody levels and opsonophagocytic antibody activity against pneumococci in HIV positive patients (including those with low CD4+ T cell counts) after a single dose, with further doses providing little advantage for increasing antibody levels.(45, 46) A single dose of PCV13 is recommended for all HIV positive patients regardless of CD4+ T cell count, 12 months after PPV23 if this was given first.

23-valent pneumococcal polysaccharide vaccine (PPV23)

There is substantially reduced PPV23 vaccine immunogenicity in HIV patients compared with young healthy controls, particularly among those with low CD4+ T cell counts.(47) Numerous observational studies have reported varying clinical effectiveness of PPV23, ranging from 20-79%, against IPD with factors associated with clinical failure including low CD4+ T cell count (<200/mL), African-American race and HIV viral load >100,000 copies/mL.(48) Administration of PPV23 at least 12 months after PCV13 is recommended, to increase pneumococcal serotype coverage of antibody responses, with a repeated dose 5 years later.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Vaccination recommendations for children with HIV infection

Despite the uptake of ART, HIV-infected children have higher risks of vaccine-preventable disease than HIV-uninfected children.(54, 55) Immunological impairment may result from viral replication in lymphoid tissue prior to immunological maturation and the development of protective immune responses.(56) In general, infants should be immunised according to local immunisation schedules and 'non-live' vaccines should not be delayed.(57) However, if ART is indicated for older children with non-protective or absent antibody levels, delaying immunisations until suppression of HIV replication and CD4+ T cells >15% for 6 months should be considered. It should also be noted that the definition of severe immunosuppression by CD4+ T cell count differs according to age in the paediatric population (see table 2).

Table 2: Age-related indicators of severe immunodeficiency in children (56)

Age	CD4+ T cell count (cells/mL)	CD4+ T cell %
< 1 year	< 750	15
1 – 5 years	< 500	15
≥ 6 years	< 200	15

Live vaccines in HIV-infected children

Live vaccines such as MMR and VZV vaccines are a routine component of the childhood immunisation schedule but are contraindicated in severely immunosuppressed children (see table 2). The *Bacillus Calmette-Guérin* (BCG) vaccine is another live vaccine, contraindicated due to the risk of disseminated BCG infection.(58, 59)

MMR is recommended for children who are not severely immunocompromised as per the routine immunisation schedule. It is recommended that VZV-seronegative HIV-infected children should receive 2-dose VZV immunisation(60) and that the doses should be administered at least 2 months apart. Whilst tetravalent MMR-V vaccine is available, the mumps antigen content is higher than the MMR preparation. MMR-V therefore is not recommended due to lack of safety and efficacy data.(56) MMR and VZV vaccines may be administered on the same day, or at least 4 weeks apart.

Rotavirus vaccine

There is significant morbidity and mortality associated with rotavirus infection, although it is unclear whether rotavirus disease is any more severe in HIV infected children.(61) Although the rotavirus vaccine is a live vaccine, there is evidence to suggest that it can be safely administered to infants with HIV who are clinically well.(62-64)

Poliovirus vaccines

The Inactivated Polio Vaccine (IPV) is administered as a part of the childhood immunisation schedule. There is limited data on the effectiveness of IPV in children with HIV infection, however it is thought that vaccine effectiveness is likely related to immunological status.(65) It is recommended that IPV is given as per local immunisation schedules. The oral polio vaccine (OPV) is a live vaccine that is no longer used in Australia.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Influenza virus vaccine

Children aged <5 years have a higher risk of hospitalization and morbidity from influenza.(66, 67) Influenza vaccine is recommended for all children with HIV infection aged ≥6 months of age. In the first year of administration if the child is less than 9 years of age, 2 doses should be administered 4 weeks apart. The vaccine can be administered as a single dose annually thereafter.

Pneumococcal vaccines

In addition to the routine childhood immunisation schedule, it is recommended that children with HIV infection receive a dose of PCV13 at 6 months of age and PPV23 at 4 years of age.(68, 69)

Varicella zoster virus vaccines

Varicella zoster virus (VZV) is a herpes virus that causes primary infection (chickenpox) and reactivation (shingles) after establishing latency within neurons. The rate of VZV seronegativity amongst HIV positive patients in the UK was 1.5%, with those acquiring primary infection more likely to present with severe disease (49). The incidence rate of shingles in HIV positive individuals remains 3-5 times higher than in HIV negative controls in the ART era, associated with low CD4+ T cell counts and high HIV viral loads. HIV-infected individuals have a higher incidence of cutaneous, neurological and visceral complications.(50)

Chickenpox vaccine

This is a live attenuated vaccine using the *Oka* strain of VZV, which can reactivate to cause shingles (although less commonly than wild type virus). It is not recommended for patients with a CD4+ T cell count of <200/mL. In nonimmune (VZV IgG antibody negative) HIV positive individuals with a CD4+ T cell count of >200/mL, vaccination should be considered based on safety and immunogenicity data obtained from HIV positive children.(51) Two doses are recommended given 3 months apart. The combination MMRV vaccine is not recommended.

Shingles vaccine

The currently available vaccine is a more potent high-titre live attenuated vaccine designed to boost natural immunity and reduce the incidence of shingles and post herpetic neuralgia in people >50 years of age. Two doses were found to be safe and immunogenic in a trial of HIV-positive patients with CD4+ T cell counts >200/mL),(52 and should be considered in those patients with CD4+ T cell counts >200-350 /mL with serological confirmation of previous VZV infection. A new zoster vaccine consisting of recombinant viral proteins has shown safety and efficacy in a cohort of HIV positive patients, including a small number with CD4+ T cell counts between 50-200/μL.(53)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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A large white circle is centered on a blue background. It is surrounded by several other circles: a dark blue circle at the top right, a light blue circle on the left, and a red circle at the bottom left. A thin black line forms a circle around the white circle, with a small red dot on its left side.

9. Co-Morbidities

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Atherosclerotic vascular disease in people with HIV infection

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Last reviewed: October 2019

Introduction

While antiretroviral therapy (ART) has led to dramatic improvements in life expectancy for people with HIV infection,⁽¹⁾ there is evidence that individuals receiving effective ART remain at increased risk of a number of serious, traditionally age-related, co-morbidities including cardiovascular disease (CVD),⁽²⁾ which is now one of the leading causes of morbidity and mortality.⁽³⁾ In fact, HIV infection is associated with an increased risk of CVD that has been estimated at ~50% after adjustment for traditional risk factors.⁽⁴⁾ As the average age of people with HIV infection increases,⁽⁵⁾ there is likely to be a corresponding increase in the prevalence of CVD which will have significant impacts on both the health of people with HIV infection and their care requirements from the medical community. It is therefore increasingly important that clinicians and individuals with HIV infection are aware of this increased risk and how to reduce it through lifestyle modifications, personalized ART choices and the use of risk modified medications (such as statins) in those who warrant it.

Pathogenesis of cardiovascular disease in people with HIV infection

HIV-associated CVD is the result of complex interactions between traditional cardiovascular risk factors, side effects of ART and the chronic inflammation and immune activation associated with long term HIV infection. It is important to acknowledge, however, that the assessment and management of traditional CVD risk factors according to standard guidelines is still the cornerstone of clinical practice and should be prioritised among people with HIV infection on at least an annual basis.

Cigarette Smoking

Cigarette smoking is directly responsible for a significant proportion of the CVD experienced by people with HIV infection, partially because smoking rates are well above that reported in the general population but also because of an interaction between smoking and HIV-associated inflammation, which magnifies the negative effects of smoking above the already significant levels experienced in the general population.⁽⁶⁾ It is estimated that more than 40% of heart attacks experienced by people with HIV infection could be prevented through smoking cessation.⁽⁶⁾ Importantly, it is also clear that smoking cessation is associated with a substantial reduction in CVD risk (estimated at ~30%) that is evident within 2-3 years.⁽⁷⁾ Smoking cessation interventions remain challenging among the relatively high proportion of people with HIV infection who are smokers (~30% in a recent Australian study),⁽⁸⁾ particularly those with ongoing recreational drug and alcohol use. However, the diagnosis and treatment of HIV infection provide opportunities for successful intervention as a part of a discussion around improving general health.⁽⁸⁾ Smoking cessation can also be supported by treatments such as varenicline, which has been shown to be safe and effective in people with HIV infection in a placebo-controlled trial.⁽⁹⁾

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Dyslipidemia

Dyslipidemia is also an important driver of CVD, with elevations in total and low-density lipoprotein (LDL) cholesterol and deficiencies in high-density lipoprotein (HDL) cholesterol strongly related to the development of CVD.(10) HIV infection, independent of the effects of ART, can lead to significant alterations in cholesterol levels, predominantly characterized by decreases in total, LDL and HDL cholesterol with mild elevations in triglycerides.(11) In general, initiation of ART leads to further increases in triglycerides, along with increases in total and LDL cholesterol, sometimes to well above pre-seroconversion levels, but only modest, if any, correction in HDL.(12) Different antiretroviral drugs (as discussed below) have differing impacts on lipid levels which may be important when choosing an antiretroviral regimen for an individual at high risk of CVD.

In terms of evaluating cholesterol levels and considering the benefits of cholesterol lowering therapy in people with HIV infection, current evidence indicates that standard population-based calculators of CVD risk are still appropriate and valuable tools.(13) In this context, attempts have been made to develop CVD risk calculators that incorporate HIV-specific risk factors, although these have not been shown to improve the prediction of CVD events in a large population-based study,(14) and have the potential to underestimate risk compared to standard tools such as the Framingham Risk Score.

From a practical perspective, there is a concern that true CVD risk in people with HIV infection is prone to underestimation when using all available risk calculators,(15) which may reflect the 1.5-fold increased risk that has been attributed to HIV infection per se as noted above. The benefits of statin therapy in primary CVD prevention among people with HIV infection, and particularly among those with estimated CVD risk <15%, will ultimately be addressed by large-scale studies such as the REPRIEVE trial that has enrolled >7,500 participants across 11 countries.(16) In the meantime, it is reasonable to offer statin therapy to all people with HIV infection for whom this is recommended under current Australian guidelines,(17) including those with an estimated 5-year CVD risk of >15%, as well as those with moderate risk (10-15%) and limited reversible risk factors.

Hypertension

CVD develops in 63.3% of hypertensive individuals (defined as a blood pressure $\geq$ 140/90) compared with 46.1% of normotensive controls. It also accelerates the development of atherosclerosis with cardiovascular events occurring on average 5.0 years earlier than would otherwise be expected.(18) Hypertension is common in people with HIV infection, with rates of 13-45% reported.(19,20) It is likely that both HIV infection and ART are contributing to the development of hypertension in this group but determining the relative contribution of ART, chronic inflammation due to HIV infection, traditional cardiovascular risk factors, and the interactions between these factors, is very difficult to determine. In people with HIV infection, elevated rates of CVD have been detected in those with pre-hypertension (systolic blood pressure 120-130 mmHg or diastolic blood pressure 80-89 mmHg) as well as hypertension (blood pressure $\geq$ 140/100 mmHg) (HR 1.81 [95%CI: 1.22-2.68] and 2.76 [95%CI: 1.9-4.02] respectively),(21) meaning that even small increases in blood pressure can have significant consequences.

At present there are no evidence-based guidelines that have been developed specifically for the management of hypertension among people with HIV infection, although the available data would indicate that this is an important risk factor for CVD and stroke that is increasing in prevalence among those that are receiving ART.(22) In this context, the implementation of standard management guidelines (23) is appropriate and warrants attention as part of overall CVD risk management.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Gender

In the general population, CVD mortality is 1.4 times higher in men than in women,(24) yet in HIV positive populations women appear to be disproportionately at increased risk of CVD. While absolute CVD rates remain low in women, HIV infection increases the baseline risk twice as much in women with HIV infection than it does in men with HIV infection,(25,26) perhaps as the result of proportionally greater increases in immune activation.(27)

Effects of ART on cardiovascular risk

It is important to highlight that CVD and all-cause mortality is overall dramatically decreased by ART, and that any side effects in terms of dyslipidemia or hyper-coagulation are clearly outweighed by the dramatic reduction in AIDS and non-AIDS related mortality.(28) However, given that a 20 year old who acquires HIV infection is likely to be on ART for 50-60 years, it is important to understand how different agents may be impacting on risk and select a regimen with the smallest side effect imprint whenever possible.

Different types of antiretroviral drugs can increase CVD risk in differing ways. Many 'first generation' HIV protease inhibitors (particularly indinavir and lopinavir) that were used in Australia in the early 'HAART era' were associated with significant metabolic complications including dyslipidaemia and elevated CVD risk. A recent analysis of contemporary HIV treatment involving 49,709 participants in the D:A:D observational cohort study has identified increased relative risk of CVD associated with cumulative exposure to darunavir after adjustment for other risk factors (59% increase per 5 years of additional use, confidence interval 33-91%). No association between CVD risk and atazanavir therapy was identified,(29) in keeping with other evidence that atazanavir has a relatively favourable effect on CVD risk in comparison with other HIV protease inhibitors, as well as with other HIV medications.(30) It is therefore clear that there is no generalised HIV protease inhibitor 'class effect' on CVD risk, and that each medication needs to be considered individually.

The use of non-nucleoside reverse transcriptase inhibitors (NNRTIs) has not been associated with elevated CVD risk to date, including a recent updated meta-analysis.(31) Within this class, there is some evidence for more favourable lipid outcomes associated with rilpivirine compared to efavirenz treatment, both in treatment-naïve individuals,(32) and in switching studies.(33) However, there is no evidence that efavirenz treatment is associated with elevated CVD risk in large population-based analyses.(34)

With regard to nucleoside reverse transcriptase inhibitor (NRTI) therapy, cohort studies have identified an association between abacavir exposure and CVD events that appears to be related to current treatment rather than cumulative drug exposure. This was first identified in the D:A:D cohort study in 2008 (35) and the association was confirmed in an updated analysis published in 2016.(36) In these analyses and in a subsequent meta-analysis of 17 epidemiological studies,(37) current abacavir treatment was associated with an estimated 1.6-1.9-fold relative increase in underlying CVD risk; although this has not been replicated in an analysis of pooled clinical trial data involving abacavir therapy.(38) The underlying mechanism remains unclear, although there is some evidence that abacavir may be promoting a prothrombotic state and unmasking subclinical atheromas and promoting symptomatic CVD.(39-41) Based on this evidence, it seems prudent to avoid abacavir use, where possible, in individuals who have elevated CVD risk (ie >10-15%) and, in particular, in cases where these risk factors are not modifiable.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

To date there has been no suggestion that integrase strand inhibitors (INSTIs) are associated with increased CVD risk or that INSTI treatment contributes to risk of metabolic complications, such as hyperlipidaemia or insulin resistance. There is emerging evidence that their use may be associated with increased fat accumulation and body mass.⁽⁴²⁾ This is an emerging area of research, with current indications that demographic factors may be important (with higher risk associated with female sex and black race) and that treatment-associated risk may be modified by choice of INSTI as well as NRTI therapy (including tenofovir alafenamide versus tenofovir disoproxil fumarate). Further results are awaited with interest.

Inflammation and immune activation as a cause of atherosclerosis in HIV infection

Atherosclerosis is primarily a disease of inflammation. When the lining of the arterial wall (the endothelium) becomes inflamed, lipid laden foam cells are promoted and drive progression from asymptomatic fatty streaks to pathological atherosclerotic plaques. Foam cells are generated when activated monocytes ingest cholesterol, take up residence in the endothelial wall and then secrete inflammatory cytokines and chemokines to promote ongoing inflammation. Monocytes from people with HIV infection are more prone to transform into foam cells,⁽⁴³⁾ and higher levels of monocyte-derived molecules, such as soluble CD14 (sCD14), have been associated with HIV infection.⁽⁴⁴⁾ Furthermore, elevated plasma levels of sCD14 and other markers of monocyte activation have been shown to predict mortality among people with HIV infection,⁽⁴⁵⁾ as well as in the general population.⁽⁴⁶⁾

It has been proposed that acute HIV infection leads to CD4+ T-cell depletion in the gut and loss of mucosal integrity (the so-called “leaky gut syndrome”), thus allowing microbial products, particularly lipopolysaccharide, to leak into the systemic circulation where it stimulates monocytes and promotes inflammation.⁽⁴⁷⁾ More recent studies suggest more complex underlying mechanisms,^(48,49) and there is also emerging evidence that markers of monocyte activation are reduced in the context of integrase inhibitor therapy.^(50,51) The impact on CVD risk remains to be determined, although it is an interesting possibility that choice of ART may have an impact on inflammatory pathways that are important for the development of atherosclerotic disease.

Impact of co-infections on cardiovascular disease risk

Co-infections with other viral or bacterial pathogens may increase CVD risk by enhancing HIV-associated immune activation and inflammation or through direct effects on the vascular endothelium. The best studied of these pathogens is cytomegalovirus (CMV), which can activate endothelial cells, promote inflammation and has been associated with serious non-AIDS events, including CVD.⁽⁵²⁾ As yet, there is no evidence-based strategy to modify CMV infection in people with HIV infection receiving ART, with no available vaccine and no studies to date indicating that antiviral therapy (eg. valganciclovir) is a means of reducing CVD risk.

Co-infection with hepatitis C virus (HCV) has also been associated with increased rates of CVD,⁽⁵³⁾ although the specific benefits of treatment for HCV infection on CVD has not been established to date.⁽⁵⁴⁾

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Coronary artery disease outcomes

As discussed above, people with HIV infection experience coronary artery disease at approximately 1.5 times the rates seen in the general population. While initially thought to occur not only at higher rates but also prematurely,(55) recent analyses have shown that coronary artery disease occurs at similar ages in people with HIV infection and the general population (adjusted mean difference in age at time of CVD diagnosis of -0.11 years [95%CI -0.59 – 0.37]).(56)

People with HIV infection have an increased incidence of subclinical coronary artery disease and a higher plaque burden when compared to appropriately matched controls.(57) Notably, people with HIV infection have a greater burden of non-calcified (or 'vulnerable') plaque which has been shown to correlate with a higher risk of subsequent rupture and acute coronary events.(58) They are also more likely to present with an ST-elevation acute myocardial infarction compared to a non-ST-elevation infarction or angina,(59) and experience re-infarction and re-stenosis at higher rates.(60) There is a trend towards increased in-hospital cardiovascular mortality and re-hospitalization with heart failure compared with the general community.(61,62) These observations would argue for close monitoring following the diagnosis of coronary artery disease, and attention to secondary prevention strategies, including consideration of modifiable risk factors in accordance with standard guidelines.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Endocrine disorders in people with HIV infection

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Last reviewed: November 2019

Introduction

Endocrine conditions occur commonly in HIV infection, due to specific effects of the virus, HIV-related disease, the effects of reconstitution of the immune system after the commencement of combination antiretroviral therapy (cART), complications of cART, or drug-drug interactions (Table 1).

Table 1. Endocrine disorders due to effects of HIV, HIV-related disease, immune reconstitution and drug therapy

	Direct HIV-1 virus effects	HIV-related disease	Immune reconstitution	Drug effects
Adrenal disease	Adrenalitis (rare)	Infections: CMV Toxoplasmosis Mycobacterial Malignancy: KS	Addison's disease (rare)	Reduced corticosteroid synthesis: antifungals (ketoconazole) Pituitary suppression: cytochrome P450 3A4 drug interactions with inhaled or oral steroids
Thyroid disease			Graves' disease Hashimoto's hypothyroidism	Interferon-induced thyroid disease
Diabetes mellitus	–			Pentamidine-induced insulin deficiency (T1D) Insulin resistance due to protease inhibitors and NRTIs (T2D)
Calcium metabolism	Osteoporosis			NRTI-related osteoporosis
Sex hormones		Androgen deficiency		Androgen deficiency

Diabetes mellitus

Disturbances in glucose metabolism, such as insulin resistance, impaired fasting glucose, impaired glucose tolerance and diabetes mellitus, are amongst the most common endocrine disorders found in treated HIV infection.^(1, 2) Diabetes and its prediabetic disorders of impaired fasting glucose and impaired glucose tolerance are defined using the American Diabetes Association criteria,⁽³⁾ using either fasting glucose, random glucose or HbA1c or glucose responses to glucose tolerance test, as shown in Box 1. Diabetes may

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

be preceded by a prodrome of either impaired fasting glucose or impaired glucose tolerance which may be present for some 5-10 years prior to progression to overt diabetes mellitus. Detecting prediabetes is a golden opportunity for diabetes prevention, as will be discussed below. Insulin resistance is difficult to measure in individual patients and is not recommended. Measures such as fasting insulin levels or insulin levels following an oral glucose load are unreliable and accurately not-reproducible.(4)

Box 1. Criteria for diagnosis of diabetes mellitus and other glucose disorders (American Diabetes Association).

	Fasting glucose ¹	2 hour glucose ²	Random glucose	HbA1c ³
Normal	< 5.6 mmol/L			
Diabetes mellitus	> 7.0 mmol/L	> 11.1 mmol/L	> 11.1 mmol/L with symptoms ⁴	> 6.5%
Impaired fasting glucose	5.6 – 6.9 mmol/L			
Impaired glucose tolerance		7.8 – 11.0 mmol/L		

1: fasting is defined as no caloric intake for at least 8 hours.

2: following 75g of an anhydrous glucose load, dissolved in water.

3: HbA1c: glycated haemoglobin, measured on non-fasted blood.

4: polyuria, polydipsia or unexplained weight loss.

Prior to the availability of cART, most diabetes cases occurred in patients treated with pentamidine for *Pneumocystis jirovecii* infection and were characterised by rapid onset of insulin deficiency and ketoacidosis (type 1 diabetes mellitus; T1D), since pentamidine destroys pancreatic insulin-secreting beta-cells.(5-7) The most common form of diabetes mellitus in HIV-infected patients in the cART era is type 2 diabetes (T2D), due to a combination of insulin resistance and insufficient insulin secretion to meet demand.(1)

The exact prevalence and incidence of diabetes in treated HIV infection has been difficult to establish precisely and is affected by a number of factors, including exposures to different cART medications such as HIV nucleoside reverse transcriptase inhibitors (NRTIs) and HIV protease inhibitors, in addition to different prevalence rates in promoters of diabetes such as obesity, high-energy diets and sedentariness. Further, there are clear ethnic groups with high genetic susceptibility to diabetes. Prevalence rates for T2D with the use of older cART regimens (to which many surviving patients were exposed) range from 7%–13%.(8-10) More recent studies show diabetes rates in HIV patients to be twice that of age-matched controls,(11) with rates of impaired fasting glucose and diabetes of 9.1% and 4.5% respectively in an Italian cohort.(12) The Swiss HIV Cohort reported diabetes rates of 7%,(13) higher than the 3% rate found in the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study.(14) Incidence studies report 5.72 cases /1000 patient-years of follow-up in the D:A:D Study after 3.8 years follow-up(14) and 14.1 cases/1000 patient-years after 10-years follow-up in a large French study.(15) Recent observational data on diabetes in US youth with HIV-infection show a 5-fold rate increase in the periods of time between 2004-7 and 2008-2014.(16) This may reflect the impact of the US obesity epidemic in promotion of diabetes, differences in ascertainment and diabetes screening over the observation period or differences in cART used over time.

The longest longitudinal study of diabetes incidence has been undertaken in our cohort followed at St Vincent's Hospital for up to 18 years, where we recently reported incident rates of prediabetes at 33% and incident diabetes at 13%,(17) according with other international studies of shorter duration.(18-25) In accord

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

with US data where obesity has likely impacted diabetes incidence, Australian data showed that a modest gain of 250-330g of central abdominal fat in mostly healthy weight patients was associated with a 3-fold increase risk of diabetes incidence.⁽¹⁷⁾ The USA Veterans Aging Cohort Study reported that every 2.3kg of weight gained in the 12 months after cART initiation, increased the risk of diabetes by 14%.⁽²⁶⁾ The D:A:D cohort study found that every 1.0 kg/m² BMI gain was associated with a 12% increased risk of incident diabetes over the 12 months after cART initiation, with a 2.6-fold increased risk in those in the highest quartile of BMI gain regardless of the pre-cART BMI category.⁽²⁷⁾ Together, these studies show that even modest weight gain in cART recipients increases the risk of metabolic comorbidities and suggest that efforts should be aimed at preventing weight gain in healthy weight people living with HIV infection or addressing overweight or obesity.

The treatment of T2D in people with HIV infection requires lifestyle changes with an emphasis on healthy weight and, more importantly, healthy waist circumference, with appropriate nutritional and physical activity intervention. Since the epidemic of overweight and obesity now affects more than 50% of Australians, this has also affected people with HIV infection. Those at higher risk of T2D include people with a family history or ethnic susceptibility (eg people with Indigenous Australian, South East Asian, South Asian, Pacific Islander or South American Indian heritage), who need particular consideration for assessment of diabetes risk, diabetes screening for early detection, and early intervention.

In addition to weight-optimisation and physical activity, metformin is the first line glucose lowering medication. In people with treated HIV infection, metformin is an insulin sensitiser, reduces abdominal obesity, reduces hepatic glucose uptake and improves glycaemic control.⁽²⁸⁾ Metformin is contraindicated in the presence of severe renal impairment or cardiac failure, where it may induce lactic acidosis. Care should be taken in patients receiving NRTIs, who have impaired renal function or elevated plasma lactic acid levels. Further, the integrase inhibitor dolutegravir can markedly increase circulating metformin levels. Metformin is eliminated by active renal tubular secretion through the organic cation transporter molecules, the action of which dolutegravir inhibits, thereby increasing post-dose metformin levels substantially. The maximal recommended metformin dose in people receiving dolutegravir is 1000mg daily. The risk of lactic acidosis is further increased where there is renal impairment and in states of dehydration. The clinical manifestations of hyperlactinaemia are non-specific. Diagnosis may be delayed by unpredictability in the onset of mitochondrial toxicity. Symptoms include abdominal pain, nausea, vomiting, weight loss, fatigue, dyspnoea, seizures, impaired cognition, arrhythmias and heart failure. Blood investigations may reveal anaemia and leukopaenia as well as elevation in aminotransferases, lipase and creatinine phosphokinase. All NRTIs may also cause hyperlactinaemia, however older drugs carry the highest risk (zidovudine, lamivudine, stavudine and didanosine).⁽²⁹⁾

In a patient who develops lactic acidosis, the NRTI medication or dolutegravir should be immediately ceased. Supportive care is the mainstay of treatment, aiming to optimise tissue oxygen delivery by cardiopulmonary support. This includes fluid resuscitation and mechanical ventilation, if required. Resolution of hyperlactinaemia requires replenishment of mitochondrial DNA which may take 4-28 weeks to recover.⁽²⁹⁾ After normalisation of lactate levels a new antiretroviral drug regimen should be considered, with non-nucleoside reverse-transcriptase inhibitors (NNRTI) and protease inhibitors being a safer regimen for these patients. In those patients on dolutegravir plus metformin, an alternative glucose-lowering medication should be considered.

Other glucose lowering medications available to use in T2D include oral (sulfonylureas, dipeptidyl peptidase IV inhibitors, sodium glucose co-transporter 2 inhibitors) and injectable (glucagon-like peptide-1 analogues, insulin) agents. An individualised therapeutic approach should be undertaken to bring glucose levels to target, using glycated haemoglobin (HbA1c) as an index of glucose levels over three months. HbA1c targets are individually set, based on age and the risk of adverse effects from hypoglycaemia. Usual HbA1c targets

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

are 6.5-7.0% for most adults with T2D and 7.0-7.5% for adults with type 1 diabetes. Higher HbA1c targets are appropriate in the elderly, those with hypoglycaemia unawareness or with a history of severe past hypoglycaemic events.

In addition to glucose level control, standard diabetes care includes aggressive cardiovascular risk reduction (applying secondary prevention targets for fasting lipid levels and blood pressure), with annual review for diabetes complications, including examination for neuropathy, retinopathy and measurement of urinary microalbumin level. Despite these standards of diabetes care, there is evidence from both local and international studies of lower rates of achieving target glycaemic, lipid and blood pressure control and lower rates of complications screening in people living both with HIV infection and diabetes, compared to people without HIV infection.(30-33) These data suggest there may be treatment disparities, perhaps related to clinical differences, greater clinical complexity or, perhaps, clinical inertia. As people living with HIV infection are enjoying near-normal life expectancy and are at greater risk of diabetes-related complications and cardiovascular disease, it is critical benchmarked standards of care are achieved. Strategies to support best practice may include focused diabetologist education on HIV infection, internal audits of diabetes care clinical targets and adherence to complication screening. Greater emphasis on nutrition therapy and physical activity in conjunction with pharmacotherapy may reduce the metabolic and cardiovascular burden. We have previously recommended embedding a specialised diabetologist within HIV specialist services as an opportunity to ensure the standards of care are met for people living with both HIV infection and diabetes.(30) however this model of care has not been investigated for efficacy.

Prevention of diabetes is feasible in people with HIV infection. Many cases of T2D can be prevented by modest weight reduction, increased physical activity, a reduction in sedentariness and a diet that limits energy-dense foods. If prediabetes is detected, lifestyle management with modest weight reduction can prevent almost half progressing to diabetes mellitus. This can be augmented by the addition of metformin.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Thyroid disease

Autoimmune thyroid disease is encountered in HIV infection either as a consequence of immune reconstitution related to the use of cART or as a complication of immunomodulatory therapy. Graves' disease and, less commonly, primary hypothyroidism due to Hashimoto's thyroiditis may occur as a consequence of aberrant immune tolerance during immune reconstitution, with development of thyroid receptor antibodies and/or thyroid peroxidase antibodies.(34-38) Immunomodulatory therapy with agents such as interferon- α , which was previously used in the treatment of hepatitis C infection,(39) can result in production of stimulatory antibodies that results in Graves' disease and thyrotoxicosis.(38) Clinicians should be alert to the possibility of hypothyroidism or thyrotoxicosis following immune reconstitution (40). The advent of hypothyroidism requires treatment with thyroxine replacement, aiming to bring elevated thyroid stimulating hormone levels back into the reference range. Graves' disease requires treatment with thionamide therapy (carbimazole and, less frequently, propylthiouracil); where Graves' disease does not remit after 18-24 months of thionamide therapy, definitive therapy with either total thyroidectomy or radioactive iodine therapy require consideration.

Adrenal disease

Adrenal insufficiency is uncommon in HIV infection, but can occur as a consequence of infections (HIV-1, cytomegalovirus, toxoplasmosis, mycobacterial infections), neoplastic disease (Kaposi's sarcoma or other malignancies) or, very rarely, autoimmune disease (Addison's disease). Adrenal insufficiency is more common in the setting of AIDS, with subnormal stimulated cortisol responses in 26% of tested subjects.(41)

The symptoms that should alert a clinician to the possibility of adrenal insufficiency include unexplained fatigue, weight loss, nausea, weakness, postural presyncope, myalgias, arthralgias, sweatiness and confusion. Drug therapy can be associated with reduced synthesis of adrenal hormones (e.g. ketoconazole) or induced metabolism of steroids (e.g. rifampicin, phenytoin).(42) A history of recent withdrawal of oral or inhaled corticosteroid drugs should be sought.(43) Clinical features of adrenal insufficiency include cachexia, pigmentation of the skin or oral mucosa, or a postural drop in blood pressure. Pigmentation will not be found in adrenal insufficiency of pituitary origin, due to deficiency of adrenocorticotrophin hormone (ACTH), which is rare. Biochemistry tests may show hyponatremia, hyperkalemia, or hypoglycaemia. The diagnostic test for primary adrenal insufficiency is the short synacthen test, where a normal stimulated cortisol response would exceed 550nmol/L. Secondary adrenal insufficiency (due to pituitary disease) will produce a normal response to cosyntropin testing and can be diagnosed by an insulin-induced hypoglycemia test. Pituitary imaging is indicated in this setting to exclude infiltrative or destructive pathology.

Primary adrenal insufficiency is treated with glucocorticoid and mineralocorticoid therapy. Corticosteroid requirements vary and should be individualised to ensure symptomatic improvement, normalisation of electrolytes and alleviation of any postural blood pressure drop. Examples of glucocorticoid replacement types and doses are: prednisone 2.5-5 mg on waking, 1.0-2.5 mg early afternoon; or cortisone acetate 12.5-25 mg on waking, 10-12.5 mg early afternoon; or hydrocortisone 10-20 mg on waking, 4-8 mg early afternoon. Patients will also require mineralocorticoid support with fludrocortisone. 0.05-0.1 mg/d in two divided doses, adjusted to clinical response in blood pressure, aiming for normotension and no postural drop.

Acute adrenal insufficiency may occur in the setting of acute infection, surgery or other physical stress and may manifest with vomiting, hypotension, hemodynamic shock, coma. It is prevented and treated with intravenous glucocorticoids. For example, intravenous hydrocortisone 50-100mg twice daily with acute illness or at surgery and 1-2 days following surgery, for prevention. Higher doses are required with severe illness, such as hydrocortisone 100mg every 6-8 hours.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

People with adrenal insufficiency or chronic corticosteroid therapy use who experience acute minor illness should be advised to take double the usual doses of corticosteroids for 2-5 days, until the illness has passed.

An excess of adrenal hormones (Cushing's syndrome) can occur in patients receiving HIV protease inhibitors. Interference with the cytochrome p450 3A4 enzyme system results in the reduced elimination of oral and inhaled steroids. Cushing's syndrome can occur rapidly in patients receiving standard doses of oral steroids, in addition to inhaled steroids (for example, fluticasone), with pituitary-adrenal suppression occurring with long term therapy.(43) Cushing's syndrome should be suspected on historical and clinical evidence and diagnosed by detection of low or undetectable plasma cortisol levels in a clinically Cushingoid patient. Treatment is by reduction of oral steroid doses or gradual reduction in inhaled steroids, where the underlying respiratory disease permits. For those patients receiving inhaled steroids, simple strategies will reduce steroid exposure and its side effects. These include using dosing devices with lower oral cavity deposition (eg aerosolised rather than inhalers) with spacers and always rinsing/gargling and spitting (not swallowing). Other strategies may include changing the inhaled steroid therapy to agents that are not predominantly metabolised by the specific cytochrome p450 isoenzymes.

Disorders of calcium metabolism and osteoporosis

Hypercalcemia is uncommon in HIV infection. Primary hyperparathyroidism with hypercalcemia occurs at the same rate as the non-infected population. If hypercalcaemia is found with low parathyroid hormone (PTH) levels, underlying infection, malignancy or lymphoma require active exclusion.

Bone loss, low bone density and osteoporosis are found in HIV wasting syndrome and patients receiving long term cART.(44) Multiple factors specific to HIV-infection and its treatment contribute, including viral effects, medication effects (tenofovir, protease inhibitors) and low androgen levels. Other secondary causes for osteoporosis should be excluded, such as hypogonadism, thyrotoxicosis, primary hyperparathyroidism, Cushing's syndrome, renal phosphate wasting, coeliac disease and multiple myeloma. In patients with established osteopaenia or osteoporosis, clinicians should ensure an adequate intake of dietary calcium (at least 1000 mg/d) and that serum levels of 25-hydroxy vitamin D are about 80 nmol/L or higher. Weight bearing physical activity is encouraged (20 minutes of walking at least thrice weekly and, if possible, a weight training, core strengthening program), in addition to other lifestyle interventions such as reducing excessive alcohol and caffeine consumption and smoking cessation. In men with androgen deficiency, treatment with androgen supplementation has shown benefit.(45) Other therapies such as the bisphosphonates alendronate and zoledronic acid have been shown of benefit in HIV-infected people with osteoporosis.(46,47) Consensus expert opinion on osteoporosis treatment in treated-HIV infection recently recommended medication switches: tenofovir to abacavir or raltegravir; and protease inhibitor-based regimens to raltegravir-based regimens.(47)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Sex steroids

Male hypogonadism

Low androgen levels in HIV-infected men appear relatively common, often in the setting of low or inappropriately normal gonadotrophin levels. The cause of this is not completely understood, however contributors include the usual causes of hypogonadism in men. There appears to be an association with HIV wasting and lipodystrophy. [\(48\)](#)

Androgen deficiency in men leads to lean tissue and bone loss, fatigue and mood disturbance. Other symptoms may include a loss of body hair, testicular atrophy, reduced pubic hair and reduced libido. Clinical confirmation includes the findings of gynaecomastia, reduced secondary sex characteristics and small, soft testicles. Clinical signs that may suggest a secondary cause, including the presence of a goitre and thyrotoxicosis, a testicular mass, signs of chronic liver or pituitary disease. Biochemical confirmation is undertaken by measuring two early morning testosterone levels (at 8-9am), along with FSH and LH levels, prolactin and TSH levels. Diagnosis and examination for causes of testicular failure are detailed elsewhere. [\(49\)](#)

PBS prescribing of androgens in Australia require two early morning testosterone levels <8.0 nmol/L and endocrinologist evaluation. Treatment options include injectable testosterone (testosterone esters, 200-250 mg every 2-3 weeks, or long-acting testosterone undecanoate 1000mg IMI every 10-12 weeks), transdermal testosterone by patch, gel or lotion applied daily. Men receiving androgen supplementation require annual digital rectal examination of the prostate and annual measures of plasma prostate specific antigen levels.

Female hypogonadism

Secondary amenorrhoea is common in women with HIV infection, affecting about one in four women. [\(50\)](#) The prevalence of amenorrhea is higher among women who have lost significant amounts of weight in the setting of HIV-related wasting. [\(50\)](#) Evaluation should exclude pituitary disease (by measuring prolactin, LH and FSH), thyrotoxicosis, premature menopause, polycystic ovary syndrome, in addition to rare causes of hyperandrogenism.

Treatment in women with premature menopause (ie age <45 years) usually takes the form of the oral contraceptive pill or hormone replacement therapy, to alleviate symptoms of oestrogen deficiency and maintain bone mass. Therapy should be offered until the age of 50-53 years, that is, about the usual age of menopause. The presence of a past history of stroke, deep vein thrombosis or pulmonary embolism, or current cigarette smoking may alter recommendations for hormonal therapy.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Obesity

In considering weight gain in treated HIV infection, it is important to distinguish the “return to health” weight gain that can occur in the setting of cART initiation from the trajectory of undesirable and unhealthy weight gain that reflects modern western living and transition towards obesity. The ‘*return to health*’ describes the weight gain that follows cART initiation which ameliorates the debilitating catabolic infection that has depleted body fat and protein stores that characterise untreated HIV infection. This phenomenon and the studies documenting it are reviewed in detail elsewhere.[\(51\)](#) With international practice and guidelines recommending cART initiation after HIV infection detection, fewer people with untreated HIV infection in Australia experience the cachectic and wasted nutritional state that characterised earliest clinical experience.[\(52\)](#) Suppression of HIV replication by cART and normalisation of the associated increases in systemic inflammation restore resting energy expenditure,[\(52\)](#) representing effective viral suppression and CD4+ T cell recovery.[\(53\)](#)

Separate to the weight gain which characterises suppression of HIV infection and the “return to health”, is the weight gain that reflects the individual living with HIV infection caught in the modern obesogenic environment. Overweight and obesity currently affects 50-60% of Australian adults. Recent studies find that people with HIV infection have overweight and obesity rates similar to the uninfected population.[\(52, 54-58\)](#) US data from 2000 onwards show high rates of overweight and obesity in 40-63% of people with HIV infection, both pre-cART and on cART, paralleling US obesity statistics in the general population.[\(56-58\)](#) Recent US data also show that 44-54% of people initiating cART are either overweight or obese, prompting the query “where did all the wasting go?”.[\(20, 23\)](#)

Studies on weight gain after cART-initiation and transition into harmful categories of excess weight show that 20% of people with healthy weight at baseline become overweight or obese by 24 months following cART-initiation.[\(52\)](#) These studies highlight the elevated and rising obesity rates in people with HIV infection from well-nourished nations. Health care practitioners are encouraged to address overweight and obesity as part of standard cardiometabolic care for people with HIV infection, as they would for any individual with increased cardiometabolic risk, with standard practice of dietary intervention (focusing on energy restricting diets with psychological support for chronic behaviour change), pharmacotherapy, or bariatric surgery. Referral to a specialist obesity service is recommended where initial dietary interventions do not succeed.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

References

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Bone disease in patients with HIV infection

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Last reviewed: November 2019

Introduction

Age-related co-morbidities, such as osteoporosis, become more important as the HIV population ages. Added to aging, associated co-morbidities, anti-retroviral therapy and the effect of HIV itself contribute to bone diseases in HIV. This review will examine bone disease in HIV populations including osteoporosis, osteonecrosis, osteomalacia followed by a discussion of bone disease in those receiving PrEP and bone disease in children.

Osteoporosis

Definitions

Osteoporosis is characterised by low bone mineral density (BMD), and changes in bone architecture, leading to decreased bone strength and an increased fracture risk.⁽¹⁾ The World Health Organisation (WHO) has defined osteoporosis on the basis of the T-score.² Osteoporosis is defined as a T-score of -2.5 or below, osteopaenia as a T-score of between -1.0 and -2.5 and normal as -1.0 or above.

Prevalence

In the general Australian population of those in the 50-69 age group, 3% of men and 13% of women have osteoporosis. Higher levels are seen in those aged over 70 years.⁽¹⁾ Rates of osteoporosis appear to be higher in those with HIV. A meta-analysis showed an overall prevalence of 15% and a 3.68-fold increased risk of osteoporosis compared to their HIV-uninfected counterparts.⁽³⁾ In addition, the risk of fracture in these individuals is increased. A US study found an increased risk of fracture in HIV-infected persons, starting after age 30 in men and age 40 in women. This risk continued to increase with age.⁴ Other studies have confirmed increased fracture rates in HIV-infected populations with rates 30-70% higher than among uninfected matched controls.⁽⁶⁾ In a meta-analysis, the pooled estimate incidence rate ratio (IRR) was 1.58 for all fractures and 1.35 for fragility fractures.⁽⁷⁾

Aetiology

The cause of accelerated osteoporosis in HIV appears to be multifactorial including factors such as inflammation, HIV medication, established risk factors for osteoporosis, and high rates of tobacco and alcohol use.^(7,6) HIV itself has effects on bone, causing loss of bone mass. HIV proteins increase osteoclastic activity and promote osteoblast apoptosis, leading to decreased bone formation.^(6,2) HIV gp 120 has been shown to increase the rate of apoptosis in primary osteoblasts and can induce a shift of mesenchymal cell differentiation from osteoblasts to adipocytes.⁽⁵³⁾ HIV gp 120 modulates the function and development of osteoclasts by upregulating RANKL, thus increasing osteoclastic activity. Systemic inflammation associated with HIV infection is associated with increased levels of cytokines such as macrophage colony stimulating

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

factor and tumour necrosis factor. These increase osteoclast activity and subsequent bone resorption.

(53) The HIV proteins Tat and Nef have been shown, in vitro, to promote mesenchymal stem cell senescence and alter osteoblastic differentiation. (54) B cell dysfunction associated with HIV has also been postulated to contribute to bone loss. (38) Associated co-morbidities that are themselves associated with low bone mass are common in HIV-infected populations. (47) In particular, hypogonadism is common in HIV, and is associated with osteoporosis. (5)

Regardless of what initial anti-retroviral therapy (ART) is used, initial therapy is associated with a 2-6% loss of BMD. (6) In the START bone sub-study, early initiation of ART was associated with greater bone loss than delayed therapy. In the first year of this study, 2% loss of BMD was observed, similar to the bone loss that occurs with the administration of glucocorticoids. (36)

Certain antiretroviral drugs, such as the nucleoside reverse transcriptase inhibitor tenofovir disoproxil fumarate (TDF), have been more strongly associated with decreases in BMD. Protease inhibitors have been implicated to a lesser extent. (8) The bone toxicity associated with TDF is thought to be associated with proximal tubule toxicity, resulting in phosphate wasting and increased bone turnover. (6)

Rates of osteoporosis and fracture have been found to be higher in HIV/HCV co-infected patients. A meta-analysis found a prevalence of osteoporosis of 22% in co-infected patients with an unadjusted OR of 1.63, compared to those with HIV mono-infection. (37) The risk of fractures was 2-fold higher in the co-infected group. It is not clear why HCV infection increases the risk of low BMD. (38)

Screening tests for osteoporosis

It is recommended to assess the risk of fragility fracture and low BMD in all patients with HIV infection. (9) Important risk factors for fracture include:

1. Previous history of fragility fracture
2. Glucocorticoid therapy for more than 3 months
3. High risk of falls

Those with these risk factors should be assessed with dual-energy X-ray absorptiometry (DXA). In others, age-specific recommendations apply. (9) Australian osteoporosis guidelines state that all individuals who sustain a fracture following minimal trauma should be considered to have a presumptive diagnosis of osteoporosis. A presumptive diagnosis can also be made if a spinal compression fracture is found. (1) The presence of a vertebral fracture is a risk factor for further fractures developing (10) and a loss of height or more than 3 cm indicates the need to assess for a vertebral fracture with a standard spine X-ray. (1) The factors that should be considered when assessing the risk of osteoporosis are presented in Table 1.

Table 1. Risk factors for Osteoporosis

- History of minimal trauma fracture
- Height loss ≥ 3 cm and/or back pain suggestive of vertebral fracture
- Female
- Older than 70 years of age
- History of falls
- Parental history of hip fracture

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

- Premature menopause or hypogonadism
- Prolonged use of glucocorticoids (at least three months cumulative prednisone or equivalent ≥ 7.5 mg per day)
- Use of other medications that cause bone loss
- Conditions or diseases that lead to bone loss
- Low body weight Low muscle mass and strength
- Low physical activity or prolonged immobility
- Poor balance
- High alcohol intake
- Energy, protein or calcium undernutrition
- Vitamin D insufficiency
- Smoking

Assessing absolute fracture risk

Absolute fracture risk can be calculated using algorithms such as the Garvan Fracture Risk Calculator (GFRC) (www.garvan.org.au/bone-fracture-risk) or the Fracture Risk Assessment Tool (FRAX) (www.shef.ac.uk/FRAX). These assessment tools take into account multiple risk factors in addition to any history of fracture and BMD to calculate an absolute fracture risk. When calculating the FRAX score, HIV infection should be listed as a secondary cause.(9)

DXA screening

Australian osteoporosis guidelines suggest the following groups be screened by DXA:

1. Younger than 50
 - Minimal trauma fracture as individual case decision
2. 50 to 60 years
 - Vertebral fracture
 - Minimal trauma fracture
 - Disease or condition associated with bone loss
 - Medications increasing bone loss
3. 60 to 70 years
 - Vertebral fracture
 - Peripheral minimal trauma fracture
 - Disease or condition associated with bone loss
 - Hip fracture in a parent
 - Underweight
 - Multiple falls
 - Immobility

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Recommendations for DXA scanning in patients with HIV infection

Men aged 40-49 years or premenopausal women aged 40 years or older who have intermediate or high-risk stratification by FRAX (>10% 10-year risk of major osteoporotic fracture)

1. All post-menopausal women
2. All men 50 years of age or older
3. Adults with fragility fracture regardless of age

In addition to these indications, current European Guidelines suggest DXA if there is a high risk of falls or clinical hypogonadism.(11) Recent US guidelines recommend baseline BMD testing in postmenopausal women and in anyone over 50 years of age.(13) When interpreting DXA results, T-scores should be used for postmenopausal women and men 50 years of age or older and Z-scores for those less than 50 years of age.(9) To assess efficacy of treatment, DXA scans should be repeated in 2 years. If BMD is stable, then longer intervals can be considered. Conversely, in those at high risk of fracture, shorter intervals between DXA scans may be appropriate.(1) The optimal interval of time for repeating a BMD after the initial screening BMD in the non-osteoporotic population is unknown. OREP guidelines, using data from the general post-menopausal population and the HIV positive population, advise timing a repeat BMD based on the T-score of the initial BMD(9). For patients with a T-score of -2 to -2.49 a repeat BMD at 1-2 years is advised and for a T-score of -1.01 to 1.99 a repeat at 5 years. For patients with a normal BMD (T-score >-1) an interval of up to 15 years can be used. If during the recommended interval the patient has a fragility fracture or a new risk factor for osteoporosis develops then the repeat BMD should be performed earlier. A specific Medicare rebate for DXA scans for HIV is not available in Australia.

Screening for secondary causes of osteoporosis and assessment of falls risk

Once the diagnosis of osteoporosis is established, secondary causes should be looked for. The most common causes are presented in Table 2.

Table 2 Secondary causes of Osteoporosis

- Vitamin D deficiency
- Hyperparathyroidism
- Hyperthyroidism
- Hypogonadism
- Cushing's syndrome
- Phosphate wasting
- Idiopathic hypercalciuria
- Coeliac disease
- Multiple myeloma

If a history of falls is obtained or the patient reports poor balance, a falls assessment should be conducted.(15,16) This involves a medical history, a review of medications that may be contributing, and a physical examination that includes neurological and functional assessment. An occupational home therapy assessment and podiatry review may be warranted.(1)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Management of osteoporosis

Anti-retroviral therapy

In those with low BMD or osteoporosis, tenofovir disoproxil fumarate should be avoided.(35) A new formulation of tenofovir, tenofovir alafenamide (TAF) is associated with less bone and renal toxicity compared to TDF. In those at high risk of bone toxicity, TDF therapy should be changed to TAF.(12,13,35) Studies examining switching from regimens containing TDF to TAF containing regimens have shown improvement in bone mineral density whilst being non-inferior in maintaining viral suppression.(52,13) Boosted protease inhibitors have been implicated in causing bone loss in some studies and should be avoided if possible in those with low bone density.(6) Therapy with integrase inhibitors is associated with less bone loss.(28)

Diet and lifestyle

General recommendations include ensuring an adequate calcium and protein intake, cessation of cigarette smoking, avoiding excessive alcohol, maintaining a healthy body weight and ensuring an adequate but safe exposure to sunlight as a source of vitamin D.(1) The Australian recommended dietary intake of calcium is 1300mg per day for women over 50, 1000mg per day for men 50-70 years and 1300mg per day for men over 70 years.(14) Calcium should be obtained through dietary intake when able. At least three serves of dairy food per day is recommended.(14) Regular exercise is also recommended, especially progressive resistance training either alone or combined with weight-bearing exercise.(1,9) In those patients taking dolutegravir as part of their antiretroviral drug regimen, calcium supplements should be taken 6 hours before or 2 hours after the dose of dolutegravir as calcium may reduce the absorption of this agent.(34)

Vitamin D levels should be measured, and supplementary vitamin D should be given to those with vitamin D insufficiency (< 50 nmol/L) or deficiency (<25 nmol/L).(9) A serum 25-hydroxy vitamin D level of > 50nmol/L should be maintained.(1) Vitamin D replacement should be undertaken before bisphosphonate therapy is begun.

Pharmacological therapy

Agents used to treat osteoporosis in Australia include the bisphosphonates (alendronate, risedronate and zoledronic acid), denosumab (a therapeutic monoclonal antibody that neutralises RANKL) and teriparatide (a recombinant N-terminal portion of parathyroid hormone). Each agent is supported under the Pharmaceutical Benefits Scheme (PBS) with varying indications (Table 3).(1) If a patient does not meet PBS criteria but has a calculated 10-year fracture risk of either 3% or greater at the hip or 20% or greater for a major osteoporotic fracture then non-PBS subsidised treatment should be considered and discussed with the patient.

Alendronate has been shown to be effective in increasing BMD in HIV-infected populations.(17,20) Zoledronic acid has also been shown to be effective and a single dose of intravenous zoledronic acid prevents ART-induced bone loss in treatment-naïve HIV-infected patients.(21) Zoledronic acid has been shown to be more effective in increasing BMD than switching TDF in HIV-positive adults with low bone mass.(22)

Denosumab (Prolia) is a commonly used osteoporosis medication with good fracture risk reduction data for post-menopausal females(49). It is delivered as a subcutaneous injection every 6 months. There is no data on its efficacy in the HIV positive population. Its rapid offset of action means that it must be given every 6 months with delays or cessation resulting in losses of previous BMD gains(50). Recent case studies have also suggested that during this period of rapid offset there is an increased risk of vertebral fractures(51). Denosumab should not be used if the prescriber is not confident of patient compliance with the treatment

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

regimen. Teriparatide (Forteo) is currently the only anabolic agent available in Australia for the treatment of osteoporosis. There are restrictive PBS prescription criteria for teriparatide including having a fracture after 12 months of anti-resorptive therapy. There is very little data on its use in the HIV positive population.

Unlike studies in the general population, no agent has been shown to decrease fractures in HIV-infected groups. In those who have responded well to therapy (T-score more than -2.5 and no recent fractures), treatment can be ceased after 5-10 years but restarted if further fractures are sustained, a significant drop in BMD occurs or if a new issue develops that increases fracture risk.⁽¹⁾ Side-effects of bisphosphonate therapy include gastrointestinal irritation, medication-related osteonecrosis of the jaw and atypical fracture of the femur.^(1,23) Before and whilst taking bisphosphonates, dental review is recommended.¹ In cases of treatment failure or medication intolerance, referral to a specialist is indicated. HMG-CoA reductase inhibitors show a beneficial effect on BMD in HIV-infected adults on ART. Compared to placebo, patients receiving rosuvastatin modestly increased their BMD over 48 weeks. This change was significantly different to placebo.⁽³⁹⁾

Table 3. Pharmaceutical Benefit Scheme indications for osteoporosis medications

Medication	PBS Indication
Alendronate, Risedronate, Denosumab	1. Patient is aged 70 years or older and has a BMD T score of -2.5 or less or 2. Patient has had a minimal trauma fracture
Zoledronic acid	1. Patient is aged 70 years or older and has a BMD T score of -3 or less or 2. Patient has had a minimal trauma fracture
Teriparatide	1. Patient has had at least 2 minimal trauma fractures, with one new symptomatic fracture occurring after at least 12 months of anti-resorptive therapy, and patient has a BMD T-score of -3 or less

Osteomalacia

Osteomalacia is characterised by impaired mineralisation of bone, usually caused by vitamin D deficiency but can also be secondary to several other rarer conditions. It is associated with low BMD, as measured by DXA, and fractures.⁽⁶⁾ Phosphate wasting caused by the use of TDF may be associated with osteomalacia. The clinical presentation is characterised by bone pain and inability to walk due to microfractures.⁽²⁴⁾ Laboratory findings in osteomalacia are dependent on the cause and can include a low serum vitamin D level, hypophosphataemia and an elevated serum alkaline phosphatase level. As DXA scanning may not differentiate between osteoporosis and osteomalacia, the presence of osteomalacia may not be appreciated.⁽²⁵⁾ Specialist referral is indicated if this condition is suspected.

Osteonecrosis

Also known as avascular necrosis of bone (AVN), this condition results from deficient blood supply to bone resulting in bone death and has been long described in HIV-infected persons.⁽²⁷⁾ Subsequent studies showed that the risk of this condition is increased 100-fold in the HIV-infected population compared to the general population.⁽²⁶⁾ MRI studies have shown that this condition may be found in asymptomatic HIV-infected populations.⁽⁶⁰⁾ Established risk factors for osteonecrosis include steroids, alcohol use, smoking and

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

coagulopathies.(55) Vasculitis may have a role in causing osteonecrosis in HIV infection, possibly related to anticardiolipin antibodies. These antibodies are associated with endothelial disruption, platelet aggregation and vascular thrombosis, representing a possible contribution to the development of osteonecrosis.(56,60) HIV infection is also associated with immune activation, chronic inflammation and activation of coagulation pathways. These factors may contribute to the development of osteonecrosis. For example, elevated plasma levels of D-dimer and CRP have been associated with osteonecrosis of the hip in HIV-infected adults.(57) Increased production of proinflammatory cytokines such as interleukin-6 and tumour necrosis factor have also been implicated in the pathogenesis of osteonecrosis.(58) Further support of the role of inflammation in this disorder is the finding of raised levels of IgE associated with osteonecrosis.(59) High levels of IgE are associated with Th2-type cytokines and high IgE levels may promote platelet activation with subsequent formation of intravascular thrombi.

In a recent large cohort-study involving 11820 participants, there were 89 cases of osteonecrosis of the femoral head giving an incidence rate per 1000 person-year follow-up of 1.0.(29) In this study, there was no association between cumulative exposure to antiretroviral drugs and osteonecrosis although a small risk from these agents could not be excluded. Risk factors for osteonecrosis were a history of AIDS-defining conditions, lower CD4+ T cell counts, white race and a history of prior fracture and prior osteonecrosis.(29) However, no data was collected on the use of alcohol, corticosteroids, megestrol acetate or testosterone. Use of these agents has been related to the risk of osteonecrosis in earlier studies.(31,32) An association between the use of protease inhibitors and osteonecrosis had been suggested in earlier studies.(30) Progression of disease may necessitate total hip replacement and disease may subsequently develop in the other hip.(43)

Bone Disease in other groups

HIV-negative persons receiving Pre-Exposure Prophylaxis (PrEP)

PrEP is recommended in HIV-negative persons who are at high-risk for HIV infection.(13) The recommended regimen for PrEP involves a fixed-dose combination of oral emtricitabine/tenofovir disoproxil fumarate (FTC/TDF). Given the association of TDF with bone loss, concern exists about bone toxicity in those receiving PrEP. A sub-study from an earlier trial of PrEP conducted in San Francisco, showed a small but significant decrease in BMD from baseline, greater at the femoral neck.(40) These changes occurred in the first 12 months of tenofovir therapy with no further decline at 24 months. A similar decrease in BMD was seen in a pre-exposure prophylaxis study in Botswana, involving both men and women.(41)

More recent data comes from a DXA sub-study of the Pre-exposure Prophylaxis Initiative (iPrEx), a large trial conducted using FTC/TDF.(42) This study found that BMD decreased in those randomised to FTC/TDF in the spine and at the hip. In the spine, the net difference was -0.91% and the net difference at the hip was -0.61%. Changes in BMD at week 24 correlated inversely with intracellular tenofovir diphosphate. In this study, almost 50% of the study subjects were aged less than 25 years of age, making the study findings less applicable to older HIV-infected populations. Further studies to examine the risk of bone loss in those receiving PrEP are required. In the meantime, those commencing PrEP should be informed of this potential risk.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Children and adolescents

In this population, the impact of HIV and its therapy on developing bones may be different from adult populations. The assessment of potential effects needs to be counterbalanced by the expected changes in bone throughout childhood and adolescence.(44) Most studies of perinatally infected children have shown lower than expected bone mass.(6) The prevalence of low BMD may be lower in high-income settings than in middle-income settings, perhaps explained by lower nadir CD4+ T cell count, poorer nutritional status and more advanced HIV disease stage.(44)

Studies have reported variable effects of ART on bone density in this population. Most data are provided by switch or salvage studies with little data available from treatment-naïve populations. In children, tenofovir and boosted protease inhibitors are most often associated with low BMD. (44,45) The impact of in utero exposure to antiretroviral agents is an area of ongoing investigation. Recent studies suggest that in utero exposure to TDF has minimal effect on infant bone mass.(45) Current WHO guidelines continue to support the use of TDF containing regimens in pregnancy.(46) Maintaining good bone health is essential in children. This includes obtaining adequate nutrition and physical activity and avoiding cigarette smoking.(48)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Renal disorders in people with HIV infection

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Last reviewed: November 2019

Introduction

Renal disease has emerged as one of the predominant non-infectious comorbidities (NICMs) seen among people with human immunodeficiency virus (HIV) infection.^(1,2) It has long been recognised that people with HIV infection are at particular risk of renal disease, although the pattern of disease has changed significantly over time. Rather than the previously seen HIV-related renal disorders, such as HIV-associated nephropathy (HIVAN),⁽³⁾ the chronic kidney disease (CKD) now seen often relates to sequelae of chronic NICMs, such as diabetes and hypertension.⁽⁴⁾ In addition, the widespread use of antiretroviral therapy (ART) and improved patient survival has resulted in ageing of the patient cohort and increased exposure to potentially nephrotoxic medications, including antiretroviral drugs.⁽⁵⁾ Consequently, in the era of modern ART, the burden of renal disease has increased, despite a reduction in renal diseases caused directly by HIV infection. The increased prevalence of CKD in this patient group has led to an emerging focus on delivering models of care for multiple NICMs efficiently and effectively, as well as concerns regarding polypharmacy and geriatric-specific considerations.⁽⁶⁾ In addition, the recognition of a genetic predisposition to kidney disease in this patient group is important, with some patients still at risk of HIV-induced renal disease, particularly those patients of sub-Saharan African origin.⁽⁷⁾

Renal disease is important in this patient group because the presence of CKD is associated with increased rates of morbidity and mortality.⁽⁸⁾ Increasing numbers of HIV-infected patients are observed with CKD, as well as increasing numbers of HIV-infected patients requiring dialysis or kidney transplantation.⁽⁹⁾ Early detection of renal disease and effective screening and management of risk factors for renal disease in HIV-infected people may help reduce the current burden of CKD.⁽¹⁰⁾

Epidemiology of renal disease in HIV-infected people

CKD is reported commonly in people with HIV infection, although estimates of the prevalence of renal disease vary according to study design, location and the definition of renal impairment used.⁽¹¹⁾ A global prevalence of CKD of 6.4% in HIV-infected patients using the MDRD formula, or 4.8% using the CKD-EPI formula, has been reported in a systematic review of studies from 60 countries world-wide; however, the African continent demonstrated the highest prevalence of CKD with 7.9% of HIV-infected patients affected overall, according to the MDRD formula.⁽¹²⁾ Some studies have reported a much higher prevalence of CKD within Africa, with 44.4% of HIV-infected patients affected by CKD in Cameroon using the CKD-EPI formula. The variability of prevalence may relate to true differences in disease patterns, but may also reflect variability in the methods used to estimate renal function in the clinic and in the equations used to estimate a patient's renal function.⁽¹³⁾ The reported prevalence of CKD, defined as a glomerular filtration rate (GFR) <60 mL/min on two separate occasions 6 months apart, ranges from 4.7 – 9.7% in the United States of America (USA) and Europe.⁽¹⁴⁾ Rates of up to 30% are reported in some studies.⁽¹⁵⁾ As well, proteinuria is common in these patients with rates of up to 10% reported in the Australian population.⁽¹⁶⁾

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

The higher prevalence of CKD in HIV-infected patients in Africa may be explained by the 18- to 50-fold higher risk of patients of African descent world-wide developing HIV-related end-stage renal disease (ESRD) compared to Caucasian patients.(14) The susceptibility to the development of kidney disease in these patients is primarily due to genetic factors.(7) Black African patients in the Western and Southern African continent are more likely to carry certain polymorphisms of the apolipoprotein-1 (APOL-1) gene that have been linked to an aggressive course of HIVAN.(17) More recently, this genetic marker has also been linked to susceptibility to a wide-range of renal conditions, such as hypertension-related renal disease and Focal Segmental Glomerulosclerosis (FSGS) in HIV-negative individuals.(7) The risk alleles G1 and G2 of the APOL-1 gene, located on chromosome 22, have not only been strongly associated with the development of HIVAN but may be a pre-requisite for the development of HIVAN.(18) These APOL-1 gene risk alleles are found in 70-80% of persons of African origin.(17)

Importantly, the prevalence of NICMs, particularly hypertension and diabetes, are significantly associated with the prevalence of CKD in HIV-infected patients; the higher the prevalence of NICMs, the higher the prevalence of CKD.(19)

Risk factors for renal disease in HIV-infected people

Risk factors associated with an increased risk of CKD are well recognised. Some of these are modifiable, emphasising the importance of their early detection and management.(19) Renal risk factors may be specific to patients with HIV; other 'traditional' renal risk factors have overlap with those seen in the HIV non-infected patient group, as shown in Table 1.(20,21) It is important to consider an individual patient's overall risk of renal disease at the time of diagnosis, and to modify their ART and subsequent monitoring accordingly, though even patients on non-nephrotoxic ART remain at high risk of renal disease.(21)

Table 1. Risk factors for renal disease in patients with HIV infection (adapted from Estrella *et al* (20) and Lucas *et al* (21))

TRADITIONAL RISK FACTORS
• Older age • Hypertension • Diabetes • Obesity • Cigarette smoking • Co-infection with hepatitis C virus and/or hepatitis B virus • APOL-1 risk alleles
HIV-SPECIFIC RISK FACTORS
• Some antiretroviral drugs • Low CD4+ T cell counts • High HIV viral load • History of AIDS-defining illness

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Detection of renal disease

Clinically, CKD is often asymptomatic and is often detected on routine screening.(22) Patients who are at risk for renal disease should be routinely screened for the presence of CKD.(23) In addition to a full clinical assessment for risk factors for renal disease and measurement of blood pressure, at risk patients should have a urine test for albuminuria and a blood test for creatinine to estimate their renal function.(24)

The measurement of renal function, or the GFR, is complex and the most commonly used methods are imperfect.(25) The estimated GFR (eGFR) is the most widely used clinical measure of renal function. This value is derived from the level of serum creatinine, a breakdown product of muscle metabolism. The serum creatinine level is not an ideal measure of GFR, as creatinine is both filtered by the glomerulus and actively excreted by proximal renal tubular cells.(26) Therefore, medications interfering with the excretion of creatinine may alter the serum creatinine level, without an actual change in GFR. This has implications for some antiretroviral drugs, which can interfere with the tubular transport of creatinine. As well, the serum creatinine level is determined by muscle mass and so varies by sex, race, age and body mass index. The serum creatinine level must be interpreted mindful of these individual patient factors.(27,28)

Urinalysis, or the urine dipstick, is used to detect proteinuria, as well as to provide information regarding other markers of renal pathology, such as haematuria and glycosuria. The urine dipstick predominantly detects albuminuria, a hallmark of glomerular disease, and may not detect other urinary proteins. This characteristic is important, as other proteins may predominate in certain clinical situations, such as tubular proteinuria, which may be seen with the use of tenofovir disoproxil fumarate (TDF).(29) Therefore, a urinary protein:creatinine ratio (uPCR) is preferable in patients with HIV infection, particularly those patients receiving TDF. As well, patients receiving TDF may have abnormalities of their serum phosphate level; a low serum phosphate level may be seen with proximal tubular dysfunction.(30)

Screening for renal disease

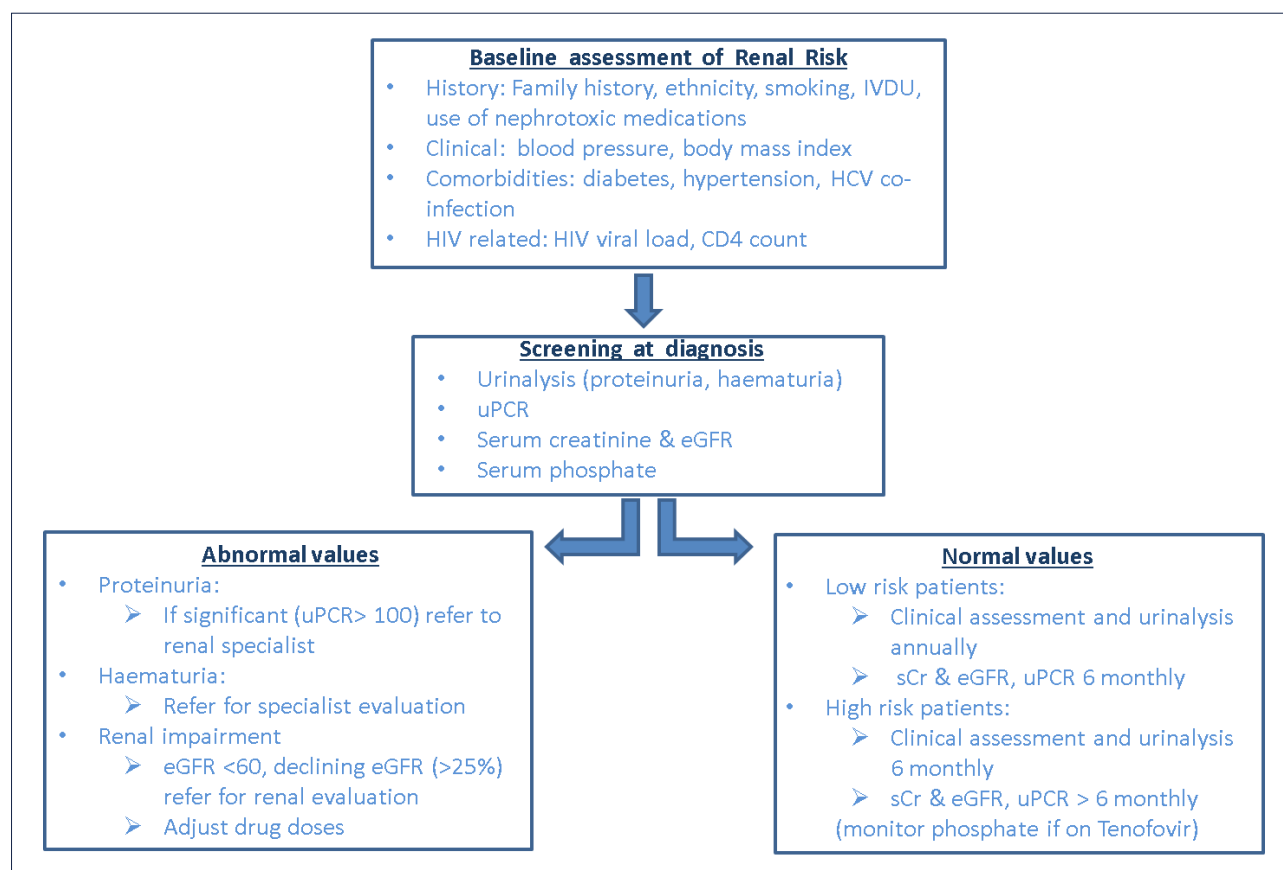
International guidelines recommend that HIV-infected patients should be screened regularly for CKD to allow for its early detection and prompt management.(21,29) Because of the high risk of CKD in this patient group, it is recommended that these patients have their GFR estimated at least every 6 months and should have either a urinalysis or a quantitative assessment of their urinary protein excretion at least annually. Patients whose eGFR has declined by 25% or more, or to a level below 60mL/min/1.73m², or who have protein excretion of over 300mg/day, should be referred for evaluation by a Nephrologist.(29) Patients who are found to have haematuria with any level of proteinuria or GFR should also be referred for assessment.

In patients receiving TDF, it is recommended that the serum phosphate level be monitored and that more frequent screening for CKD is undertaken.(30) An Australian consensus statement regarding the monitoring of patients receiving TDF suggested that patients be tested at baseline for serum creatinine, eGFR, serum phosphate level, urinalysis and assessment of the uPCR. Repeat screening was suggested at 3-monthly intervals for the first year of therapy and then at least annually in all patients; more frequently if any abnormalities are detected.(30)

Adherence to accepted guidelines for screening for CKD in HIV-infected patients is variable.(16) A suggested approach to screening for renal disease in patients with HIV is shown in Figure 1.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Figure 1. Screening for renal risk in patients with HIV infection (adapted from Holt *et al*30., Lucas *et al* (21). and European AIDS Clinical Society [EACS] guidelines (29)).



Management of abnormal screening tests

If a patient's baseline screening tests or clinical assessment demonstrate an abnormality, underlying reasons for renal disease should be sought. Further investigation of the aetiology of renal impairment may be required, and referral to a Nephrologist is recommended if there is CKD, significant proteinuria, haematuria or difficult-to-control hypertension.(29) Referral to a Nephrologist should also be considered for patients after the commencement of ART with the development of any of these features, as well as those patients with progressively declining renal function, or in the setting of the clinical suspicion of ART-related nephrotoxicity. (21,29,30)

A patient's risk of developing kidney disease should also be evaluated and modifiable risk factors addressed. The close association between renal and cardiovascular disease mandates that the patient's risk of cardiovascular disease should also be addressed in those at risk and in those with abnormal baseline screening tests.(29) Management approaches include lifestyle modification, such as weight loss and smoking cessation. As well, pharmacological control of hypertension with an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB) should be commenced, especially if there is proteinuria at baseline. Other modifiable risk factors which should be addressed include dyslipidaemia and hyperglycaemia.(31) Some improvement in renal function and proteinuria has been described after commencing ART.(32) Other specific therapy may be required, depending on the aetiology of the patient's renal disease. These therapies are usually commenced by a Nephrologist.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Consideration should also be given to the identification of any reversible factors, such as the cessation of nephrotoxic medications, and attention should be paid to dose adjustment of medications excreted through the kidneys. (33) An important consideration is the renal profile of ART and the renal risk factors of an individual patient. In most circumstances, potentially nephrotoxic antiretroviral drugs should be avoided if a patient is at very high risk of renal disease or has established renal disease at baseline. (34) Importantly, all patients with HIV-infection, regardless of type of ART used, remain at risk of CKD and should be routinely screened for clinical risk factors and for the presence of CKD.

Specific renal disorders in patients with HIV infection

The aetiology of renal disease in HIV-infected patients may be related to the HIV infection itself or, more commonly, be a manifestation of NICMs or an adverse effect of ART. (34) Acute kidney injury of any aetiology is associated with an increased risk of CKD in the longer-term. (35) To differentiate with certainty between the wide-range of different renal pathologies that are possible in HIV-infected patients, a renal biopsy may be indicated, although, even with a renal biopsy it can be difficult to absolutely attribute the causation of HIV infection in the pathological features demonstrated. (36) A useful classification system of the aetiology of renal disease in HIV infection is based on the predominant tissue compartment affected by the renal pathology; glomerular, tubulointerstitial, vascular or other, as shown in Table 2. (37)

Table 2. Classification of HIV-associated renal pathology based on predominant tissue compartment affected.
(adapted from Swanepoel *et al* (37))

Glomerular compartment
HIV-associated nephropathy
Focal segmental glomerulosclerosis
HIV immune-complex kidney disease
IgA nephropathy
Membranoproliferative glomerulonephritis*
Tubulointerstitial compartment
HIV-associated nephropathy
Acute tubular necrosis
Tubulointerstitial nephritis, often drug-related
Diffuse infiltrative lymphocytosis syndrome (DILS)
Vascular compartment
Atherosclerosis
Thrombotic microangiopathy

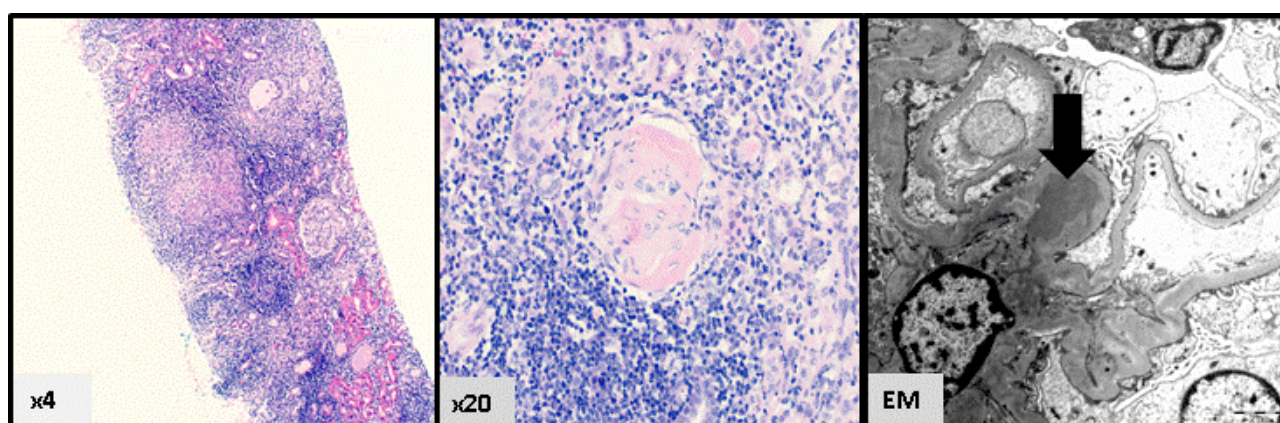
CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

HIV-related renal disease

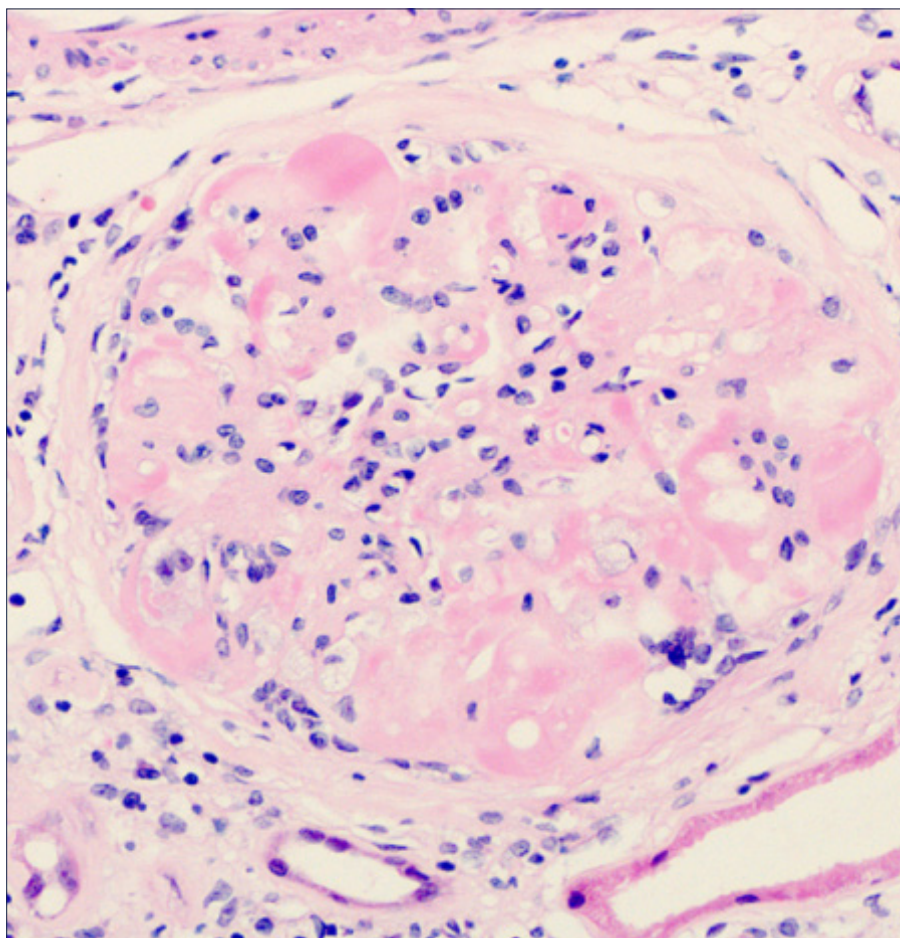
HIVAN and HIV immune complex kidney (HIVICK) disease are the most frequent forms of renal disease directly related to HIV infection.⁽³⁷⁾ HIVAN is seen almost always in patients with advanced HIV infection and occurs predominantly in patients of African descent, explained by a genetic predisposition. Increased susceptibility to HIVAN among this group of patients is associated with polymorphisms in the APOL-1 gene.⁽⁷⁾ HIVAN typically manifests clinically with heavy proteinuria, without haematuria. There is usually a rapid decline in renal function and increased echogenicity of the kidneys on renal ultrasound. Histologically, the lesion seen is a collapsing FSGS.⁽³⁸⁾ The mainstay of treatment for the underlying renal lesion is ART. Prednisone and antiproteinuric agents (ACE inhibitors, ARBs) may also be used.⁽³⁹⁾ Supportive treatments such as dialysis and renal transplantation may be required. The prognosis for patients with HIVAN remains poor but has improved following the widespread introduction of ART. Because of modern ART, HIVAN is now much less common among people with HIV infection. Indeed, non-collapsing FSGS is now more commonly seen than classic HIVAN at renal biopsy.⁽³⁷⁾ In these patients, plasma HIV RNA is usually undetectable and they are usually receiving ART. The histological findings may be difficult to distinguish from secondary FSGS in the general population.⁽⁴⁰⁾

Numerous forms of immune complex kidney disease may also be seen in patients with HIV infection. Although the term HIVICK has been used to describe these conditions, a specific description of the pattern of immune complex deposition in the setting of HIV infection is preferred because of the lack of certainty regarding causality of the HIV infection and because of the heterogeneous nature of these conditions.⁽³⁷⁾ HIVICK is composed of a variety of histological conditions, including immunoglobulin A (IgA) disease, and a lupus-like syndrome.^(41,42) It is characterised by the deposition of immune complexes within the kidneys, associated with cellular proliferation, inflammation and damage. Tubulointerstitial inflammation may be prominent, as shown in Figure 2. Clinically, these conditions have heterogeneous presentations; there may be microhaematuria, a variable degree of proteinuria and impairment of renal function. HIVICK benefits from ART and the prognosis appears to be more favourable when compared to HIVAN.⁽³⁷⁾ Other HIV-related renal diseases, such as thrombotic microangiopathy and diffuse infiltrative lymphocytosis syndrome (DILS) have been also reported but are not common.⁽³⁷⁾

Figure 2. HIV immune complex kidney (HIVICK) disease, with prominent interstitial inflammation and glomerular hypercellularity (Figure 2a); glomerulosclerosis (Figure 2b); and deposits of IgA on electron microscopy (arrow) (Figure 2c) (Reproduced with permission of Dr Lyndal Anderson and Associate Professor Paul McKenzie, Tissue Pathology and Diagnostic Oncology, Royal Prince Alfred Hospital, Sydney NSW).



CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		



Other forms of renal disease

As in HIV seronegative people, the commonest causes of CKD in people with HIV infection are related to NICMs, in particular, hypertension and diabetes³¹. With the ageing of the HIV-patient cohort on ART and the increased burden of NICMs seen, renal disease related to these conditions is increasingly common.⁽⁴³⁾ The clinical and histological features of these conditions are similar to the general population, although some studies suggest an additional role for HIV infection in the progression of renal disease in this setting.⁽³⁷⁾ It can be difficult to separate the causation of non-classical FSGS in some patients; secondary FSGS may be

related to hypertension, however, there may also be overlap with an HIV-related effect on the glomerulus.⁽³⁷⁾ Both conditions may be associated with proteinuria and CKD, although haematuria is less commonly seen. Their progression is usually insidious but may be abrogated by stringent attention to the patient's vascular risk profile.⁽⁴⁴⁾ Diabetic nephropathy is characterised by nodular expansion of the glomerulus, with associated scarring and fibrosis, as shown in Figure 3. Hepatitis C virus co-infection may also increase the risk of CKD in HIV infection, particularly with a higher HCV viral load.⁽³⁷⁾

Figure 3. Diabetic nephropathy in a patient with HIV infection. The glomerulus is expanded and exhibits nodular change (arrow) and patchy inflammation (Reproduced with permission of Dr Lyndal Anderson and Associate Professor Paul McKenzie, Tissue Pathology and Diagnostic Oncology, Royal Prince Alfred Hospital, Sydney NSW).

Antiretroviral therapy and renal disease

In addition to those conditions mentioned above, data suggest a role for antiretroviral drugs in adding to the risk of CKD in patients with HIV infection.⁽⁴⁵⁾ The risk of CKD relates not only to the use of potentially nephrotoxic antiretroviral drugs but also to the patient's comorbid conditions, polypharmacy and advancing age, as well as to HIV-specific factors.^(37,46) Some antiretroviral drugs, in particular, may place a patient at increased risk of CKD, as shown in Table 3.⁽³⁷⁾ In addition, some antiretroviral drugs may increase the serum creatinine level because of their effect on the excretion of creatinine by the proximal renal tubule, as seen in Table 3, causing an apparent change in glomerular function, without any real change in the patient's actual GFR.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Table 3. Renal effects of current antiretroviral therapy (adapted from Swanepoel *et al.*(37)).

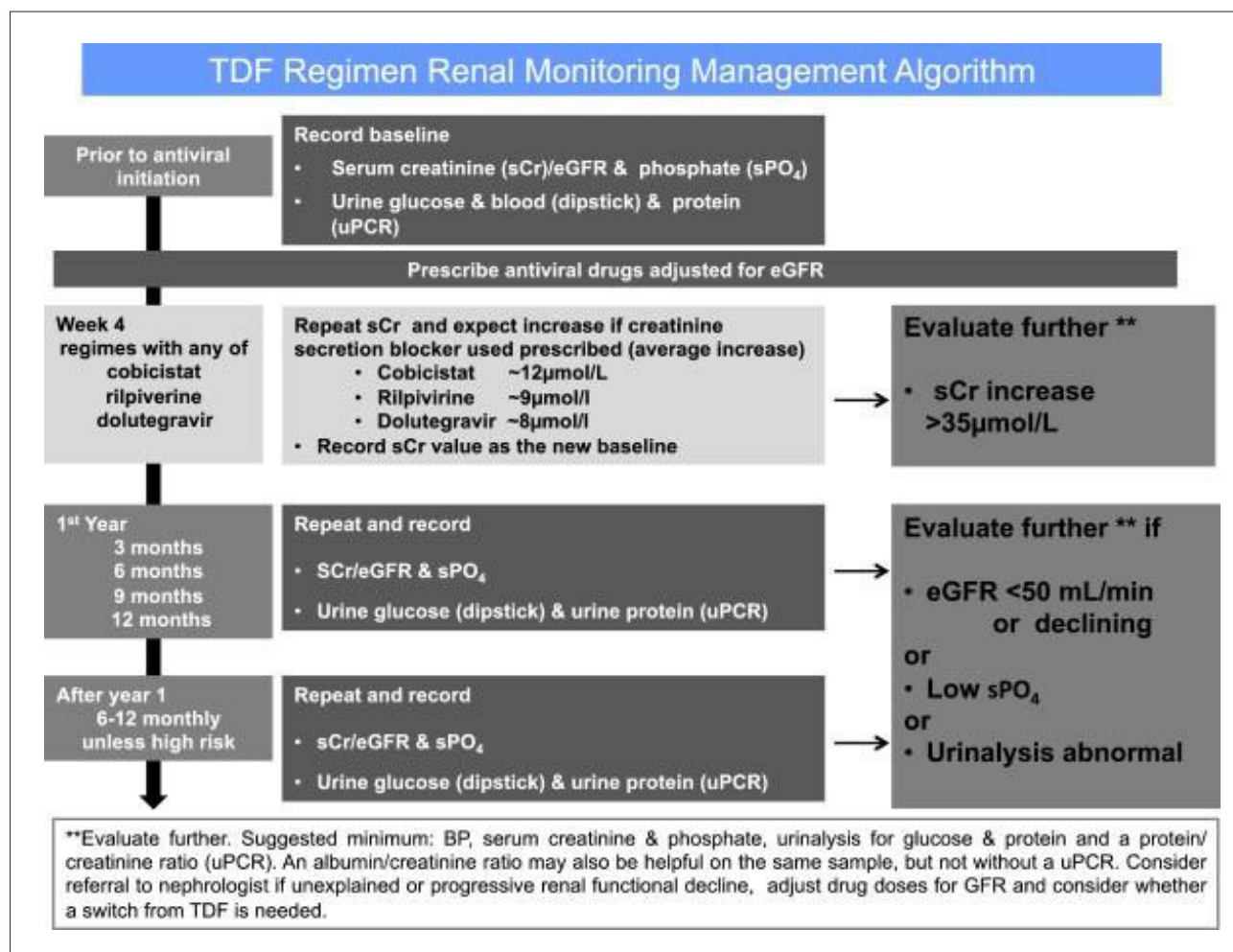
Antiretroviral agent	Possible renal effects
Tenofovir disoproxil fumarate	Renal dysfunction (acute or chronic) Proximal tubular dysfunction Fanconi syndrome (rare)
Ritonavir/lopinavir	Chronic kidney disease
Ritonavir/darunavir	Crystalluria
Ritonavir/atazanavir	Inhibition of tubular creatinine excretion Renal dysfunction (acute or chronic) Crystalluria
Cobicistat (with elvitegravir, tenofovir disoproxil fumarate, emtricitabine)	Inhibition of tubular creatinine excretion
Cobicistat/atazanavir (with elvitegravir, tenofovir disoproxil fumarate, emtricitabine)	Inhibition of tubular creatinine excretion
Dolutegravir	Inhibition of tubular creatinine excretion
Rilpivirine	Inhibition of tubular creatinine excretion

TDF is a widely prescribed and a very effective antiretroviral drug that is excreted by the kidneys. Dose adjustments are required in patients with significant CKD.(47) TDF may also be prescribed for the prevention of HIV infection in people who are at high risk of HIV acquisition.(37) TDF may cause acute renal impairment, CKD and proximal renal tubular dysfunction. TDF is found at high concentrations in the proximal renal tubular cells and can cause mitochondrial toxicity. In some cases, the tubular dysfunction may be subclinical but in some patients it may be associated with the Fanconi syndrome; a clinical triad consisting of proteinuria, hypophosphataemia and renal glycosuria.(48) If the Fanconi syndrome is seen in patients on TDF, the drug should be ceased, as these effects may be significant, and in some cases life-threatening. Subclinical proximal tubular dysfunction may also be clinically important for long-term renal function, as well as bone health. In this situation there are limited data to suggest a uniform clinical approach to these adverse effects and dose reduction, increased vigilance with monitoring, or cessation of TDF may be appropriate. Overall, serious adverse renal effects are uncommon with TDF; however, because of the potential clinical importance of these effects, increased vigilance with screening for nephrotoxicity is suggested, as shown in Figure 4 .(30,37) Around 1-2% of all patients on TDF will need to stop treatment because of tubulopathy.

The newer formulation of tenofovir (TFV), tenofovir alafenamide (TAF), is metabolised differently to TDF and demonstrates increased intracellular levels of TFV in lymphocytes, but lower levels in the plasma and proximal renal tubules. Studies suggest much less renal toxicity with this new formulation.(49) Longer-term safety data for this novel agent are emerging. No specific screening tests are recommended in addition to the usual health checks in HIV-infected patients receiving TAF. HIV-infected patients treated with TAF remain at high risk of CKD and should be screened regularly for renal risk factors, and for the presence of CKD. There is also some evidence to suggest that TAF is effective for HIV pre-exposure prophylaxis, and it may also have a superior side-effect profile for this purpose, when compared to TDF.(50)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Figure 4. A suggested approach for renal monitoring in patients treated with potentially nephrotoxic antiretroviral agents, and agents which may artefactually affect the serum creatinine (Reproduced with permission, from Holt *et al.*(30)).



Some antiretroviral drugs are recognised to inhibit the excretion of serum creatinine by proximal renal tubular cells by the blockade of specific transporters. These agents; cobicistat (COBI), dolutegravir (DTG) and rilpivirine (RPV), act on different transporters in the proximal tubular cell, but are not directly toxic to the cell itself.(45) These drugs may increase the serum creatinine level, without altering the patient's glomerular function. The actual GFR is unchanged; however, the serum creatinine level is artificially increased, with a resultant apparent reduction in the eGFR₃₇. This effect is seen because serum creatinine is not an ideal measure of glomerular function; it is both filtered by the glomerulus (80-90%), as well as excreted by the proximal tubular cell (10-20%). The increase in the serum creatinine level seen after starting these agents occurs early, usually within 2-4 weeks, and is not progressive.(29) The increase in eGFR should not usually exceed 25% in patients with normal renal function but may be higher in those patients with pre-existing CKD. The evaluation of renal impairment and the calculation of drug doses may become challenging in patients treated with these agents, particularly those with established CKD. (37) The detection of TDF-related nephrotoxicity may also be an issue and tubular function should be closely monitored, as shown in Figure 4.(29,30,37)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Polypharmacy and the risks of drug-drug interactions are high in HIV-infected patients, particularly in the older patient group.(51) This is relevant given the ageing of HIV-infected patients and the associated increasing burden of NICMs, requiring treatment with additional non-ART medications. Polypharmacy is also associated with adverse drug reactions and drug-drug interactions and with poor treatment adherence. Drug dosing and interactions are important considerations, particularly in HIV-infected patients with CKD. (52) Medication issues are much more frequently seen in HIV-infected patients, when compared to the uninfected population. In recent times there has been a move to simpler two-drug ART regimens in an attempt to simplify therapy and improve tolerability.(53)

Treatment of renal disease in people with HIV infection

CKD has important implications for clinical outcomes, with a higher burden of morbidity and mortality. It is associated particularly with ESRD and a high burden of cardiovascular disease.(37) Patients with HIV infection and renal impairment in the presence of albuminuria are at particular risk of increased morbidity and mortality. (54) These patients should be closely assessed for reversible factors placing them at risk of progression of renal disease; these risk factors should be addressed early. Attention to blood pressure control, treatment of hyperglycaemia, hyperlipidaemia and lifestyle factors, such as weight loss and smoking cessation, are important considerations. As well, pharmacological control of hypertension with an ACE-inhibitor or an ARB should be commenced, particularly if there is proteinuria at baseline.(37) Other reversible causes for renal impairment should be sought, such as the use of nephrotoxic medications, and underlying renal conditions such as HIVAN should be excluded. Patients with HIVAN should be placed on ART if they are not receiving it already.(32) Patients with CKD or ESRD should also be commenced on ART, as this is associated with better outcomes in this patient group. Dose adjustment of medications excreted by the kidneys should also be undertaken, and the use of potentially nephrotoxic agents should be avoided.(29) The management of patients with HIV infection who have established renal impairment is usually undertaken in conjunction with a Nephrologist.(29,30,37)

Dialysis and renal transplantation

The number of HIV-infected patients with ESRD is increasing.(55) These patients may require treatment with dialysis or renal transplantation, usually in centres with expertise in this area. The one-year survival rate of patients with HIV infection on dialysis has improved recently, although the rate remains inferior to that of the population without HIV infection.(56) These improvements may reflect the changing aetiology of renal disease in people with HIV infection. Renal transplantation is safe and effective in patients with HIV infection.(57) Assessment of a patient's suitability for renal transplantation is recommended for all Australian patients with HIV infection and ESRD. Patient selection for transplantation is usually performed in centres with experience in both the management of HIV infection and in renal transplantation.(58) Results of renal transplantation in HIV-infected patients are favourable, particularly if these patients have an undetectable HIV viral load and no history of opportunistic infections or cancer, although, reported outcomes are inferior to the patient group without HIV infection.(37,58) Acute renal allograft rejection is reported more commonly in patients with HIV infection undergoing renal transplantation. Medication interactions and polypharmacy are also important considerations in this setting.(37)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Summary: renal disease in HIV-infected patients

HIV-infected patients are at particular risk of CKD, which is often related to CNICM, such as diabetes and hypertension. Non-infectious comorbidities are increasingly common, with the increased survival and ageing of the HIV-infected patient population.

- CKD in HIV-infected patients is associated with poorer patient outcomes, including higher morbidity and mortality. CKD is often associated with cardiovascular disease.
- HIV-infected patients should be screened regularly for CKD to allow for its early detection and management.
- Potentially nephrotoxic antiretroviral drugs should be avoided if a patient is at high risk of renal disease, or if there is evidence of established renal disease. Regardless of the type of ART used, all HIV-infected patients are at risk of CKD and should be routinely screened for renal risk factors and for the presence of CKD.
- For HIV-infected patients at high risk of CKD, blood pressure control, treatment of hyperglycaemia, hyperlipidaemia and attention to lifestyle factors, such as weight loss and smoking cessation, are important. Control of established hypertension with an ACE-inhibitor or an ARB is indicated, particularly if there is proteinuria at baseline.
- The number of patients with HIV infection and ESRD is increasing. These patients may require treatment with dialysis or renal transplantation.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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10. Special Patient Populations

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Ageing with HIV infection

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Last Reviewed: 2020

Introduction

The average age of people with HIV infection in Australia has increased substantially since 1986, due predominantly to the availability of combination antiretroviral therapy (ART), associated with improved survival and reduction in AIDS-related complications. (1-6) Non-AIDS related mortality has now surpassed AIDS-related mortality as the major cause of death in people with HIV infection. (4) In 2017 in Australia, 46% of people with HIV infection were aged over 50 years, reflecting a global trend of prolonged survival and late acquisition of HIV infection among older people. (2, 6)

Despite increasing longevity, ART has not enabled a complete return to normal health among older people with HIV, who have a well-recognised increased burden of non-communicable age-associated comorbidities. (1-4, 6-8) The pathogenesis of these conditions in this setting may involve an accelerated (premature, faster) and/or accentuated (more frequent) ageing process related to a burden of harmful lifestyle behaviours and their effects, such as smoking and central fat accumulation; effects of persistent HIV infection in cellular reservoirs; increased permeability of the gut to microbial products and alterations in the gut microbiome; ART toxicity, and co-infection with cytomegalovirus or hepatitis C virus (HCV). (1, 3, 5, 6, 8-11) Many of these factors contribute to HIV-associated immune activation and chronic inflammation, which, while blunted by ART, are not eliminated. In particular, activation of innate immune responses has been implicated in non-AIDS co-morbidities, and when observed in older people, is described as 'inflammaging.' (9) (1) (3-5, 7, 10) (11) In spite of this, there is clear evidence of benefit for early ART in all people with HIV infection to help reduce chronic inflammation. (10)

Subclinical chronic inflammation associated with HIV infection and its relationship with age-related complications and decreased survival has evolved as a top priority in the HIV research agenda. (4, 5) Specifically, data from the Strategies for Management of Antiretroviral Therapy Study (SMART study) demonstrated that elevated plasma levels of IL-6 and D-dimer were strongly related with non-AIDS-defining co-morbidities and all-cause mortality in patients on ART. (5) (12) The concept of immunosenescence, 'a functional limitation of immunity resulting from age-associated changes in a variety of cells involved in both innate and adaptive immunity, and an imbalance between the two arms, describes a similar immune senescent phenotype and T-cell abnormalities common to both ageing in the general population and untreated HIV infection. (5)

This complex interplay of factors has been associated with an increase in the number of people with HIV infection who are also living with co-morbidities. (6, 13, 14) These co-morbidities include, but are not limited to, neurocognitive disorders, cardiovascular disease (CVD), chronic kidney disease (CKD), metabolic syndrome, type 2 diabetes mellitus, osteoporosis and cancers. (9) (3, 7, 8) (4, 5) (6) The accumulation of these co-

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

morbidities in multiple systems has led to a rising incidence of geriatric syndromes in older people with HIV infection, including multimorbidity and polypharmacy, delirium, frailty, incontinence, falls and fragility fractures, and cognitive dysfunction, further compromising quality of life and often occurring much earlier in comparison to HIV-negative counterparts. (9) (3-5, 7, 8)

The rate of ageing can differ significantly between individuals, dependent upon both genetic and environmental factors. (15) The Australian Bureau of Statistics defines age chronologically; hence persons aged over 65 years are classified as 'older.' (16) Chronological age however may not be the most accurate way of measuring ageing or predict an individual's trajectory and total lifespan. (17, 18) To address this inadequacy, the notion of 'biological age', which encompasses the use of biomarkers to describe age-related changes in body function and composition, has been developed, and helps predict the onset of age-related morbidity and/or mortality. (17) (7) A number of biomarkers have been proposed to investigate the association between HIV infection and ageing and include plasma biomarkers of chronic immune activation, inflammation and hypercoagulation; decreased chromosome telomere length; increased mitochondrial DNA somatic mutations; ophthalmological parameters; and age-related brain atrophy. (1) (3, 6) (11) (19) (20-26) Telomere shortening in people with HIV infection has been attributed to the effects of the virus itself as well as exposure to some nucleoside analogue reverse transcriptase inhibitors (NRTIs). (1)

With the average age of those attending HIV clinics increasing, and with this expected to continue into the future, along with the burden and complexity of non-communicable co-morbidities, healthcare needs and associated costs are expected to increase. (6) Guidelines to help direct the optimal clinical management of older people with HIV infection are therefore likely have a positive impact on the health system. (4) A recently convened workshop on HIV and ageing emphasised the importance of instituting holistic comprehensive care for people ageing with HIV infection, that not only includes HIV care, but also management of the many other psychosocial, mental health and co-morbid medical issues contributing to reductions in quality of life. (27) Suggested approaches include behavioural and cognitive diagnostic screens and educational activities on topics such as smoking cessation and cardiovascular health. (27) Social interaction was also highlighted, given the overwhelming isolation that people with HIV infection experience, related to persistent stigma associated with HIV infection and 'HIV survival fatigue.' (27) Social engagement and interaction with other people with HIV infection may help to address this. A recent National HIV, Ageing and Quality of Life Roundtable (2019) highlighted similar findings and stressed the importance of improvement in geriatric models of care for people with HIV infection, support for Aged Care Services (including My Aged Care and National Disability Insurance Scheme) to meet the needs of diverse groups of individuals, elimination of both perceived and actual stigma and discrimination through peer educators and advocates, and continued HIV education for the revolving door of aged care workers.

Optimising ART in the older HIV patient

Early initiation of ART is still of utmost importance in older people with HIV infection and is probably of more significance, compared with younger people, due to the potential for poorer immune recovery on ART and a higher risk of serious non-AIDS events in older people with HIV infection. (28-30) This approach is supported by data from observational cohort studies and a post-hoc analysis of data from the START study. (28, 31-33) Education should be provided that suppression of HIV replication (HIV viral load < 200 copies/mL) improves overall health, as well as prevents transmission of HIV infection, including from people ageing with HIV infection. (28)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

A change in ART regimen (cessation, switch or dose adjustment) may be required to minimise toxicity and/or drug-drug interactions, when older people with HIV infection develop non-AIDS co-morbidities, such as bone disease, CKD, CVD, or frailty. (4, 28) For example, Tenofovir Disoproxil Fumarate (TDF) has been associated with an increased risk of CKD (34) and a higher prevalence of osteopenia and osteoporosis (35), and it is now expert recommendation to switch TDF or boosted protease inhibitors (PIs) to another antiretroviral drug in those at high risk for fragility fractures. (28, 36) Similarly, in people with declining renal function, a drug regimen that avoids TDF or atazanavir should be considered. (28, 37)

Given that multiple treatment options now exist, the ART regimen that is prescribed should take into consideration not only the individual and provider preference but also be informed by the patient's co-morbidities. (4) Clinicians should be aware that hepatic metabolism and renal elimination of some drugs decline with age and may result in increased drug exposure and risk of adverse drug reactions. (28) Most clinical trials have included only a small proportion of participants over the age of 50 years and current ART dosing recommendations are based on younger persons with normal renal and hepatic function. (28) Close monitoring for adverse effects is recommended.

The significant increase of age-related co-morbidities in people with HIV infection has led to increased healthcare utilization and associated higher costs. (28) Out-of-pocket expenses and loss of employment related to the burden of chronic disease can lead to financial strain/insecurity, and possible inability to pay for ART medication – this should be avoided whenever possible. Increasing life expectancy and multi-morbidity can place greater demand on HIV services – thus an approach where modifiable health-related problems are prioritized should be employed. (28)

Even in people with a severe, debilitating non-AIDS related condition, the general consensus is to continue ART if there is no overt harm or negative impact on quality of life. (28) If the ART is contributing to harm or diminished quality of life, the decision for ART cessation should be made in conjunction with the patient and partner/family. (28)

Key recommendations

1. Early ART initiation in older persons with HIV infection is of utmost importance.
2. The optimal ART regimen should be tailored to the individual – their preferences, co-morbidities and non-AIDS associated complications should all be considered.
3. ART regimens may need to be changed on the basis of the risk, or confirmation, of non-AIDS co-morbidities, such as bone disease, CVD and CKD.
4. The metabolism of medications may be altered or impaired in the ageing individual and adverse drug reactions should be closely monitored for.
5. People ageing with HIV infection who have multiple co-morbidities will incur increased healthcare expenditure and medication costs and may encounter financial strain. The HIV clinician should screen for this, and where possible, resources and support be offered in order to avoid ART treatment interruption.
6. The decision to continue ART in an older person with HIV infection, in the context of a severe, debilitating non-AIDS associated condition, is a risk versus benefit decision that takes into account individual and partner/family preferences.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Disease and disease-related disability from non-AIDS co-morbidities

There is clear evidence that the burden of HIV-associated non-AIDS co-morbidities has been increasing steadily in people with HIV infection, with an increasing prevalence of CVD, CKD, osteoporosis, cancer and type 2 diabetes mellitus. (4, 38)

Bone disease

The primary objectives of bone health programmes in healthy adults are to prevent bone loss occurring prematurely and decrease fracture risk later in life. In addition to traditional risk factors, people with HIV infection are at increased risk of bone disease attributable to HIV-associated immune activation and exposure to antiretroviral drugs. (36) Those people on effective ART have lower bone mineral density (BMD) than those not on ART. They also experience more fractures than age and sex-matched people in the general population. (28, 39) Loss of height is a clue that subclinical vertebral fractures have occurred, necessitating further investigation with radiography and dual energy X-ray absorptiometry (DXA) scans. Bone disease in people with HIV infection is characterised by a high rate of bone turnover evidenced by elevated markers of bone formation and resorption. (40) Risk of fragility fracture can be assessed by using the [Fracture Risk Assessment Tool](#) (FRAX®) further informed by DXA scan to determine bone mineral density. (36, 41)

The classical risk factors for osteoporosis to consider in people with HIV infection include older age, female gender, hypogonadism, family history of hip fracture, low body mass index (BMI) ($\leq 19 \text{ kg/m}^2$), vitamin D deficiency, smoking, physical inactivity, history of low trauma fracture, alcohol excess (> 3 units/day), glucocorticoid exposure (minimum prednisone 5 mg/day or equivalent for > 3 months). (42) Causes of secondary osteoporosis to consider include hyperparathyroidism, vitamin D deficiency, hyperthyroidism, malabsorption, hypogonadism or amenorrhoea, diabetes mellitus, and chronic liver disease. (42)

It is well known that initiation of ART is associated with increased bone turnover and loss of BMD over the first 1-2 years of ART which tends to stabilise thereafter (36). For example, the START BMD substudy showed a greater decline in BMD in the immediate ART group compared with the deferred ART group. (43) ART regimens containing TDF, boosted PIs, or both have been associated with significantly greater loss of BMD than regimens containing other NRTIs and integrase strand inhibitors (INSTIs). (28, 42, 44-47) Additional loss and gains in BMD have been observed with switch to, and away from, TDF-containing ART regimens, respectively. (42) However, the clinical relevance for fracture risk is unknown. (42) Abacavir, NRTI-sparing regimens, and tenofovir alafenamide (TAF) may be considered alternatives to the use of TDF in older people with HIV infection at risk of osteopenia or osteoporosis. (28) The benefit of a switch from TDF to abacavir should be balanced with the potential increased risk of cardiovascular disease. (28)

Expert recommendations currently advise screening for low BMD by DXA scan in men aged ≥ 50 years and postmenopausal women, patients with a history of fragility fractures, those on chronic glucocorticoid treatment or with a high risk of falls. (28, 36) The risk of falls can be assessed using the [Fall Risk Assessment Tool](#) (FRAT) – The frequency of subsequent DXA scans is determined by the result of the initial screen: if the T-score is normal at both the hip and spine, repeat screening is recommended in 5 years, if the T-score is between -2 and -2.5 (advanced osteopenia) the DXA should be repeated in 1-2 years (36)

Treatment of osteoporosis in older people with HIV infection is generally similar to that in the general population and is addressed in the section on Osteoporosis

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

There is evidence that anti-resorptive agents are safe and effective in increasing BMD in people with HIV infection and reducing fracture risk. (39, 48, 49) The safety and efficacy of denosumab (RANK Ligand inhibitor) has not been established in HIV infection to date. While switching ART to replace TDF and/or PIs has been shown to increase BMD, 2 infusions of zoledronic acid 12 months apart demonstrated that treating low BMD with zoledronic acid was superior to switching from TDF, with a trend to fewer fractures (in a randomised controlled trial, the ZEST study). (39, 50)

For current recommendations regarding calcium and vitamin D supplementation and their clinical relevance to bone health, please go to the section on Bone Disease.

Supervised exercise programs for people with advanced osteoporosis can help avoid fractures, prevent falls, and reduce declines in quality of life. Programs for older adults focus on weight bearing exercise, posture and balance, gait and co-ordination, with hip and trunk stabilization.

Key recommendations

1. People with HIV infection are at increased risk of osteopenia and osteoporosis, and fragility fractures compared with the general population. Risk of fragility fracture should be assessed using the Fracture Risk Assessment Tool (FRAX®) in all people with HIV infection aged 40 years and over, and further informed by DXA scan to determine bone mineral density.
2. Expert opinion recommends the measurement of bone mineral density using DEXA scanning in men over 50 years, post-menopausal women, patients with a history of fragility fractures, those on chronic glucocorticoid treatment or with a high risk of falls. Frequency of subsequent screening is dictated by results of the initial DXA scan
3. Regularly screen people with HIV infection for traditional and secondary risk factors for osteoporosis, regardless of age, and institute appropriate management (eg. smoking cessation, increased physical activity).
4. Treatment of osteoporosis with zoledronic acid is more effective in increasing bone mineral density and the effect more durable compared with switching ART
5. The ART regimen in people with potential (i.e. high FRAX score) or confirmed osteoporosis should be reviewed and a switch from TDF or boosted PIs to an alternate ART regimen should be considered. Abacavir, NRTI-sparing regimens, and TAF are potential alternatives to TDF.
6. Measure and record height every 2 years in those over the age of 50 years
7. Supervised exercise programs focusing on balance, co-ordination and weight bearing should be encouraged

Renal function and ageing

Renal disease in ageing people with HIV infection, has important clinical implications, given the estimated prevalence of between 2.4% – 17%, and association with adverse long-term outcomes. (51-54) The expected physiological decline in renal function with ageing combined with increased comorbidities place older people with HIV infection at risk for polypharmacy and subsequent medication-related toxicity. (51, 55) In addition, progressive loss of renal function in people with HIV infection may also be caused by HIV-associated glomerular disease (non-collapsing focal and segmental glomerulosclerosis), co-infection with HCV, HIV-associated immune complex disease, and antiretroviral drugs. (56) The overall risk of CKD is reduced by

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

ART through the prevention or treatment of HIV-associated nephropathy, opportunistic infections and/or immune complex deposition. (51) This may come at a cost, however, as some antiretroviral drugs cause renal impairment. (51, 56) The high prevalence and faster progression of CKD in older people with HIV infection requires regular monitoring of kidney function. (28, 55, 57)

Both hypertension and diabetes are common comorbidities in older people with HIV infection and intensive screening and risk factor modification is indicated to help preserve renal function. (28, 42) For example, if there is evidence of hypertension and/or proteinuria, antihypertensives that reduce proteinuria; angiotensin-II receptor inhibitors or ACE inhibitors, are recommended as first-line treatment. (42) Guidelines on risk factor modification (28, 42) are detailed in the section of this PDF on Atherosclerotic Vascular Disease in People with HIV Infection.

The physiological increase in serum creatinine/reduction of eGFR (10-15 mL/ min/1.73m²) observed with the use of dolutegravir (DTG), bictegravir, rilpivirine (RPV), cobicistat (COBI) and ritonavir boosted PIs, is due to inhibition of proximal tubular creatinine transporters, without impairing actual glomerular filtration. This can result in a misdiagnosis of new renal impairment, especially in older people with HIV infection and other comorbidities. (51, 58-60)

In older people with HIV infection and evidence of, or an increased risk for, declining renal function, ART regimens containing TDF and atazanavir should be avoided. (28, 37) Guidelines recommend consideration of replacing TDF by a non-tenofovir drug or TAF if there is evidence of tubulopathy. The use of TAF in the context of an eGFR < 30ml/min has limited data, with longer term outcomes unknown – expert opinion should be sought. (28)

General measures to help maintain kidney function include avoidance of nephrotoxic drugs, lifestyle measures (smoking cessation, weight, diet), treatment of dyslipidemia and diabetes, and the adjustment of ART medications as necessary. A detailed table outlining dose adjustment of antiretroviral drugs for impaired renal function is provided elsewhere –

Key recommendations

1. Renal disease in ageing people with HIV infection has important clinical implications and is frequently multifactorial; renal function should be monitored regularly and screening should be undertaken for risk factors of CKD (i.e. hypertension, diabetes mellitus, polypharmacy) and if found managed intensively.
2. General measures to help maintain kidney function include avoidance of nephrotoxic drugs, lifestyle measures (smoking cessation, weight management, diet), treatment of dyslipidemia and diabetes, and the adjustment of ART medications as necessary.
3. Renal function should be measured at HIV diagnosis, and annually, using urea and electrolytes, eGFR, and urine protein assessment. Urine protein/creatinine ratio should be performed in people receiving TDF therapy.
4. Switching to alternate antiretroviral drugs is recommended when impaired renal function is demonstrated in people taking antiretroviral drugs with nephrotoxic potential, including TDF and atazanavir. Other antiretroviral drugs may require dose adjustment in the presence of impaired renal function.
5. Guidelines recommend switching from TDF to TAF or a non-tenofovir containing regimen in older people with HIV infection and risk for or evidence of declining renal function.
6. Older people with renal failure are at increased risk of CVD and should have a FRS estimated (BP, lipids, smoking status and diabetes) and statin medication considered.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Malignancy in older people with HIV infection

There is no evidence to support cancer screening at an earlier age in people with HIV infection. At each clinic visit, the opportunity should be taken to address cancer risk factors by advising smoking cessation, alcohol reduction, obesity management and treatment for HCV infection. Age-appropriate general population screening guidelines should be followed for all people with HIV infection. The only caveat to this is HPV-related cancers; annual digital ano-rectal examinations are recommended for MSM with HIV infection over 50 years of age, due to significantly higher rates of anal cancer, and improved outcomes if diagnosed at earlier pre-symptomatic stages.

Liver function and ageing in people with HIV infection

Liver disease has emerged as a major cause (up to 20%) of morbidity and mortality in ageing people with HIV infection on effective ART. (28, 61-63) Age-related declines in liver volume (20-40%) and blood flow (35-50%) and reduced cytochrome P450 content result in impaired drug elimination and increased drug exposure in the older general population. (28, 64) This becomes important for people with HIV infection as clearance of several antiretroviral drugs is via hepatic metabolism, necessitating close monitoring and awareness of potential adverse effects of ART and other medications. In general, dose modification of antiretroviral drugs is only required when end stage liver disease is present. A detailed table outlining dose adjustment of antiretroviral drugs for impaired hepatic function is provided elsewhere. People with HIV infection are also vulnerable to liver injury through persistent HIV replication (chronic immune activation and inflammation), diabetes mellitus, substance use (particularly alcohol) and untreated HCV or hepatitis B virus (HBV) infection. (65, 66) Hepatitis C virus infection is curable and reduces the long-term complications of liver fibrosis, cirrhosis and hepatocellular carcinoma. The direct-acting antivirals (DAAs) have proven to be well tolerated and highly efficacious in the context of co-infection with HIV, and every effort should be made to cure HCV infection in people with HIV infection, regardless of age. (66) Suppression of HBV replication with appropriate ART will also reduce hepatic complications. Specific ASHM guidelines for HCV and HBV management can be found here <https://ashm.org.au/learning-hubs/hepatitis-c/> and HBV: <https://ashm.org.au/learning-hubs/hepatitis-b/> Treatment and Monitoring of Persons with HCV/HIV Co-infection and Treatment and Monitoring of Persons with HBV/HIV Co-infection. (42)

Older people with HIV infection found to have raised serum levels of hepatic transaminases need to have the following considered; (1) recent introduction of hepatotoxic medication, hepatotoxic herbal products or recreational drugs; (2) recent change in ART regimen or a potential drug-drug interaction (to determine attribution to the ART regimen, return to the original regimen if virologically suppressed, and observe change in ALT/AST in the next 4-8 weeks); (3) HBV reactivation, which may occur when ART regimens are changed leading to failure to control HBV replication; new HCV or hepatitis A virus (HAV) infection; (4) alcohol induced liver disease; (5) severe right heart failure and (6) non-alcoholic steatohepatitis (NASH) and non-alcoholic fatty liver disease (NAFLD) – the most common cause of liver function test derangement.

Almost half of all people with HIV infection investigated for deranged liver function tests are found to have NAFLD, and the prevalence of NAFLD (25-35% worldwide) is now higher than in the general population. (42, 67, 68) Both ageing and metabolic dysregulation have been proposed as underlying mechanisms. (69) In population studies of people with HIV infection, NAFLD was found to be associated with high BMI, visceral adiposity, insulin resistance, dyslipidaemia and a high alanine aminotransferase/aspartate aminotransferase ratio. (68, 70-73) HIV infection may itself be associated with a fatty liver, as a result of multiple viral and host factors (69) and is associated with increased morbidity and mortality. (72)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

NAFLD is defined as having hepatic steatosis involving >5% of hepatocytes; with the exclusion of secondary causes including alcoholic fatty liver disease (≥ 30 g alcohol for men and ≥ 20 g for women of daily alcohol consumption). (42) NAFLD is often associated with other components of the metabolic syndrome (central obesity, dyslipidemia, hypertension, insulin resistance +/- glucose intolerance, proinflammatory state, prothrombotic state). (74) Hepatocellular carcinoma (HCC) is also a well-recognised complication of NAFLD and can occur in the absence of cirrhosis and histological evidence of NASH. (42)

Hepatic ultrasound is the preferred diagnostic measure for imaging of NAFLD, whereas liver biopsy is gold standard – demonstrating steatosis, hepatocyte ballooning and lobular inflammation. Once NAFLD is suggested by ultrasound, risk of advanced fibrosis can be estimated by calculating the FIB-4 or Non-alcoholic fatty liver disease Fibrosis Score. (42) Lifestyle modification and weight loss are currently the main therapeutic interventions, (42) and entails caloric restriction, aiming for a target of 7-10% weight loss in persons with central obesity and exercise of at least moderate intensity at 150-200 min/week. (42) An antiretroviral drug regimen that does not increased serum lipids is also recommended for those with confirmed NAFLD.

Transient elastography, a non-invasive approach to a 'liver stiffness measurement', can be used to assess the degree of liver fibrosis and presence of cirrhosis. The severity of the chronic liver disease will determine ongoing management and surveillance, including need for liver biopsy, and screening for HCC and oesophageal varices if severe fibrosis is detected (F4). All people with HIV infection who have cirrhosis, including those with HBV infection that is medically suppressed or cured HCV infection, require screening for HCC by assay of serum alpha-fetoprotein levels and/or liver ultrasound every 6-12 months. Screening for oesophageal varices by upper gastro-intestinal tract endoscopy is recommended in any person with HIV infection who has liver cirrhosis and a liver stiffness measurement ≥ 20 or a platelet count $\leq 150,000/\text{mL}$.

Key recommendations

1. Liver disease has emerged as a major cause of morbidity and mortality in people with HIV infection. Therefore, screen for liver disease regularly, with liver function tests performed at least 6 monthly.
2. Expected age-related decline in hepatic metabolism may lead to inadvertent increased drug exposure, and subsequent hepatotoxicity. Close monitoring and awareness of potential adverse effects in this population is recommended.
3. Older people with HIV infection who develop derangement of liver function tests should undergo a full review of medications, including over the counter medications and supplements, alcohol use, and recreational drug use. New drug-drug interactions should be considered. Viral hepatitis serology should be performed and updated and depending on risk, repeated at regular intervals (i.e. 3-6 monthly if high risk). Immunisation with HAV and HBV vaccines is strongly recommended for those who are susceptible to HAV and HBV infection.
4. Treatments for HCV infection are highly successful and well-tolerated and should be offered, if indicated.
5. People with HIV infection have a high prevalence of NAFLD, the liver manifestation of metabolic syndrome. Ultrasound is the preferred diagnostic measure for imaging of NAFLD. Lifestyle modification and weight loss are currently the mainstay therapeutic interventions.
6. The severity of the chronic liver disease as measured by APRI, FIB-4 or transient elastography will determine ongoing management and the need for surveillance and screening for HCC and oesophageal varices. HCC screening every 6 months and screening for oesophageal varices by upper gastrointestinal endoscopy, as required, are recommended.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Cardiovascular disease and associated risk factors

Cardiovascular disease is of particular concern in people with HIV infection – with at least twice the risk of ischaemic heart disease and heart failure compared to non-HIV patients, even in the context of HIV viral suppression. **(8)** The rates of stroke, and other CVD manifestations, including pulmonary hypertension and sudden cardiac death are also higher. The increased risk of CVD and other atherosclerotic vascular disease can be associated with, or a direct consequence of, using some antiretroviral drugs as well as a result of the high and increasing prevalence of traditional risk factors for CVD (smoking, hypertension, dyslipidemia, diabetes, recreational drug use) – see section of this PDF on: [Atherosclerotic vascular disease in people with HIV infection](#).

Guidelines for the screening of people with HIV infection for CVD follow recommendations for the general population, with a focus on obtaining virologic suppression and appropriately managing traditional risk factors. **(4)** Cardiovascular disease risk calculators, including the Framingham risk score often underestimate the risk of CVD in people with HIV infection. **(4, 76)**.

Key recommendations

1. Screen for CVD in all age-appropriate people with HIV infection; in particular those with traditional CVD risk factors
2. CVD risk prediction tools used in the general population may underestimate the risk of CVD in people with HIV infection.
3. Strongly encourage smoking cessation in all older people with HIV infection.
4. If possible, avoid ART regimens that include abacavir or boosted protease inhibitors (except atazanavir) in older people with HIV infection and increased CVD risk.

Neurocognitive impairment in the older person with HIV infection

Cognitive impairment in people with HIV infection is an issue of increasing concern. Prior to the widespread use of ART, HIV-associated dementia (HAD) occurred in almost 50% of people with HIV infection prior to death. **(77, 78)** Effective ART has resulted in a dramatic reduction, with HAD now occurring in <2% of individuals. **(78, 79)** The current prevalence of cognitive impairment is variable and dependent on the definition used, with estimates of HIV-associated neurocognitive disorder (HAND) affecting up to 30% of people with HIV infection who have suppressed HIV replication on ART. **(3, 28, 78-80)** Neurocognitive impairment appears to increase with age, **(28, 81-83)** and with the presence of certain co-morbidities such as CVD, metabolic syndrome, co-infection with HCV and sleep and mood disorders. **(78)** Advancing age itself increases susceptibility to HAND, leading to an increase in the proportion of older people with HIV who experience HAD. **(28, 81-84)** Neurocognitive impairment may also differ by gender, due to hormonal shifts that occur with ageing. **(28, 85)** These impairments may be further exacerbated by a higher frequency of factors associated with neurocognitive impairment namely, drug use, stress, insulin resistance and liver fibrosis. **(13)** As these may become more prevalent and severe with age, they may further exacerbate neurocognitive impairment, and interact with HIV to “accelerate or accentuate cognitive ageing”. **(13)**

The pathogenesis of HAND is underpinned by viral, ART and host factors, as well as premature ageing and neurodegeneration. It has been linked to a combination of immune activation, neuroinflammation, ART neurotoxicity, co-morbidities such as vascular disease and depression, and lifestyle factors including recreational

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

drug use. (3, 78, 86-88) It is important to consider all potential factors including those not directly related to HIV. (78) HIV replication in the CNS has been strongly associated with neuronal damage and the development of HAD. There is also evidence that chronic sustained immune activation in the CNS leads to the production of neurotoxic products, such as nitric oxide, arachidonic acid, and proinflammatory cytokines. (78, 89)

HIV associated neurocognitive disorder consists of a spectrum of neurocognitive impairment, from asymptomatic to mild cognitive impairment; and HIV-associated dementia. (78) It is characterised by deficits in mental slowness, attention and memory, and impaired executive functioning as well as extra pyramidal features. (90-92) The cross-links between premature ageing and neurodegeneration are also important in the consideration of cognitive impairment in people with HIV infection. Cerebrovascular disease can occur because of traditional risk factors or from the metabolic and systemic effects of HIV and ART on endothelial function. (78) On brain MRI imaging, white matter hyperintensities are more common in people with HIV infection, increase with age and are associated with increased rates of cognitive impairment. (78, 93) The neurofibrillary tangles composed of phosphorylated tau, a hallmark of Alzheimer's Disease, also occur in people with HIV infection (94)

The maintenance of cognitive function for the individual translates to better health and quality of life; in the context of HIV, impaired functioning can have significant detriment including lower likelihood of retention in care, poorer health outcomes, and compromised medication adherence. (3, 95, 96, 111, 110) Other impacts of impaired neuro-functioning include mood and behaviour disorders, and an adverse effect on employment, driving capacity and interpersonal relationships. (78) (3, 78)

Most guidelines now recommend screening for cognitive impairment only in symptomatic people with HIV infection. (28, 42, 78) Because of the overlap in clinical presentation, imaging, CSF findings (CSF beta-amyloid) and neuropsychological deficits, differentiation between HAND, Alzheimer's Disease and vascular dementia can be difficult and expert neurological opinion/geriatric assessment should be sought. Tools for screening and differentiating different causes of cognitive impairment range from bedside screening assessments, formal neuropsychological assessments, biomarker assessments in both plasma and CSF, and the use of neuroimaging techniques. (28, 78)

It is important to acknowledge that mental health disorders are common in HIV positive patients and can contribute to poor cognitive performance. In turn, a decline in cognitive performance can lead to depressive symptoms. (78, 97, 98)

The cornerstone of the clinical management of HIV-associated cognitive impairment is ART, and if the patient is not on ART, it should be initiated to prevent ongoing neuronal damage from uncontrolled viral replication. (78) There is sparse evidence that specific ART regimens correlate with improvement in cognitive function, and in general, standard first line ART regimens are recommended. (78) The exception is the avoidance of efavirenz, on the basis of results of cohort studies suggesting poorer cognitive function in those receiving efavirenz-based ART. (78, 99, 100) If HIV RNA is not detected in CSF, then reassessment for other contributing factors should take place. (78) A change in ART regimen in patients with cognitive impairment and documented CSF virus escape (presence of HIV RNA in CSF when virologically suppressed in plasma) should be based on current and historic drug-resistance profiles of CSF and plasma virus, and/or potential ART neurotoxicity, and the ability of ART to penetrate the central nervous system. (78) Other non-pharmacological interventions are encouraged – including exercise, managing stress and low mood, sleeping well and instituting a healthy diet, as well as smoking, drug and alcohol cessation. (78, 99)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Key recommendations

1. Screening for and assessment of cognitive impairment in people with HIV infection should be performed if the person is symptomatic (self-reported or family members).
2. This assessment may be difficult in people with co-morbidities that may be responsible for, or contribute to, cognitive impairment, such as cerebrovascular disease, neurodegenerative conditions, HCV co-infection, and mood and sleep disorders.
3. Once mood disorders are either excluded or optimised, and cognitive impairment is suspected, formal assessment by a neuropsychologist or referral to a neurologist is recommended.
4. Ancillary investigations to aid clinical assessment include imaging (MRI brain), blood investigations (i.e. syphilis serology, plasma HIV RNA), and lumbar puncture to investigate for CSF virus escape. Further investigations and functional imaging may take place with specialist referral.
5. If CSF HIV RNA is detected after lumbar puncture, antiretroviral drug resistance testing should be performed to help guide possible change in ART regimen.
6. The optimal ART regimen in the context of suspected or confirmed cognitive impairment is based on best clinical practice, with a regimen that accommodates past and/or present available genotype susceptibility results, and possibly CNS penetrance of the medication. Expert assistance may be required.
7. There is no specific ART regimen that is recommended for people with HIV infection who have cognitive impairment, with the exception of avoidance of efavirenz.
8. Non-pharmacological interventions to consider and encourage include smoking and recreational drug cessation, alcohol reduction, exercise, and healthy eating and sleep hygiene practices.

Sexual function and sexuality

People with HIV infection can be expected to experience the usual age-related milestones in decline of sexual function but can also face additional challenges with regard to sexual function and sexuality. In terms of sexual function, sex hormone levels responsible for libido and secondary sexual characteristics, decline with age: testosterone drops from peak levels at age 30 by about 1% per annum; and, oestrogen falls more precipitously in the peri-menopausal period. (101) These changes may vary greatly between individuals, and within individuals and can impact sexual function, sexual identity and relationships. Males can expect a decline in erectile function, with early manifestations represented by less nocturnal tumescence. This can affect turgidity and duration of erections, delay arousal and orgasms, potentially creating psychological tensions, which exacerbate the physiological functions. Erectile dysfunction may be amenable to specific therapy, but other medications can jeopardise performance, enjoyment or have limited impact on underlying problems. Females may experience vaginal dryness, delays in arousal and dyspareunia in the extreme. Libido is primarily driven via testosterone, which will decline with advancing age. (102)

These concerns may be associated with a diminution in quality of life and may not be addressed in the clinical consultation. Questions about sexual and reproductive health and sexual function should be routinely asked at HIV consultation. This includes characterising the sexual problem, including at what phase in the sexual cycle the problems occur. Easy to use, online clinical questionnaires for men and women exist. (42) The next stage of assessment is to screen for an endocrine cause, i.e. related to hypogonadism. If there are signs or symptoms of hypogonadism in men, hormonal assessment via blood tests are suggested. These include serum levels of luteinizing hormone (LH), follicle stimulating hormone (FSH), total testosterone

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

and sex hormone-binding globulin to calculate free testosterone. If hypogonadism is present, referral to an endocrinologist is suggested. In women, signs of hypogonadism are those related to oestradiol insufficiency/ menopause, and if present, can be confirmed with testing for LH, FSH and oestradiol levels. If symptoms of menopause are present, referral to an endocrinologist or gynaecologist should be considered. (42)

The third part of the clinical assessment for sexual dysfunction is to screen for other causes; including psychosocial problems, urogenital infections, medications, drugs and lifestyle factors. (42) Common medication classes associated with sexual dysfunction include psychotropics, lipid-lowering and antihypertensive drugs in men. (42) The contribution of ART is controversial and a change in regimen is not recommended. Treatment of erectile dysfunction in men is primarily with oral PDE5 inhibitors (sildenafil, tadalafil, vardenafil). (42) Dosage should be lowered if the patient is receiving a boosted PI as part of their ART regimen. Of importance, 'poppers' can have a synergistic effect with PDE-5 inhibitors and lead to profound hypotension – concurrent use is not recommended. Treatment of premature ejaculation includes behavioural interventions, psychosexual counselling, SSRIs, tricyclic antidepressants, clomipramine and topical anaesthetics. (42) Drug-drug interactions may necessitate dosage adjustment. (42)

There is now clear evidence that people with HIV infection do not transmit HIV in the context of at least 6 months of effective, fully suppressive ART and no concomitant STIs. This concept, of Undetectable = Untransmittable (U=U), has been reported in both HIV serodiscordant MSM and heterosexual couples. (42, 103-105) With the knowledge of U=U, people with HIV infection should be empowered by their HIV clinician, and fears allayed of transmitting the infection to their partner, in order to help restore intimacy and sexual fulfilment.

Ongoing sexual activity should be reviewed in the context of infection risk, transmission potential (HIV, HCV, HBV, other sexually-transmitted infections (STIs)), new STIs, the presence of other chronic health conditions (106-108) and perceptions of wellbeing. Notably, psychological wellbeing appears associated with protected sex behaviour. (109) Screening for STIs should continue at recommended intervals suggested by guidelines; and people counselled in relation to risk. (28) Older people with HIV infection may have a higher risk of transmission if not virally suppressed, in the context of a change in risk-related behaviours (i.e. no condom use due to less concern about pregnancy and high-risk sexual activity with increased use of medication for erectile dysfunction). (28) Reduced mucosal and immunological defences (e.g. post-menopausal atrophic vaginitis) may also lead to an increased risk of acquisition of HIV. (28) Screening practices for HIV infection in older adults may also be low. (28) In those whom may be at risk of acquiring HIV, prevention strategies should be emphasised, as well as PrEP – age alone is not a reason for exclusion. (28)

Key recommendations

1. Assessment of sexual function should be performed in all people with HIV infection.
2. The assessment of sexual dysfunction includes three main aspects for men and women: characterising the sexual dysfunction, screening for hypogonadism, with appropriate hormonal tests and endocrinology or gynaecology referral if required, and screening for other causes (i.e. psychosocial, urogenital infection, medication-related).
3. ART does not appear to contribute to sexual dysfunction and switching of ART regimen is currently not recommended.
4. Treatment of erectile dysfunction and/or premature ejaculation can be considered, potential for drug-drug interaction with current ART regimen, however, should be checked for with dosage adjustment if necessary.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

- There is now clear evidence that people with HIV infection who have suppressed HIV viral load (<200 copies/mL) while receiving 6 months of effective, fully suppressive, ART will not transmit HIV to a serodiscordant partner. The concept of U=U may be important for the HIV physician to emphasise in those who have a fear of transmitting the virus, which may be impacting on current sexual function.
- In those ageing people with HIV infection who are sexually active (requires direct questioning), assess the risk of STIs and screen on a regular basis as per routine practice.

Mental health and psychosocial functioning

Physical, mental and psychosocial factors associated with HIV infection have shaped the lives of people affected. Episodic illness and treatment, anxiety and depression and threats to psychological wellbeing presented by HIV-related stigma have resulted in diminished health-related quality of life. However, improved treatment, lifestyle and psychosocial interventions can mitigate detrimental impacts of HIV infection and increase the possibility for improved coping, optimism and social support. (110, 111) Inherent resilience to stressful circumstances can also buffer negative HIV-related psychosocial pressure.

Subclinical mood and anxiety disorders are common in people with HIV infection as is susceptibility to HAND, major depression, dysthymia, generalised anxiety disorder and panic attacks. As life expectancy increases, the impact of ageing effects on the brain and psychosocial changes associated with ageing per se are likely to present further challenges. Although rates of reported depression vary between studies, mood disorders are common in men and women, although men appear to have fewer positive relationships, which may affect their capacity to maintain and develop supportive networks.

Episodic illness and treatment-related side effects of ART compromised the employment opportunities and finances for a generation of people with HIV infection. Neurocognitive impairment may necessitate early retirement and limit employment. Lack of employment and meaningful work can negatively affect social engagement and self-worth leading to reduced psychological health. Financial insecurity can increase stress, anxiety and depression and lead to reduced opportunity to engage in health-seeking behaviours.

A common concern for people with HIV infection is uncertainty about the future and ageing in the context of HIV infection. Will they receive quality aged care? What will they be able to afford? Will they be more vulnerable to stigma and discrimination that they may have experienced in the past, by virtue of frailty? Will they need to negotiate disclosure in a potentially unsupportive setting?

Supportive social ties have been shown to enhance physical functioning and mental health in older adults and stressful social ties are recognised as detrimental. (112) Social support networks are dynamic and shaped by need and circumstance over the life course. (113) These networks are recognised as an important adjunct of successful HIV care, particularly supporting medication adherence; psychological wellbeing and mental health; positive states of mind; coping with the stress of disease and quality of life. Assessing risk of those characteristics that may increase vulnerability to social isolation is an important aspect of HIV management. Some studies have found that older adults have lower levels of social functioning, and report that emotional support is inadequate to their needs. In addition, older adults who find barriers to accessing services have reported more depressive symptoms.

Sexual orientation influences relationships with families and many gay and lesbian adults have formed families of choice and may have similar social network capacity as individuals without infection. This may not be true across cultures and highlight the cultural nuances of stigma concerns.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Key recommendations

1. Assess risk of social isolation (age, gender, sexual orientation, ethnicity, poverty, unemployment, family and friendship ties)
2. Strengthen social assistance packages incrementally and appropriately
3. Screen regularly for depression and anxiety
4. Consider quality of life issues that might impact on psychosocial functioning e.g. financial concerns
5. Identify triggers influencing psychosocial functioning e.g. significant life events: loss of relationship, death in the family, job loss or change.
6. Help people with HIV infection manage HIV disclosure and understand their rights (aged-care accommodation)
7. Target modifiable factors to increase opportunities for social interaction
8. Encourage people to find meaningful activity if deemed of benefit e.g. volunteering, peer navigators.

The Geriatric Syndromes: Frailty, Multimorbidity and Polypharmacy

Major reductions in HIV-associated mortality have increased the median life expectancy of adults with HIV infection. However, immunodeficiency and illnesses involving inflammatory processes e.g. cardiovascular, bone, renal and liver disease, cancers and neurocognitive decline are clustering in older people with HIV infection leading to a “geriatric syndrome” not usually seen in individuals without HIV infection until later in life. (3, 5) This syndrome is characterised by multimorbidity, consequent polypharmacy, delirium, falls, incontinence and frailty, (114) which reduce function and quality of life. (3) This “geriatric syndrome” is highly prevalent, affecting up to 30-50% of people with HIV infection over 50 years of age in some cohorts. (3) As half the current population of people with HIV infection is over 50 years of age in Australia, there is a pressing need to manage multimorbidity in older people with HIV infection, with a major shift in the notion of care delivery to this group, and a call for a new clinical care framework incorporating the principles of geriatric medicine. (10, 115)

Frailty

Frailty can be measured by different algorithms, with the definition of frailty being controversial. Using the Fried criteria, the Frailty Phenotype has been defined by the presence of three or more of five criteria: unintentional weight loss of 4.5 kg in the past year; exhaustion; diminished grip strength; slow walking speed; and low physical activity. (4) (10) These criteria may occur more frequently in people with HIV infection. The cumulative burden of co-morbidities and their respective therapies contributes to frailty in people with HIV infection, with an estimated prevalence, depending on definition and cohort, of 5-19%. (4, 116) Another validated measure is the Frailty Index, where frailty is the result of an accumulation of health deficits over time, and the severity of frailty can predict adverse health outcomes (4, 117, 118) Frailty is also conceptualised by a “biologic age”, describing an overall physiologic vulnerability to various stressors. (4, 10, 117) Frailty is a “significant variable”, its presence indicates greater risk for negative health outcomes including falls, reduced mobility, and independence, accompanied by increased hospitalizations, and increased need for medical care and death. (4, 10)

The prevalence of frailty and relationship with quality of life was assessed in older (>50 years) Australian men living with HIV utilising three different frailty measurements. (119) Over one quarter had four or more co-morbidities, one third had depression and over one half were receiving five or more non-ART medications.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

The prevalence of frailty varied from 10.8% to 22.6% depending upon which Frailty measurement tool was used. (119) The Frailty phenotype was significantly associated with pre-1996 ART initiation (OR 3.56, CI 1.23-10.36, $p = 0.020$) and depression (OR 3.74 CI 1.24- 11.27, $p = 0.019$). Frailty defined by any of the instruments was associated with significantly poorer quality of life, emphasizing the importance of identifying frailty and measuring quality of life. (119)

Frailty in the general population has been associated with activation of the innate immune system, and HIV infection has been recognised as a driver of age-related comorbidities, including frailty, through chronic activation of the innate immune system and immune senescence. (117) An important element of clinical frailty is loss of skeletal muscle mass, or sarcopenia, which is associated with extrinsic factors including lifestyle, nutrition and comorbidities, all of which are common to HIV infection. As a result, impairment in objective measures of physical function occurs. (4) Predicted mortality is significantly greater with the combination of both HIV and impaired physical function. Other clinical consequences of these impairments in physical function and frailty include and falls, impaired quality of life and hospitalisations. (4, 120-123)

In the general population, interventions aimed at increasing physical activity and improving nutrition have been shown to be effective and are recommended for integration into an HIV model of care. (4, 124-126) In the clinic setting, simple measures can be instituted to assess physical function and capacity, such as gait speed on a 4.5 metre walk, time to rise from a chair and grip strength. (122, 127) Repeat measurements can be used for monitoring and therefore guide interventions to prevent, slow or reverse impairments and frailty. (4)

Key recommendations

1. Multi-morbidity and associated medical therapies can lead to polypharmacy and frailty, both associated with poor outcomes in older people with HIV infection. The definition of frailty is controversial, but can be measured with several clinically applicable tools, including the Frailty Phenotype and the Frailty Index.
2. The recognition of frailty in the ageing HIV population is important; in population studies it has been associated with poorer quality of life. It also can be used by the HIV provider to individualize treatment goals for chronic comorbidities and therefore help to improve health outcomes.
3. Consider screening people with HIV infection at risk of frailty by monitoring for functional physical impairment; by measuring gait speed on a 4.5-metre walk, time to rise from a chair and grip strength.
4. Consider implementation of lifestyle measures, such as increasing physical activity and improving nutrition to help decrease or modify the risk of frailty in older people with HIV infection.

Multimorbidity

Multimorbidity is defined as 'the co-existence of two or more chronic conditions, each one of which is either a physical non-communicable disease, a mental health condition or an infectious disease'. (128) Older people with HIV infection exhibit a significantly higher prevalence of multimorbidity than their age-matched counterparts. (10, 115) This has been associated with increased mortality, complexity of care and healthcare costs while reducing quality of life. (129)

In the Australian context, the prevalence and factors associated with multimorbidity among people with HIV infection is high, with 54.5% of individuals having two or more chronic health conditions together with HIV, the most common being a mental health disorder, the next most common CVD. (129)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Key recommendations

1. Appropriately screen older people with HIV infection for chronic disease(s), acknowledging a high prevalence of multimorbidity and associated decreased quality of life and poor outcome including unplanned admission to hospital.
2. Actively assess older people with HIV infection for multimorbidity patterns – which may be interwoven by a common underlying risk factor, including lifestyle or risk-taking behaviour(s).

Polypharmacy

Polypharmacy is common in older people with HIV infection, and more common compared to the general population of a similar age. (3, 4, 8, 28, 130) This places them at higher risk for clinically significant drug-drug interactions between ART and other prescribed medications. (3, 8, 28) Polypharmacy (the use of 5 or more prescription medications) is associated with worse health outcomes in older people with HIV infection, (4, 8, 131) and may include excessive, unnecessary or non-indicated medications. (4) Prescribers should also be aware of substance use (e.g. alcohol, marijuana), which is common and can impact risks associated with polypharmacy, including suboptimal adherence and increase susceptibility to adverse drug reactions. (3) Negative consequences arising from polypharmacy are compounded in the elderly and include an increased risk of falls, drug-drug interactions, toxicity, geriatric syndromes (falls, fractures and cognitive decline) and poor adherence. These consequences translate into increased clinic and hospital visits as well as emergency admissions. (3, 4)

Medication review should occur regularly, given the high potential for drug-drug interactions, particularly at the time of starting or switching ART and concomitant medications, but also when there is a new clinical concern or biochemical abnormality on recent laboratory investigations. (28) Drug-drug interactions are common and can be missed by prescribers (4, 28, 35) and may be greater than predicted in older people with HIV infection, who often have multiple healthcare providers.

Ritonavir inhibits cytochrome P450 3A4 (CYP3 A4) and other hepatic cytochrome P450 enzymes and therefore inhibits the hepatic metabolism of many medications with resulting increased blood levels of concomitant medication and potential toxicity. (132) Cobicistat, an alternative boosting agent is a more specific inhibitor (i.e. no inhibitory effects on CYP2C8 and is a weaker inhibitor of CYP2D6). (132) Therefore, expected drug-drug interactions can be different and the two boosting agents should not be used interchangeably when considering drug-drug interactions. (132) Other effects of ritonavir and cobicistat include inhibition of intestinal transporters P-gp which will affect the absorption and metabolism of other drugs.

The absorption of some antiretroviral drugs may be altered by other medications through chelation of divalent cations (e.g. integrase inhibitors) and through changes in gastric pH (e.g. atazanavir, rilpivirine). (4) A recent retrospective study found that people with HIV infection aged 50 years and older had a higher rate of potential drug-drug interactions compared with younger people. (8) Antiretroviral drugs may act as both “perpetrators” and “victims” of drug-drug interactions; for example, if they are combined with other CYP 3A4 enzyme inducers (e.g. rifampicin, older anti-epileptic drugs) or enzyme inhibitors. (4)

It is important to check for drug-drug interactions whenever there is a change in ART or co-medications, for example at the **Liverpool HIV drug interaction database** at <http://www.hiv-druginteractions.org>, which contains information on the metabolic pathway and related risk of drug-drug interactions with antiretroviral drugs and co-medications.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

An example of an important interaction common for older people with HIV infection is the use of ticagrelor, an antiplatelet therapy, one of the preferred agents in the management of ischaemic heart disease. It is primarily metabolised by CYP 450 3A4, and therefore subject to significant drug interactions with ART. Co-administration with PIs, ritonavir or cobicistat, all potent inhibitors of CYP3A4, is not recommended given significant increases in serum concentrations of ticagrelor and increased risk of bleeding. In addition, co-administration with NNRTIs – such as nevirapine, efavirenz, or efavirenz, which are moderate CYP3A4 inducers, may result in reduced efficacy of ticagrelor. (8)

Some studies have shown better adherence to ART among older people with HIV infection compared with their younger counterparts. (28) (133-135) Reasons for potential suboptimal adherence and subsequent treatment failure in older people with HIV infection include complex dosing, high pill burden, polypharmacy, inability to pay for medications, limited health literacy, mood disturbance and neurocognitive impairment. (28) (136) Older women with HIV infection and severe menopausal symptoms may also be at greater risk of suboptimal ART adherence and adverse HIV outcomes. (28, 137)

In summary, regular medication reviews by either an experienced HIV pharmacist or clinician should be performed on a regular basis. Unnecessary medications should be discontinued, regimens simplified and adherence aids (pillboxes, daily calendars, family support) recommended. (4, 28) Specific information on drug-drug interactions should be sought, and HIV care providers should be proactive in terms of anticipating and monitoring drug-drug interactions when either starting, changing or discontinuing a new medication. (4)

Key recommendations

1. A full medication review by either an experienced HIV pharmacist or clinician should occur at each clinic or hospital encounter.
2. Clinicians should be proactive in the cessation of unnecessary medications, and monitoring for drug-drug interactions when either starting, changing or discontinuing any medication.
3. HIV care providers should practise heightened awareness of polypharmacy (5 or more medications) in older people with HIV infection, given the associated negative health outcomes.
4. The medication history must also include over-the-counter medications, herbal supplements and lifestyle related substance use.
5. Older people with HIV infection are strongly encouraged to engage with evidence-based memory aids for medications (i.e. pillboxes, medication calendars, family support) in order to optimise medication and ART adherence.
6. Clinicians are advised to encourage adherence and screen for potential barriers, including reduced health literacy, cost, neurocognitive impairment, and severe menopausal symptoms.
7. ART can be both responsible for and vulnerable to drug-drug interactions; there are readily available online drug-drug interaction resources which should be accessed for all people with HIV infection receiving other medications.

Whilst ritonavir and cobicistat are equivalent in their inhibition of the cytochrome P450 3A4, cobicistat is more limited in other enzymatic inhibition and is not responsible for enzyme induction. If there is a switch in ART between either agent, a comprehensive review of current medications should be undertaken.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Comprehensive geriatric assessment and a change in approach to the care of ageing people with HIV infection

“Ageing with HIV” is associated with a higher frequency of (1) multimorbidity, possibly attributable to previous toxic exposure to ART and lifestyle factors; (2) polypharmacy due to ART and other medications for co-morbidities, compared with “typical” ageing.(10) It is clear a structural and cultural change in standard patient assessment and transition in care, needs to take place, extending HIV care beyond viral suppression and retention in care. It should be inclusive of the principles of geriatric medicine and include assessments of functional capacity and quality life, now essential to providing adequate care of the ageing person with HIV infection. (3)

The US Department of Health and Human Services “Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV” (followed in Australia) has recently included a section on “HIV and the older person”. This underscores the need for additional medical and social services, particularly in relation to multimorbidity and the need for a collaborative approach between HIV experts, primary care providers and other specialists. (8)(28)

The comprehensive geriatric assessment of the medical, physical, mental and social aspects of health enables ascertainment of health status and individual needs in a multi-disciplinary manner. The aim of the assessment is to improve quality of life, extend survival and reduce hospitalisation events. (3)

A practical assessment outline of general and specific considerations to aspire to for the care of older people with HIV infection in ambulatory care, including age-appropriate assessment of co-morbidities, evaluation of geriatric syndromes (falls, incontinence, sleep, confusion, vision/hearing problems, sarcopenia etc), physical function/frailty measurements, neuropsychological and psychological evaluation, evaluation of social problems has been developed by Negredo et al. (4) “Key actions” are also provided, with an emphasis on prevention of chronic conditions, early detection and control, checking for drug-drug interactions, stopping unnecessary drugs (STOP/START criteria) (133, 138) risk factor modification, ensuring maintenance of muscle mass and bone density through exercise and nutrition, cognitive remediation, mental health support if required, and social worker intervention if social problems exist. (4)

Care of the older patient with multimorbidity is best managed with the assistance of a multi-disciplinary team (MDT), where team members are able to understand the future health needs of older people with HIV infection and modify the goals of care to meet those needs. (3) This includes maximising outpatient visits with multiple providers, including primary care physicians, who would ideally lead a diverse team of disciplines, social workers and geriatricians, which may require an overhaul of current services.(3)

Key recommendations

1. Endeavour to provide a holistic model of care – with the primary care physician central to a multi-disciplinary team, working to optimize function and quality of life for the ageing HIV population
2. Consider the application of a comprehensive geriatric assessment and formal geriatrician referral in older people with HIV infection and multimorbidity who are at risk of, or has any one of the conditions that establish, a ‘geriatric syndrome’.
3. Advocate for the ageing HIV population to be included in evidence-based medicine, including interventional clinical trials where they have traditionally been excluded.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

End-of-life care

End-of-life planning is important and relevant for all people with HIV infection. Planning and advance care directives have been shown to improve care for patients and psychosocial outcomes in surviving relatives. (139, 140) HIV infection can complicate care at the end of life but past research in other contexts has indicated that people with HIV infection were less likely to discuss advanced care directives than others with serious illness. (141, 142) A focus on quality of life as a key component of HIV management at all ages should facilitate discussion and empower patients to be clear about their wishes. Formal advanced care directives would be a natural extension of an ongoing conversation with older people with HIV infection concerning their priorities. The continuity of HIV care in many Australian health settings will underpin this approach. In a multicultural context, advanced care planning has proved to be equally as acceptable in non-English speaking people in comparison with those with English speaking backgrounds. (143)

In the context of end-of-life care, decisions around cessation of ART require careful consideration. The clinical benefits of ART are undisputed – prevention of disease progression, both AIDS defining illness and non-AIDS events; suppression of HIV replication and associated immune activation and chronic inflammation; and prevention of HIV transmission. The cessation of ART may relieve ART-associated adverse effects and the potential for drug-drug interactions but also represents a significant step for people with HIV infection and their partners/family. The viral rebound associated with cessation of ART may also lead to discrimination in the high intensity care setting. It is important to weigh up the benefits and disadvantages of ART cessation to the individual in this context.

Key recommendations

1. End-of-life planning, including advanced care directives, is encouraged to be discussed by the HIV care physician with all older people with HIV infection, as it has been shown to improve care for patients and psychosocial outcomes in relatives.
2. Ongoing discussion between patient and HIV care provider, which places strong emphasis on the maintenance of quality of life, is suggested.
3. Those persons with a disease trajectory that may succumb to chronic disease and/or terminal illness should be identified early, in order to institute referral to palliative care services and other supports.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Psychiatric disorders in people with HIV infection

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Last reviewed: October 2019

Introduction

People with human immunodeficiency virus (HIV) infection suffer high rates of mental illness. Epidemiological studies indicate that the prevalence of mental illness in this population may be as high as 47.9%. Common diagnoses are depressive disorders, anxiety disorders and substance-related disorders.(1)(2) Rates of mental disorder are also reported to be high in resource-limited settings.(3) Why do people living with HIV suffer such high rates of mental illness? Firstly, there is an association between sexual risk-taking behaviours linked to HIV transmission, and mental illness.(4) Secondly, HIV infection impacts on a person's life and functioning, both directly through neurological injury producing cognitive and behavioural changes and indirectly through the impact of chronic illness on psychological function. Living with a mental disorder has a significant impact on a person's sense of wellbeing and quality of life which may be worsened by the multiple burdens and stigma of living with a mental illness associated with HIV infection. Untreated mental illness can affect a person's ability to care for themselves and others, maintain accommodation and employment and to comply with HIV treatment.(5)

People with pre-existing mental illnesses are at a higher risk of contracting HIV infection. The type of predisposing mental disorders can range from cognitive disorders (intellectual disability, dementia and acquired brain injury) to mood disorders (depression and mania), psychotic disorders (especially schizophrenia) and personality disorders (particularly borderline and antisocial personality disorder). In younger people, severe mental illness may be associated with an increased frequency of sexual risk behaviours (higher partner numbers, lower condom use),(6) higher rates of substance use, and an association with social networks that have a higher risk of acquiring and transmitting HIV infection. It is thought that adequately identifying and treating mental illness in young people is likely to reduce HIV acquisition risk behaviours.(7)

The liaison between mental health services and HIV services is important when considering prevention of HIV transmission. With understanding of the increased transmission risk behaviours that may occur in people with HIV infection and mental illness and the challenges that these individuals may encounter accessing preventative treatments, specifically pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP), medical and mental health services can work in a synergistic way to reduce transmission (8) A large percentage of men who have sex with men present unique psychological issues that come from living in a society that is often hostile to gender non-conformity, resulting in personal stigma and shame.(9) While societal attitudes to homosexuality have evolved, the developmental impact of this sense of difference, coupled not infrequently with a history of discrimination and abuse can manifest in adulthood with higher rates of mental illness and substance abuse than in the community in general.(10)

In the Australian context, the majority of people currently living with HIV are men who contracted the infection through sexual contact with other men. Among heterosexuals in Australia diagnosed with HIV infection, migrants, especially those from high-prevalence regions are significantly over-represented.(11) This group also presents unique challenges and often has suffered difficult developmental and migration histories, coupled with the challenges of adapting to a new culture and lifestyle. These individuals are thus at high risk

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

of developing a mental disorder which can manifest in differing ways due to the effects of cultural differences. (12)(13) Equally, a diagnosis of HIV infection is often highly stigmatised in communities to which these people belong, resulting in secrecy and social isolation for those with the infection. There is a need for culturally sensitive and appropriate medical practice in order to better engage, educate and treat patients from migrant communities who present with mental illness and HIV infection.

The later stages of HIV infection are commonly associated with the neurocognitive complications of HIV infection and less commonly with severe episodes of psychiatric illness such as manic episodes, psychotic illness and episodes of delirium. These later episodes, though less common, are important to identify and treat early to prevent risks to the patient and potentially others. Antiretroviral medications have also been associated with reported neuropsychiatric symptoms in patients. These can range from mood disturbance to anxiety, sleep disturbance and confusion. The non-nucleoside reverse transcriptase inhibitor (NNRTI), efavirenz, is the antiretroviral agent most frequently associated with neuropsychiatric symptoms including sleep disturbance, vivid dreams, anxiety, agitation, abnormal thinking including suicidal ideation and, less commonly, frank manic or psychotic symptoms. (14)

In people with HIV infection, different types of mental disorders occur with various stages of the infection. There are significant illness milestones that can occur, related to phases of disease progression, such as the time of initial diagnosis, commencement of ART, onset of symptomatic illness, ART failure and the need for antiretroviral salvage therapy. The later stages of illness may be associated with the increasing loss of physical functioning combined with the impaired cognitive function. These illness milestones may be associated with periods of stress or normal psychological adjustment. However, if severe they can manifest with psychological symptoms, such as anxiety or mood symptoms that may be better described as an adjustment disorder or if more severe, a major depressive disorder or an anxiety disorder. People with a prior history of mental illness and substance abuse, and those with low social support, are more at risk of suffering from major adjustment difficulties, and more likely to come to the attention of clinicians during these periods of change.

The broad principles of management in this population include a focus on engagement of the person with HIV infection and identification and containment of immediate risks. These may be immediate risks to the person (e.g. self-harm and suicidal behaviours), or less directly via self-neglect or disturbed behaviour, and also risks to others through direct violence, neglect (e.g. of children) or problem behaviours (e.g. through unsafe sexual practices). All states and territories of Australia have mental health legislation that allows for involuntary treatment of people if there are immediate safety concerns and the person is unable or unwilling to consent to treatment. It is important to have some knowledge of the legal structures involved. Treatment of mental illness involves a multifaceted bio-psycho-social approach and often requires the resources of a multidisciplinary team (e.g. psychiatrist, mental health trained nurse, psychologist, social worker and occupational therapist) to adequately assess and deliver treatment. Access to such resources are obviously more difficult in rural and remote regions where many of these functions may be provided by a sole clinician such as a general practitioner or nurse practitioner.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Depression

People with HIV infection suffer high rates of major depression. A meta-analysis found rates of major depression in HIV-positive people to be twice that of matched HIV-negative controls.⁽¹⁵⁾ Rates may increase with HIV disease progression and symptomatic illness.⁽¹⁶⁾ Certain risk factors are associated with an increased risk of depression: a personal or family history of mood disorders, substance use, anxiety disorders, suicidal episodes, being female, low social support, and current medical illness.⁽¹⁷⁾ Suicidal thoughts and acts are a common reason for psychiatric referral and can occur at times of crisis, such as at the time of HIV diagnosis and in the late stages of illness. Depression may adversely affect the outcome of treating HIV infection. There is evidence to support an association between depression and self-neglect, with implications for treatment adherence.⁽¹⁸⁾

It can be difficult to identify depression in patients with severe medical illness. Depressive symptoms may represent a normal reaction to physical illness, a manifestation of the underlying physical illness (e.g. symptoms of fatigue and anorexia) or a component of a depressive syndrome. As such, depression can be easily missed. Untreated depression in patients is associated with a worse prognosis.⁽¹⁹⁾ Cognitive-affective symptoms (as opposed to somatic symptoms) may be more discriminating in identifying depression in this population. Examples of these symptoms would be: a sense of failure, a sense of being punished, indecisiveness, reduced social interest, suicidal ideation, frequent crying and dissatisfaction.⁽²⁰⁾ In patients with HIV infection it is always important to consider an organic basis to the depression, especially when there is no personal or family history of a mood disorder, there are no obvious precipitants, when the presentation is atypical, when cognitive symptoms appear severe, if the patient is severely immunocompromised or when the patient had failed to respond to treatment. Assessment needs to include a thorough physical examination and medical workup to exclude organic pathology (Table 1).

Table 1. Assessment of patients with HIV infection attending with psychiatric symptoms

Psychosocial history	Living environment, employment, finances, relationships.
Level of functioning	Activities of daily living; presenting symptoms and relationships to psychosocial factors.
HIV status	Duration of illness; current CD4+ T cell count and HIV viral load; CD4+ T cell count nadir (indicates likelihood of CNS involvement); HIV disease manifestations, particularly opportunistic infections; current antiretroviral therapy (ART) and recent changes and adherence to ART.
Medical and psychiatric history	Other active medical problems and medications; personal and family history of previous mental illness; comprehensive drug and alcohol use assessment.
Examination	Mental state assessment with focus on cognition and risk assessment. Physical examination, as indicated to identify and exclude organic illness.
Investigations	CD4+ T cell count and HIV viral load, if not recently determined. Appropriate CNS investigations if CD4+ T cell count < 200/μL and clinically indicated, e.g. CSF examination (HIV RNA level and cryptococcal antigen) and neuroimaging. Renal and liver function tests, vitamin B12/folate, blood glucose, full blood count, serum CRP, thyroid function tests and consider pituitary function tests and serum testosterone level, urine drug screen. Review past serology tests, particularly those for syphilis.

CNS = central nervous system; CSF = cerebrospinal fluid.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

The appropriate treatment approach in the patient with HIV infection and depression depends on the type and severity of the depression (Table 2). Once organic illness is excluded or reversed, for mild depression, treatment with short-term psychotherapy alone is usually appropriate and there is evidence to suggest efficacy.⁽²¹⁾ This treatment could be supportive, cognitive behavioural or interpersonal psychotherapy and needs to be provided by trained clinicians. For moderate-to-severe depression, antidepressant medications are recommended, often in combination with psychological therapies. The choice of antidepressant depends on the patient's symptom profile and history of prior response. Though there is evidence for good effect with tricyclic antidepressants,⁽²²⁾ given their side-effect profile and risk in overdose, current first-line therapy would be a selective serotonin reuptake inhibitor (SSRI) antidepressant. It is better to choose an agent with fewer drug-drug interactions such as citalopram, escitalopram or sertraline. Second-line agents include mirtazapine, which aids insomnia and poor appetite, or venlafaxine. For more severe depression associated with melancholic or psychotic symptoms it is advisable to seek advice from a trained psychiatrist as treatment may require the use of augmentation with antipsychotic drugs or mood stabilisers, and, rarely, electroconvulsive therapy.

Table 2. Treatment of HIV patients with psychiatric symptoms

Engagement and therapeutic rapport	Identify and contain risks and consider need for involuntary treatment. Obtain further history from family or partner, as indicated. Notify child protection agencies, if indicated. Consider need for referral to specialist care.
Exclusion of organic illness	Further physical examination and investigations, as indicated
Biological	Identify and treat underlying psychiatric illness e.g. antidepressants, mood stabilisers, antipsychotics, as indicated. Consider use of short-term anxiolytic or hypnotic drug to contain symptoms and aid engagement. Consider need for drug or alcohol withdrawal regimen, if indicated. Monitor for medication side effects and review adherence.
Psychological	Educate the patient about identified illness and recovery plan. Determine if specialist psychological approaches are required: short-term cognitive behavioural, or interpersonal therapy and longer-term psychodynamic approaches, as indicated. Instigate partner and family interventions, as indicated. Consider motivational interviewing as an approach to drug and alcohol dependence. Consider if a neuropsychology assessment is required.
Social	Consider role of multidisciplinary team, including the role of social workers in housing, financial support, employment, relationships (support groups) and home supports to reduce stressors. Consider need for support from drug and alcohol services.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Anxiety

Anxiety symptoms are common in people with HIV infection, and are likely to be more prominent at times of significant life stresses and at stages of disease progression. (23) Anxiety disorders, where anxiety is severe and persistent, are also common: surveys have estimated the prevalence of generalised anxiety disorder to be up to 15% of HIV patients and the prevalence of panic disorder to be 10% of HIV patients. (24) Agoraphobia and social phobia are also common and high rates of post-traumatic stress disorder and acute stress disorder have been described. (25) The presentation of these disorders is often clouded by comorbid mood disorder, substance use and personality disorders making diagnosis more complicated. Effective treatment requires a comprehensive assessment of the presenting symptoms, life stresses and coping style.

Treatment approaches include brief psychological interventions and medication. Psychological approaches that may be helpful include behavioural techniques, such as progressive muscular relaxation, breathing exercises and systematic desensitisation. These may be incorporated within a cognitive behavioural therapy approach (26) and medications are often used concurrently. Benzodiazepines may be helpful for short-term symptom relief, and are usually best used with antidepressant agents and tapered as symptoms improve. Shorter-acting agents that produce fewer metabolites are preferred, such as oxazepam, lorazepam and temazepam, with consideration given to risks, such as abuse and dependence. Antidepressants are effective for the longer-term treatment of anxiety, with SSRIs being the first-line choice, again choosing agents that have less hepatic cytochrome p450 interactions. Mirtazapine and venlafaxine can also be effective.

Mania

Manic episodes are more common in people with HIV infection than in the general population. (27) An episode of mania is often associated with poor impulse control, impaired judgment and greater risk-taking behaviours, increasing the chance of contracting or spreading HIV infection.

A manic episode may be primary (related to a bipolar disorder) or secondary to a range of other causes. (28) Possible secondary causes are substance-induced mania related to either illicit or prescription medications including antiretroviral drugs, mania due to a medical condition such as central nervous system opportunistic infection, a manifestation of a hyperactive delirium, or related to primary HIV infection. (29)

Important clinical features to consider on history taking include a past or family history of a mood disorder, current HIV clinical parameters and stage, current medications and recent changes, substance abuse history and a cognitive assessment. Specific enquiry regarding increased libido or sexual activity should also be made as previously insightful patients may lose their usual judgment, e.g. occasionally develop delusions and believe that their HIV infection is cured. A comprehensive medical examination is required and investigations, such as neuroimaging and CSF analysis, should be undertaken to determine if there is CNS involvement by HIV infection.

Manic episodes related to HIV infection tend to be a late manifestation of HIV disease associated with a low CD4+ T cell count, high HIV viral load, evidence of structural brain damage demonstrable on magnetic resonance image (MRI) or computed tomography (CT) scans or neuropsychological deficits. (30) These episodes classically have been associated with cognitive impairment and a poor clinical prognosis, as they have been linked to the development of an HIV-associated dementia. (31) Clinically, patients may present with more irritability, talkativeness and cognitive slowing and impairment than those with primary bipolar illness. Treatment must be provided in a safe and secure environment. This recommendation may mean consideration of hospitalisation and involuntary treatment.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Evidence suggests that the most effective treatment for HIV-associated mania is ART that penetrates the CNS.(32) Symptoms may also be controlled with psychotropic medications, including mood stabilisers, antipsychotic and anxiolytic drugs. All mood stabilisers have the potential for side effects and drug interactions. Lithium is reported to be effective but has higher rates of neurotoxicity in this population. Sodium valproate is frequently used but care must be taken to monitor for liver toxicity and the theoretical risk of elevation of HIV viral load. Mood stabilisers are often combined with antipsychotic drugs to treat acute episodes. Current practice suggests that olanzapine, risperidone and quetiapine can be effective in this population, though there is an increased rate of extrapyramidal side effects. Benzodiazepines are also used for short-term sedation.(33)

Cognitive disorders

Acute changes in cognition – delirium

Sudden changes in cognitive function raise the possibility of a diagnosis of delirium. The cardinal signs of delirium are fluctuating conscious state, impaired concentration and disorientation in time or place. As the course of illness is variable there may be periods of lucidity. There may also be associated psychotic symptoms (hallucinations in any sensory modality or delusional ideas) that can be distinguished from other forms of psychotic illness on a temporal basis. Delirium is more likely to occur in the later stages of HIV infection but is not exclusively limited to this period. It is also common in hospitalised patients with rates of up to 22% described in inpatients with HIV infection.(34) A thorough medical assessment including corroborative history of substance abuse or withdrawal may help to clarify the aetiology.

The assessment of delirium includes documentation of cognitive changes both for diagnosis and monitoring progress (Table 3). Physical examination and investigation should be targeted towards likely causes. (35)

Table 3. Assessment of delirium

Physical examination	Evidence of head trauma. Neurological examination for focal neurological signs, tremor and asterixis. Ophthalmological examination.
Initial screen	FBE, ESR, CRP, liver and renal function, thyroid function, blood sugar; routine urinalysis. Urine/serum drug screen: illicit drugs. Medication level monitoring: lithium, anticonvulsants. Chest X-ray
Investigations for HIV-related infections	Serum antibodies to Toxoplasma, cytomegalovirus, herpes simplex virus, Treponema pallidum (syphilis). Serum cryptococcal antigen. Blood culture.
Further investigations	Nutritional deficiency: B12, folate. Pulse oximetry and blood gas analysis if clinically hypoxic. CSF analysis for HIV RNA and opportunistic infections. Cerebral imaging: CT, MRI. EEG

FBE = full blood examination; ESR = erythrocyte sedimentation rate; CT = computer tomography; MRI = magnetic resonance imaging; EEG = Electroencephalography; CSF = cerebrospinal fluid.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Treatment will be directed by the findings on investigation, but it is not uncommon to fail to discover a specific cause. General management includes environmental measures to increase the familiarity of the person's environment such as adequate lighting, orientation cues and limiting the number of staff involved in patient interaction. Medication can be used to decrease agitation and maintain a regular sleep cycle. It is common practice to use antipsychotic medication in these circumstances, initially at low doses and titrated accordingly. Occasionally, parenteral medication may be required and it should be used judiciously. Benzodiazepine medication is indicated in delirium secondary to alcohol withdrawal but should be used cautiously in other circumstances. Benzodiazepines can cause significant interactions with antiretroviral medications and they have been associated with increased confusion, excessive sedation and ataxia.(36)

Chronic cognitive disorders in people with HIV infection

Cognitive difficulties are often associated with chronic HIV infection. HIV enters the CNS early in the course of acute infection, infecting predominantly microglia and perivascular macrophages. Over time progressive neuronal dysfunction and apoptosis occurs.(37) producing evident deficits, especially in the subcortical regions and fronto-striatal pathways of the brain. The mechanisms of this damage is not fully understood but it may occur either due to the direct effect of viral replication and release of viral proteins by infected macrophages and microglia, or possibly secondary to inflammatory mediators released by activated macrophages and microglia over time.(38)(39)

Clinical assessment of cognitive impairment in people with HIV infection should consider the range of common comorbidities that can affect cognitive performance, in addition to the direct effects of chronic HIV infection. (39) Common physical comorbidities that require consideration include ageing, previous acquired brain injuries, cardiovascular disease, diabetes, co-infection with hepatitis C virus and sleep disorders. Consideration should also be given to psychiatric illness, such as depression and schizophrenia, and substance abuse, which also may impact on cognitive performance. A history of previous HIV-related CNS disorders (HIV-associated neurocognitive disorder [HAND] and CNS opportunistic infections) before commencing antiretroviral therapy (ART) also increases the likelihood of HAND being present on assessment.(40)

The cognitive domains most typically involved in HAND are working memory, speed of information processing, attention and active information retrieval. People with mild impairments may report minor difficulties performing complex cognitive tasks in everyday life. In more moderate to severe cognitive impairment, clinically evident slowness and apathy may be present. In advanced cognitive impairment, people may exhibit disinhibited behaviour, apathy, slowness and grossly disturbed motor functioning.(40)

The use of ART has had a significant impact on reducing the morbidity and mortality associated with HIV infection and HAND. In spite of this effect, HIV infection continues to be associated with varying degrees of cognitive impairment. The Frascati criteria(41) are the current standard for consistently describing the categories of impairment based on a clinical assessment. These criteria divide impairment into three levels of severity based on a neuropsychological assessment:

1. HIV-associated neurocognitive impairment (ANI)
2. HIV-associated mild neurocognitive disorder (MND)
3. HIV-associated dementia (HAD).

All three categories require impairments in cognitive function across two domains. With performance at least one standard deviation below the mean compared to a normal population sample for ANI and MND.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

These two diagnoses differ on their level of impact on daily function with no impact in those with ANI and mild interference in function in those with MND. A diagnosis of HAD is made when cognitive performance in two domains is two standard deviations below demographically appropriate mean scores (see section on [neurological disorders](#)) and is associated with significant functional impairment.

With the widespread adoption of ART for HIV infection in developed countries, there has been a shift in the presentation of HAND. There has been a decline in the appearance of the more severe forms of impairments such as HAD, however more mild forms of HAND such as ANI and MND persist. The CHARTER study revealed that over half of ART-treated adults with HIV infection showed evidence of neuropsychological impairments. Most of these showed evidence of mild impairments consistent with ANI (33%) and MND (12%). Only 2% had severe impairments consistent with HAD.(42)

Treatment considerations should be sensitive to the patient's care requirements and available community supports. Consideration of competence to make medical and lifestyle decisions and discussion of an appropriate proxy should be part of an overall treatment plan. It is thought that ART which better penetrates the CNS may improve some of the cognitive deficits associated with this pathology.(40) However, these improvements may only be modest and some patients remain severely impaired despite instigation of treatment.(43)

Substance abuse disorders

Substance abuse is a significant risk factor for the acquisition of HIV infection by direct means, such as sharing of injecting equipment, and indirect means such as risk behaviour associated with impaired judgment while intoxicated. Substance abuse is especially prevalent in people with HIV infection with reported rates ranging from 50-75%.(44) It is important to note that there is a common comorbidity between substance abuse disorders and other psychiatric diagnoses and patients will benefit from a coordinated assessment approach. The general approach is to: take a comprehensive history of substance use in an empathic and accepting manner; provide education about harm reduction strategies associated with drug use; and make an assessment of a person's commitment to changing behaviour. A commitment to changing behaviour has been classified according to a Stages of Change Model (45) that includes stages of pre-contemplation, contemplation, preparation, action and maintenance. There are specific psychological therapies that have been shown to be effective in helping people make and maintain changes in behaviour. Psychosocial interventions aimed at stabilising a person's living circumstances can assist and have beneficial effects on maintaining health. There are pharmacological strategies that have been shown to be beneficial, particularly when combined with psychological interventions. Initiating some of these pharmacological therapies may require specialist assessment. A person considering abruptly ceasing use, especially of alcohol, should consider a specific detoxification program to prevent the potential complications of withdrawal.

Psychotic disorders

There is a complex association between the diagnosis of HIV infection and psychotic disorders, each potentially adversely affecting the other. The nature of a psychotic illness is such that it may significantly impair a patient's capacity to participate in treatment. The diagnosis of a chronic psychosis is complex with symptoms divided into disorders of thought, perception, cognition and volition. Deficits in reasoning, impulsivity and impaired capacity to process complex information are often associated with the primary symptoms of psychosis. There is frequently deterioration in psychosocial function that further complicates the provision of

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

effective HIV care. Chronic psychotic symptoms are associated with a diagnosis of schizophrenia and schizoaffective disorder but may also be associated with dementia. Episodic psychotic symptoms may be associated with acute episodes of depression and mania in bipolar affective disorder. The abrupt onset of psychotic symptoms may be secondary to the acute effects of substance use or may be part of a syndrome of delirium.

Any treatment plan for HIV patients with psychotic illness should involve a risk assessment and consideration of the appropriate treatment environment. This is facilitated by a close working relationship between HIV and psychiatric services. Support to encourage adherence with oral medications will have benefits both for psychiatric symptom relief and adherence to ART. Most antipsychotic medications can be safely combined with ART but the potential for interactions should be considered. Due to the effects of HIV infection on the central nervous system, patients may be more susceptible to extrapyramidal side effects and monitoring should be undertaken. For this reason, the atypical antipsychotic medications are usually preferred. However, some atypical antipsychotic medications (e.g. olanzapine, quetiapine) have been associated with hyperlipidaemia and abnormalities of blood sugar metabolism, so periodic investigation is warranted in this already susceptible population.

Principles of pharmacotherapy for mental illness in people with HIV infection

Clinicians require a good understanding of the role of psycho-active medications in the treatment of mental illness and also the high risk of potential drug-drug interactions and side effects in the population with HIV infection. Certain antiretroviral drugs, in particular protease inhibitors and NNRTIs, are metabolised primarily by the cytochrome P450 3A4 and 2D6 hepatic microsomal isoenzymes, which can in turn inhibit or enhance their activity. Most psychotropic medications are also metabolised by, and can affect the activity of, these isoenzymes. Patients may also have serum protein anomalies resulting in an altered free fraction of protein-bound drugs. There is, therefore, a high potential for drug interactions when psychotropic agents are used in the setting of ART, making it important to use care and consult up-to-date drug information or an informed pharmacist before prescribing.

Commonly used agents in this population include antidepressant medications such as SSRIs to treat depression and anxiety disorders. SSRI medications that have less interaction with these enzymes (e.g. citalopram, escitalopram and sertraline) are preferred for use. Benzodiazepines are commonly prescribed for short-term use in anxiety disorders. However their half-lives can be significantly prolonged by treatments and thus agents with shorter half-lives (e.g. oxazepam, temazepam and lorazepam) are preferred. Similarly mood stabilisers, such as sodium valproate and carbamazepine, and antipsychotics can interact with certain antiretroviral drugs and care is required when prescribing [\(46\)](#). Lithium is also used as a mood stabilising agent and although its metabolism is not impacted on by hepatic enzymes, its use warrants careful monitoring in the medically unwell due to its narrow therapeutic window.

In considering the impact of antiviral medications on psychological health it is important to be aware that, although antiviral medications can be targeted towards improvement in CNS symptoms, there are specific adverse effects on mood and sleep cycles of some of these medications. A review of the AIDS Clinical Trials Group antiviral naive studies looked at the association between efavirenz and suicidal thinking and behaviour. This analysis indicated a two fold increase in the hazard of suicidality compared to non-efavirenz antiviral regimens. [\(47\)](#) When constructing an effective antiretroviral medication regimen that includes efavirenz as a component, consideration should be given to a history of mental illness and suicidal or self-harm behaviours and appropriate mental health supports be included in the treatment plan.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

References

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

HIV infection in adolescents transitioning to adult care

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Last reviewed: March 2020

Introduction

The majority of adolescents (age 10-19 years) living with HIV have acquired the infection perinatally. As such they have experienced long-term exposure to an interplay of physiologic processes associated with chronic HIV infection and antiretroviral therapy that needs to be managed during a complex period of physical and psychosocial development.^{(1),(2)} This leaves adolescents vulnerable to poorer outcomes compared to children and adults, and HIV care should be provided in specialised services with experienced adolescent health care providers where possible.⁽³⁾ This cohort, particularly for adolescents from low- and middle-income countries, may experience delays in HIV diagnosis and initiation of optimal combination antiretroviral therapy that could lead to considerable morbidity. These extend beyond opportunistic infections to include impaired growth, delayed puberty, and poor neurocognitive performance.^{(2),(4),(5)} There is also increasing awareness of their susceptibility to mental health and substance use issues.^{(4),(6),(7)} Furthermore, long-term antiretroviral therapy can lead to an array of treatment-related complications that have longer-term implications throughout adulthood.⁽⁸⁾

Disclosure of HIV infection

Sharing knowledge of a young person's HIV status with them should be an incremental process that needs to take into account their cognitive skills and emotional maturity, as well as their caregiver's views about and knowledge of HIV infection. Generally, this begins with education about the immune system and how certain viruses can damage the immune system, followed by a discussion around the role of medications to reduce HIV viral load in the blood and increase the number of white blood cells destroyed by HIV. By the time young people reach secondary school, they should be able to name the HIV virus, how it can be transmitted, and identify support people they can talk to. Disclosure should be done in an honest manner with a professional approach that nurtures the normalisation of HIV infection. Useful resources on approaching disclosure with children and adolescents are available from the [World Health Organization](#) and the [United Kingdom-based Children's HIV Association](#).

Antiretroviral therapy in adolescents

Most adolescents will have commenced ART during earlier childhood and will transition to a fixed-dose combination (FDC) regimen during early adolescence. The FDC regimen chosen will depend upon comorbidities, potential for drug-drug interactions (e.g., with oral contraceptives), prior antiretroviral drug exposure, antiretroviral drug resistance profiles, and any antiretroviral drug intolerances. There is increasing evidence and experience in transitioning adolescents to an integrase-inhibitor FDC, though there remain concerns around dolutegravir use in young women who are either pregnant or planning to become pregnant, given the preliminary

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

data suggesting an increased risk of neural tube defects in infants of mothers receiving dolutegravir during the periconception period.(9) Further research is underway to better evaluate this possible association.

For adolescents who initiate ART during adolescence there are established guidelines from the United States (<https://www.chiva.org.uk/professionals/clinical-guidelines/>) and Europe (<https://www.chiva.org.uk/guidelines/penta-treatment-guidelines>) that are readily available. The decision on which regimen to initiate will depend upon the readiness for adolescents to commence and be adherent to ART and the pill burden.

Psychosocial support

Adolescents face many challenges that can affect their psychosocial wellbeing. These include: the capacity for independence and self-management; an understanding of and ability to cope with potential stigma or discrimination; dealing with family stress, illness or death, orphanhood, and poverty; progress through education with possible cognitive impairment; disclosure to others for emotional and practical support; and an emerging sexuality. Adolescents require support in developing skills to independently manage their health, achieving acceptance amongst peers, and navigating sexuality and intimate relationships. This support should not only be provided through medical and allied health staff, but also through fostered peer support networks that provide a sense of belonging and connectedness, as well as opportunities to discuss challenges encountered in an understanding and compassionate environment.(10) Serial screening for mental health and substance use disorders is an integral component to the holistic care of adolescents. Effective psychosocial support can have a positive impact on ART adherence, engagement in care, academic performance, and interpersonal relationships; as well as adjusting to the stigma and secrecy that may arise from having HIV infection (including complex family dynamics and inter-generational HIV-related issues).

Developing health independence

Strategies to develop health independence should be a continual process throughout adolescence. This involves a more sophisticated understanding of HIV infection and the health issues arising from this, including HIV viral loads, CD4+ T counts, ART adherence, implications of antiretroviral drug resistance, and viewing HIV infection as a chronic condition that can be easily controlled by ART. Sexual health should be explored with discussion around contraception, family planning, and post exposure prophylaxis. Adolescents should also be made aware about their right for privacy and confidentiality of their health information. Caregivers should be counselled on ways to foster independence, such as ordering medications and making appointments, individual time with health care staff, and open communication within the family. Encouraging and preparing young people to take responsibility for their own health care may have challenges but emphasising what they will gain from taking an active role in managing their own health, rather than what they might lose, is a useful motivational strategy.(11)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Transition to adult HIV services

Transition from paediatric to adult HIV services should be a planned multifaceted process designed to maintain engagement in care, facilitate adolescent health autonomy, maximise adolescent and family satisfaction, and optimise health outcomes. The model of transition will be determined by the availability of services, but should at least involve an integrated process incorporating adolescent and adult HIV health care providers that respects the maturity of the adolescent undergoing transition. This can be conceptualised and prepared in paediatric health services, followed by a period of conjoint care (across paediatric and adult health services) and then ongoing care in adult health services. <https://www.racp.edu.au/docs/default-source/advocacy-library/transition-of-young-people-with-complex-and-chronic-disability-needs.pdf>

A useful list of key areas to consider when transitioning adolescents with HIV infection to adult services is available at <https://clinicalinfo.hiv.gov/en/guidelines/pediatric-arv/specific-considerations-antiretroviral-therapy-use-adolescents-hiv>

Adolescents with horizontally-acquired HIV infection

Adolescents who acquire HIV infection during adolescence (ie., by horizontal rather than vertical transmission) follow a similar clinical course to that of adults. Antiretroviral therapy should be commenced as soon as practical provided the young person is willing to adhere to therapy.^{(12),(13)} Initial ART regimens are likely to be focused on simplification, given that the young person will not have had prior exposure to antiretroviral drugs and there are fewer concerns around antiretroviral drug resistance and intolerance. Psychosocial support remains an important component of care as the young person comes to terms with their diagnosis; navigates disclosure (if they so choose) to family, peers and sexual partners; and encounters potential issues of self- and social-stigma. Particular attention should be paid to at-risk behaviours (e.g., sexual activity and substance use) through which the young person may have acquired HIV infection and may transmit it to others.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

HIV infection in Aboriginal and Torres Strait Islander people

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Last reviewed: June 2021

Introduction

Of the 4,289 HIV diagnoses in Australia between 2015 and 2019, 173 were among Aboriginal and Torres Strait Islander (ATSI) peoples, with the rate of diagnosis of HIV infection in 2019 higher among ATSI people (3.3 per 100,000) than Australian born non-Indigenous peoples (2.8 per 100,000).⁽¹⁾ In the five year period 2015-2019, the reported exposure to HIV infection in ATSI people differed from that of Australian-born non-Indigenous cases, with a lesser proportion of cases occurring among men who have sex with men (61% vs 73%) and a higher proportion of cases attributed to heterosexual contact (19% versus 11%) and injecting drug use (20% versus 3%).^(2,3,4)

Rates of other sexually transmissible infections (STIs) are also much higher in the ATSI population compared to the non-Indigenous population, with Chlamydia infection being three times higher and gonorrhoea seven times higher in 2017.^(2,3) In addition, in the Northern parts of Australia there is an outbreak of infectious syphilis spanning multiple jurisdictions. This higher prevalence of other STIs increases the risk of HIV transmission in this population. As such, ATSI people remain a key population for STI and HIV prevention and management strategies of Australian government agencies.^(5,6)

Barriers to diagnosis

There exist many barriers to the diagnosis of HIV infection in ATSI people, which may explain the higher rates of HIV infection in this population.⁽⁷⁾ Structural and social determinants such as late or non-diagnosis, less than optimal testing, lack of uptake of interventions such as TasP and PEP and discrimination and stigma regarding HIV have been previously reported.⁽⁸⁾ Others determinants include poorer physical, financial and cultural access to clinical services, as well as crowded housing, limited transport, and lower education and employment levels, all of which create competing demands on individuals, so that personal health is often de-prioritised.⁽⁹⁾

Opportunities for early diagnosis

A focus on the detection and control of other STIs in ATSI populations provides an opportunity for screening for HIV infection and a space to have a discussion related to safe sex practices and the benefits of early diagnosis and treatment of STIs and HIV infection. As it is common to find concurrent STIs, particularly in regional and remote areas, such opportunities must not be missed. Screening for HIV infection and other STIs during the antenatal period should be already happening routinely.⁽¹⁰⁾

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Management – cultural differences

Evidence from various sources has demonstrated that, to ensure similar outcomes are achieved in the management of ATSI peoples with HIV infection, it is critical that services provided are equitable (the level required to achieve the same results) and not equal (the same as provided for other populations)(11,12,13,14). This means that services may often need to be tailored to the individual, including management strategies to accommodate greater disparity in structural and social determinants. Further, HIV management services should be mindful of community and cultural issues such as enabling ATSI health staff and/or respected community members to advise on the place, timing, situation and relationship between patient and health care provider in all stages of HIV testing and care. Having experienced and well-connected ATSI and other local health service staff to carry out contact tracing also facilitates early diagnosis and promotion of timely treatment reducing the ongoing transmission of HIV infection in this population. In some remote locations in Australia, it is often difficult to ensure continuity of care and in this situation having a cohort of ATSI staff who are more likely to remain in the work force makes this more achievable.

Optimising treatment adherence

Once again, the importance of highly valued ATSI staff, the provision of continuity of care and the development of a strong relationship between patient and health care provider is critical to achieving long-standing adherence to treatment and good therapeutic outcomes. A holistic service provision that goes beyond the provision of therapeutic medical care and encompasses social supports such as assistance in finding stable housing, financial support to attend funerals and cultural events, maybe even extending to the provision of financial support for birth certificates and help in accessing food, are required.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Pregnancy and reproductive health in women with HIV infection

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Last Reviewed: 2024

Women with human immunodeficiency virus (HIV) infection in Australia are now choosing pregnancy as a proactive, positive, reproductive option. In addition, some women will be initially diagnosed as having HIV infection during a pregnancy. All with HIV women should have access to all the recommended strategies to prevent mother-to-child transmission of HIV infection. In Australia over the past thirty years, a decreasing number of HIV-infected women have had infants born with perinatally-acquired HIV infection, with no infants being infected in 2016 and 2017 (1) (Table 1), as a result of the established antenatal and postnatal strategies to prevent mother-to-child transmission. Some women with HIV infection may have an unintended pregnancy but only a few will decide to terminate their pregnancy and often this will be for reasons not always directly related to the HIV infection.

A few general comments on HIV infection in women in Australia which may reflect the incidence of women with HIV embarking on a pregnancy:

- Over the period 1993-2022, 940 cases of perinatal HIV among children born in Australia were reported. The transmission rate for the period 2018-2022 was 0.6%, compared to 24.6% for the period 1993-1997 and 5.8% in the period 1998-2022.(1)
- Over the period 2013-2021, the median age (years) of women diagnosed overseas has slowly increased from 33.0 to 44.5, and overall, median age of women diagnosed in Australia increased from 34 to 38 years. (1) In general, notifications among females were relatively stable between 2013 and 2019, followed by a 33% decline between 2019 and 2022 with 85 HIV notifications in 2022.(1)
- As at 2022, an estimated 3,400 women in Australia have been diagnosed with HIV, with an HIV prevalence of 0.03% of all females >15 years of age.(1)

Table 1. Number of perinatally exposed children in Australia who were HIV-positive, 2013-2022, by year of birth

YEAR	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
HIV positive (n)	4	3	4	5	3	2	1	1	0	2

Source: The Kirby Institute. HIV, viral hepatitis and sexually transmissible infections in Australia. Annual Surveillance Report 2023. Sydney; The Kirby Institute, UNSW: 2023.

Table 2. Number of Australian born children perinatally exposed to HIV and proportion HIV-positive by 5-year time periods 1993-2022.

	1993-1997	1998-2002	2003-2007	2008-2012	2013-2017	2018-2022
Perinatally exposed Australian born	72	121	129	246	197	175
HIV-positive (n)	19	7	12	69	12	1
(%)	26.4	5.8	9.3	28	6.1	0.6

Source: The Kirby Institute. HIV, viral hepatitis and sexually transmissible infections in Australia. Annual Surveillance Report 2023. Sydney; The Kirby Institute, UNSW: 2023.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Women with HIV infection will each have different journeys, which may include one or more pregnancies. Providing ongoing care and support to all women who do embark upon a pregnancy, and providing care to their infants after delivery, remains an extremely rewarding experience we will all face as HIV clinicians.

HIV testing in pregnancy – a priority

The National HIV Testing Policy recommends that all pregnant women should be routinely offered HIV testing. This should be performed with pre-test discussion, preferably at the first antenatal visit. (2) The risk of perinatal transmission of HIV can be significantly reduced by a number of established evidence-based antenatal and postnatal interventions and appropriate care throughout the pregnancy. Pregnancy is an opportune time for women to be tested when they present to clinicians; the consultation allows for the detection of previously undiagnosed infections, especially in a low prevalence country like Australia. Testing women in pregnancy is a high priority and ideally should be performed as early as possible during the pregnancy.

Previous policies had suggested that HIV testing in pregnancy be undertaken based on a risk assessment. However, for most women the only identifiable risk may be heterosexual exposure with a very limited number of lifetime sexual partners. Therefore, the standard risk assessment may not be adequate to test and detect all women with HIV infection. Some women may be at ongoing risk of HIV acquisition throughout a pregnancy. Testing of these women should be offered again later in the pregnancy.

Because prevention of mother-to-child transmission of HIV is highly effective if HIV infection is diagnosed antenatally, routine testing with pre-test discussion is now the standard of care for all pregnant women in Australia. In addition, it is important to offer all women with newly diagnosed HIV infection a sexual health screen.

A diagnosis of HIV infection in pregnancy can result in considerable anxiety and often guilt. It will also necessitate testing of the woman's sexual partners, which may increase the anxiety even further. Some women may be particularly vulnerable because they have fears of rejection or be at risk of physical harm, particularly if they are in a relationship that involves domestic violence. Therefore, special psychosocial support should be offered to all women diagnosed with HIV in pregnancy.

Conception counselling

Routine reproductive counselling is essential for all women with HIV infection. (3) In a survey of 700 women with HIV infection in 2011, 22% of whom became pregnant after an HIV diagnosis, 58% had never discussed pregnancy or treatment options before pregnancy and 42% had limited or no knowledge of antiretroviral therapy (ART) options. (4)

Health providers seeing women with HIV infection should initiate a non-judgmental conversation with all women of child-bearing age concerning their reproductive desires. This process is ongoing and should be initiated in an appropriate timely manner shortly after initial HIV diagnosis.

Many women are aware of their HIV status before becoming pregnant and therefore issues that affect contraception and pregnancy can be addressed during their routine visits for HIV care. Of course, not all women with HIV infection will desire to become pregnant and they may have contraceptive needs that should be addressed. Some women with HIV infection may be reluctant to initiate this discussion. Health-care providers play an important role in optimising preconception health and supporting women to make informed reproductive decisions.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Preconception counselling and care should be offered to all women with HIV infection and ideally should:

- Be incorporated into routine health visits,
- Facilitate comprehensive family planning,
- Allow a woman's reproductive wishes to be re-visited over time during her reproductive years, as relationships and circumstances may change,
- Provide education and counselling relating to contraception and pregnancy, targeted to the woman's individual needs (does she want to achieve a pregnancy or avoid an unintended pregnancy),
- Allow ongoing identification of all potential risk factors for adverse maternal or foetal outcomes (e.g. increasing maternal age),
- Address all health issues and allow for the woman's health to be optimised pre and post conception (Table 2).

Table 3. Preconception checklist

• Assess safer sexual practices and contraceptive methods (including condoms). • Discuss reproductive options including strategies for serodiscordant couples. • Discuss perinatal transmission risks and prevention of mother-to-child transmission strategies, including avoidance of breastfeeding. • Optimise mental and physical health before and during pregnancy. Assess for depression prior to, and during the pregnancy, and post-partum. • Address substance use (alcohol, illicit drugs, smoking, vaping). • Check vaccination status (influenza virus, pneumococcal, Covid-19). Vaccinate pre-conception as required. • Ensure annual influenza virus vaccination during pregnancy. • Check blood group and iron (Fe) studies. • Check infection serology – hepatitis C virus (HCV), hepatitis B virus (HBV), varicella zoster virus (VZV), measles, mumps and rubella viruses. Vaccinate as indicated pre-conception. • Assess tuberculosis (TB) exposure risk relating to past known exposure, lived in high prevalence area, health care worker exposure etc. If latent TB infection is diagnosed, refer for appropriate prophylactic treatment. • Screen for sexually transmissible infections (STIs), including syphilis serology, and provide treatment as required. Repeat syphilis serology should also be offered in the third trimester. • Rescreening for genital infections while attempting to conceive should be based on individual risk. • Perform pelvic examination and cervical screening test (CST). • Prescribe folic acid 1-5 mg/day before conception and during the first trimester. • Refer to infertility services when required. • Encourage sexual partners to have an HIV test, counselling, and to engage in care as appropriate.
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Contraception

Previous studies have indicated that one in five women with HIV infection are not using any contraceptive method, a rate which is higher than in the general population. High rates of unintended pregnancies have been reported in some settings with proportions ranging from 50-85%, with condoms often being the most commonly used contraceptive method. (5)

It is important to offer all women with HIV infection who do not desire a pregnancy, effective and appropriate methods to reduce the risk of an unintended pregnancy. Women with HIV infection can use all available contraceptive methods, including hormonal contraception, emergency contraception and long-acting reversible

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

contraceptives (LARCs). The method of contraception to be used should be chosen in discussion with the woman, and should be acceptable and medically appropriate with consideration of thrombosis, cardiovascular disease and stroke risk, together with worsening of migraine on combination hormonal contraceptives. (6)

A World Health Organization expert panel has reviewed all available evidence regarding hormonal contraception and the potential effect on HIV transmission to a partner without infection and has recommended that women with HIV infection can use all available hormonal contraceptive methods without restriction. (7)

Many of the older antiretroviral drugs have inducing or inhibiting effects on the cytochrome P450 enzyme system and, as hormonal contraceptives are metabolised by cytochrome P450 isoenzymes, there are significant drug-drug interactions between hormonal contraceptives and antiretroviral drugs, which may lead to contraceptive failure. (8) This is not a problem with currently available integrase inhibitor drugs. Detailed descriptions of interactions are available in existing antiretroviral guidelines. (9) A practical guide is summarised below (Table 3). It should be noted that data on drug-drug interactions between antiretroviral drugs and hormonal contraceptives are primarily derived from drug labels and there are limited studies of the clinical significance of these interactions. The magnitude of change in contraceptive efficacy may not be well known in all instances.

IUDs appear to be a safe and effective contraceptive option for women with HIV. Studies have primarily focussed on IUDs which do not contain hormones (e.g., copper IUDs) several small studies have shown that levonorgestrel-releasing IUDs are safe and have no associated increased genital tract shedding of HIV.

Table 4. Contraception and antiretroviral drug interactions – a brief summary of guidelines. (9)

Antiretroviral drug	Combined oral contraceptive pill	Progestogen-only pill	Contraceptive implant (Implanon NXT)	Contraceptive injection DMPA (Depo-Provera and Depo-Ralovera)	Intrauterine contraceptive device (Mirena)
Zidovudine, tenofovir, abacavir, 3TC/FTC	R	R	R	R*	R
Efavirenz, nevirapine	NR	NR	NR	R**	R
Rilpivirine	R	R	R	R	R
Raltegravir	R	R	R	R	R
Dolutegravir	R	R	R	R	R
Bictegravir	R	R	R	R	R
Maraviroc	R	R	R	R	R
Atazanavir Atazanavir/ritonavir	OK with < 30 µg EE+** OK with >35 µg EE+**	NR	NR	NR	R
Darunavir/ritonavir Lopinavir/ritonavir	NR	NR	NR	NR	R
Elvitegravir + cobicistat	NR	NR	NR	NR	R

R: Recommended without additional contraceptive protection

NR: Not recommended – use alternative or additional contraceptive method

*DMPA (depot medroxyprogesterone acetate) with tenofovir – concerns that both may decrease in bone density

+Oral contraceptives containing progestogens other than norethindrone or norgestimate have not been studied

**<25 µg ethinyl oestradiol (EE) have not been studied

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Prevention of mother-to-child transmission

The first major study of HIV prevention in pregnancy was the Paediatric AIDS Clinical Trials PACTG 076 in 1994. This placebo-controlled study demonstrated that the administration of zidovudine to pregnant women and their infants could reduce the risk of perinatal HIV transmission by 67.5% overall.[\(10, 11\)](#) More recent studies have explored the efficacy of shorter, less expensive antiretroviral drug regimens, usually more applicable to resource-limited settings, and have also examined regimens to reduce postnatal transmission during labour and breastfeeding.

A number of effective strategies have now been established to prevent mother-to-child transmission during pregnancy, at the time of labour and delivery and in the postnatal period. With the implementation of recommendations for universal prenatal HIV counselling and testing, antiretroviral drug prophylaxis, scheduled caesarean delivery when indicated, and avoidance of breastfeeding, the rate of perinatal transmission of HIV has dramatically diminished to 2% or less in the United States of America, Europe and Australia. In the developed world, the goal of HIV treatment in pregnancy is now to achieve a transmission risk of <1%.[\(1, 2 – 15\)](#) A number of factors have been identified that may affect the risk of perinatal transmission. The most significant risk factor is the maternal plasma HIV viral load. Different risks are evident during different times of the pregnancy with labour and delivery being the period of greatest risk for the infant.

There are many factors that may affect perinatal transmission:

1. Viral

- HIV viral load (cell associated/cell free)
- Phenotype (syncytium-inducing (SI), tropism)
- Genotype

2. Immunological

- Decreased CD4+ T cell count
- HIV-specific antibodies (neutralising, ADCC)
- HIV-specific T cell responses
- Mucosal immunity

3. Maternal

- Clinically advanced HIV disease – high HIV viral load
- Primary HIV infection
- Co-infection with hepatitis C virus (HCV)
- Twins – first born

4. Obstetric events [\(16\)](#)

- Duration of labour with rupture of membranes (ROM) more than 4 hours in the absence of full virological suppression [\(17, 18\)](#)
- Use of ART in pregnancy [\(19\)](#)
- Mode of delivery – benefit of caesarean section in the absence of full virological suppression [\(20, 23\)](#)
- Breastfeeding (approximately an additional 30% risk postpartum in the absence of maternal ARVs) [\(24, 28\)](#)
- Mixed feeding (increased risk over exclusive breastfeeding)
- Some interventions e.g. foetal blood sampling, scalp electrodes

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

5. Foetal/placental

- Prematurity
- Chorioamnionitis
- Infant immune responses

Significant advances have been made in the prevention of mother-to-child transmission. The proven strategies for prevention are:

1. Use of antiretroviral drugs

- ART for the mother, continuing post-delivery.
- For the baby – antiretroviral post-exposure prophylaxis (PEP). For mothers with HIV viral load <50 copies/mL and prevention of mother-to-child transmission strategies in place, zidovudine monotherapy for 4 weeks is recommended. It is a more complex situation where the risk of mother-to-child transmission is higher e.g. where mothers have not received antenatal ART, and additional ART, eg. zidovudine + lamivudine + raltegravir, for the baby may be considered by the paediatric team (20)
- In addition, intravenous (IV) zidovudine may be used during delivery if it is a late diagnosis, or the HIV viral load is >400 copies/mL. (9, 29)

2. Mode of delivery (21 – 23)

- The role of caesarean section delivery has changed over time. If maternal HIV viral load is undetectable (<50 copies/mL) and the woman has received ART for more than 4 weeks, there is no evidence of additional benefit from a planned caesarean section delivery and the majority of women are now having a vaginal delivery. (12)
- If delivery by caesarean section is planned, it should be undertaken at 38 weeks gestation.
- Avoidance of invasive measures at the time of labour and delivery e.g. scalp electrodes is advisable. The use of forceps and ventouse extraction may potentially increase the risk of transmission but this does not preclude their use if obstetrically necessary.

3. Breastfeeding (24 –27)

The many benefits of breastfeeding are acknowledged. Researchers have observed transmission through breastfeeding in the range of 0.3% (up to 6 months) and 0.6% (up to 12 months of breastfeeding) where the person was considered to be taking ART during pregnancy and the breastfeeding period. However these studies did not have routine viral load testing results available. Women who desire to breastfeed and who are totally adherent to antiretroviral medication, undergo regular recommended clinical and laboratory monitoring, and have an undetectable HIV RNA viral load (sustained for a given period), now have a choice to breastfeed (exclusive).

It is important for women who choose to breast feed to maintain regular engagement with their healthcare providers and be provided with support for excellent adherence to ARVs. Ideally maternal HIV viral loads should be monitored at four-weekly intervals during breastfeeding to ensure continued viral suppression. Refer current guidelines regarding breast feeding and HIV.

Breastfeeding (exclusive) is still recommended in resource-limited settings without access to a clean water supply.

Women who have questions about breastfeeding or who desire to breastfeed should receive patient-centred evidence-based counselling regarding infant feeding options and harm reduction measures. If women decide not to breast feed, they should have ready access to artificial feeding.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Principles of antiretroviral use in pregnancy

Antiretroviral drugs for prevention of perinatal transmission of HIV are recommended for all pregnant women, regardless of CD4+ T cell counts and HIV viral load, and will reduce perinatal transmission through a number of mechanisms. Antenatal drug administration decreases maternal HIV viral load in blood and genital secretions. A number of studies have shown that the penetration of antiretroviral drugs into the female genital tract varies for different drugs.

Initiation of antiretroviral therapy

If HIV infection is first diagnosed in pregnancy, consideration should be given to initiating ART as soon as possible. However, after discussion, some women may elect to commence treatment after the first trimester (providing it does not disadvantage her care). Ideally, ART should be commenced before 28 weeks gestation. The goal is to safely reduce the HIV viral load to undetectable levels well before, and during, delivery regardless of maternal stage of HIV disease (30) or HIV viral load. Combination ART regimens are more effective than single-drug regimens in reducing mother-to-child transmission and are the standard of care. Earlier initiation and longer duration of ART are more effective than later initiation and shorter duration because earlier suppression of HIV replication lowers the risk of transmission for the foetus (31). The use of ART is highly effective, even in women with advanced HIV disease.

Discontinuation of ART during pregnancy should be avoided as an increase in HIV viral load will result in an increased risk of HIV transmission to the foetus and possible decline in immune status of the mother (29). Pregnancy does not accelerate HIV disease progression, unless the mother already has advanced disease or AIDS.

All antiretroviral-naïve women should have a baseline HIV genotypic drug resistance assay performed. This assay should also be performed for any woman with virological failure during pregnancy requiring a treatment modification, HIV viral load permitting (>1000 HIV RNA copies/mL).

All pregnant women with HIV should also have hepatitis B serology performed and antiretroviral therapy being initiated should also be based on the woman's hepatitis B status.

Choice of antiretroviral drugs (9, 30)

In general, the same regimens recommended for treatment of non-pregnant adults with HIV infection should be used in pregnant women, with special consideration of existing safety data. However, drug treatment must always be individualised. Consult current guidelines regarding recommendations. (9)

As with all patients, genotypic drug resistance testing is recommended for all pregnant women before initiation of ARVs and for those with a detectable HIV RNA whilst on ARVs. ART initiation should not be delayed pending drug resistance assay results. Always the individualised selection of ARVs need to be based on pre-existing co-morbidities, results of drug resistance assays, known benefits and risks of a regimen in pregnancy and with consideration of the woman's expressed preference.

For women already on ART, continuation is recommended. There may be concerns about limited experience or limited safety data with newer agents in regard to drug toxicity and teratogenicity and consideration must always be given to known adverse effects for the woman, foetus or infant that outweigh the benefits.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

The goals and issues for consideration are the same as in non-pregnant women: potency, durability, preservation of future options, toxicity and tolerability, resistance and, particularly, adherence throughout the whole pregnancy. (9, 30)

The need for strict adherence to prescribed medication throughout the pregnancy should be re-enforced and factors that may adversely affect adherence should be identified and addressed. Treatment modifications during pregnancy should be avoided unless absolutely necessary. Treatment changes undertaken in pregnancy are associated with increased risk of incomplete suppression of HIV replication at the end of pregnancy. (32) Adding a single ARV drug to a virologically failing regimen is not recommended.

It is now recommended that all women continue ART following the delivery of their infant. However several studies have shown that the mother's adherence to ART may deteriorate in the postpartum period. (33) HIV viral load monitoring has been shown to be valuable in enhancing adherence. (34)

Recommendations for the use of antiretroviral drugs in pregnancy

Current recommendations for specific antiretroviral drugs are available in existing guidelines (USA and UK). (9, 30)

- Preferred antiretroviral drugs are those with clinical trial data in adults that have demonstrated:
- Optimal efficacy and durability
- Acceptable toxicity and ease of use
- Pregnancy-specific pharmacokinetic (PK) data available to guide dosing
- No associated teratogenic effects
- No reported maternal, foetal or newborn adverse outcomes

Transplacental passage of antiretroviral drugs is an important mechanism of infant pre-exposure prophylaxis (PrEP). For this reason, at least one nucleoside/nucleotide reverse transcriptase inhibitor (NRTI) with a high placental transfer should be included in the ART regimen. The US guidelines currently recommend an ART regimen in pregnancy consisting of two NRTIs and an integrase inhibitor (INSTI) or two NRTIs and a ritonavir-boosted protease inhibitor (PI/r).

Current recommendations January 31, 2024

Current recommendations for the initial commencement of specific antiretroviral drugs in pregnant women, based on the guidelines in the United States, are summarised in Table 5. The guidelines are very extensive regarding prevention of perinatal transmission and interventions during pregnancy. For reasons of brevity, only Table 5 is summarised below. Table 5 presents preferred regimens, for which there are clinical trial data in adults demonstrating optimal efficacy and durability with acceptable toxicity and ease of use, PK data in pregnancy are available, and there is no evidence of teratogenic effects or established adverse outcomes for mother, foetus, and newborn. The full guidelines should be referred to for selection rationale and full antiretroviral drug safety data (<https://clinicalinfo.hiv.gov/en/guidelines>).

Table 5. Preferred initial antiretroviral regimens in pregnancy

Preferred initial regimens are designated as *Preferred* in the Guidelines when clinical data in adults have demonstrated efficacy and durability and a favourable risk-benefit balance for mother, foetus, and infant outcomes. When considering risks associated with Preferred and Alternative ARVs, the lack of suitable data indicates neither the presence nor absence of risk.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Note, two-drug regimens are NOT recommended in pregnancy.

Also, data suggests decreased drug levels during pregnancy with associated loss of viral suppression with regimens containing cobicistat, e.g., EVG/c or DRV/c, are not recommended for initiation during pregnancy.

Recommended initial regimens	Additional information
Preferred dual NRTI backbone ABC/3TC TAF/FTC or TAF + 3TC TDF/FTC or TDF/3TC	HLAB5701 negative. ABC not active against hepatitis B When combined with DTG is associated with more treatment-associated obesity in nonpregnant adult women compared to TAF/FDC TDF – potential concerns re foetal bone abnormalities though clinical findings reassuring Potential for renal toxicity – use with caution in patients with renal insufficiency
Preferred INSTI regimens DTG/ABC/3TC or DTG + preferred dual NRTIs	Potential concerns re weight gain
Preferred PI regimen DRV/r + preferred dual NRTIs	Requires twice daily dosing in pregnancy – with food PIs may increase the risk of pre-term birth
Alternative initial regimens	Additional information
BIC/TAF/FTC	PK and safety data remains limited to small studies T3 drug levels are reduced but remain above EC95 May be associated with weight gain
RAL + dual NRTI backbone	Twice daily dosing recommended Lower barrier to resistance than DTG Specific timing/fasting if taken with calcium, iron tabs
Alternative PI regimen ATV/r + dual NRTI	ATV/r plus a preferred two-NRTI backbone – once-daily administration. Extensive experience in pregnancy Maternal hyperbilirubinemia appears to have no adverse effects on the neonate, no maternal clinical significance Increase dosing in T2 and T3 PIs may increase risk of preterm delivery Do not use with PPIs, adjust timing with H2 blockers
DRV + dual NRTI	Twice daily dosing – with food PIs may increase risk of preterm delivery
Alternative dual NRTI backbone	
ZDV/3TC	Twice daily dosing Potential side effects may include nausea, headache, reversible maternal and neonatal anaemia and neutropenia
EFV/TDF/FTC (FDC) or EFV/TDF/3TC (FDC) or EFV plus a Preferred dual-NRTI Backbone	Overall higher rates of adverse events than some Preferred drugs Requires enhanced surveillance for depression and suicidality Increased risk of adverse birth outcomes has been observed with EFV/TDF/FTC versus DTG/TAF/FTC started during pregnancy Increased risk of toxicity, including dizziness, fatigue, hepatotoxicity, vivid dreams/nightmares

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

RPV/TDF/FTC (FDC) or RPV/TAF/FTC (FDC) or RPV (oral) plus a Preferred Dual-NRTI Backbone	Limited use with high pre-treatment HIV RNA RPV is not recommended in patients with pretreatment HIV RNA >100,000 copies/mL or CD4 counts <200 cells/mm³ Requires close viral monitoring in T2 and T3 – PK data suggest lower drug levels Insufficient data to suggest dosing changes Do not use with PPIs Requires consideration of timing with H2 blockers Requires administration with food
Insufficient data	
DOR or DOR/TDF/FTC	Limited PK, toxicity and efficacy data in pregnancy Initial studies suggest potential low drug levels in T3

Source: *Recommendations for the Use of Antiretroviral Drugs during Pregnancy and Interventions to Reduce Perinatal HIV Transmission in the United States. Updated: January 31, 2024.*

Special issues when using antiretroviral therapy in pregnancy

Several pregnancy-specific issues will need special consideration when using ART in pregnant women. These include the efficacy of antiretroviral drugs in prevention of mother-to-child HIV transmission, maternal and foetal toxicity, teratogenicity, PK profile, antiretroviral drug resistance testing before and during pregnancy, transplacental transfer of antiretroviral drugs, timing of treatment initiation, hyperemesis and nausea of pregnancy.

If the mother is experiencing severe hyperemesis, ART may need to be ceased temporarily. All antiretroviral drugs will usually need to be stopped simultaneously and re-introduced simultaneously as soon as possible, remembering the potential problem that might arise with drugs that have long half-lives (e.g. nevirapine and efavirenz).

Changes in PK profile of antiretroviral drugs in pregnancy may lead to lower plasma levels of some drugs and necessitate increased dosages, more frequent dosing or boosting e.g. boosted lopinavir (commonly used in pregnancy in the past). PK studies are continuing for the newer antiretroviral drugs. For example, recent studies of once daily ritonavir-boosted darunavir (DRV/r 800/100 mg) indicated that this regimen provided adequate drug exposure to achieve suppression of HIV replication and was safe and well tolerated. (35) However, plasma concentrations postpartum were higher than in the second and third trimester, so assessment of adherence is important, as are any concomitant medications that may further decrease DRV levels. DRV/r twice daily has previously been shown to be a treatment option for women with HIV infection with or without DRV resistance-associated mutations. Further PK studies of etravirine 200 mg twice daily indicated higher levels in the second and third trimester than postpartum but this was not considered clinically relevant. (36) Further studies are ongoing in this area.

Drug safety in pregnancy

Information regarding the safety of drugs in pregnancy is derived from animal toxicity data, anecdotal experience, registry data, observational cohorts and clinical trials. Preclinical data includes results of *in vitro* and animal *in vivo* screening tests for carcinogenicity, reproductive and teratogenic effects. However, the predictive value of such tests in humans is unclear. Ultimately, it could be argued that the choice of ART in

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

pregnancy has often been based on collective experience, accumulated safety data over time and consensus guidelines, rather than on randomised trials.

ARV associated weight gain may be a factor to be considered when initiating, or changing, antiretroviral therapy particularly in women of colour. The exact underlying mechanisms for any ARV associated weight gain, (apart from reported initial weight gain that appears to be associated with the onset of wellness), and its impact on pregnancy related outcomes, are currently unknown.

Long term outcome data for infants who have been exposed at ARVs in utero, especially to the newer agents, is limited but this does not in any way, preclude the use of recommended antiretroviral drugs in pregnancy.

Clinicians who prescribe ARVs in pregnancy, are encouraged to report foetal exposure to all of the drugs to the Antiretroviral Pregnancy Registry at: <http://www.APREgistry.com>

Teratogenicity of antiretroviral drugs

There is no evidence of an increased risk of congenital abnormalities in infants born to mothers with HIV infection (Table 6). Reports of birth defects in fetuses and infants of women enrolled into observational studies are reassuring with no difference in rates of birth defects for first trimester antiretroviral drug exposure compared with later exposures being observed. The known benefits and potential unknown risks of ART during pregnancy (including limited long-term outcome data for infants with *in utero* drug exposure) should be discussed with the mother.⁽³⁷⁾ The need for strict adherence to prescribed medication throughout the pregnancy should always be reinforced.

Table 6. Rates of birth defects per live birth associated with first trimester antiretroviral drug exposure, July 2023

Antiretroviral drug	Defects/live births	Prevalence (95% confidence interval)
Lamivudine	173/5643	3.1% (2.6%, 3.6%)
Bictegravir	18/423	4.3% (2.5%, 6.6%)
Tenofovir alafenamide	42/1086	3.9% (2.8%, 5.3%)
Zidovudine	136/4254	3.2% (2.7%, 3.8%)
Stavudine	21/811	2.6% (1.61%, 3.9%)
Indinavir	7/289	2.4% (1.0%, 4.9%)
Ritonavir	88/3564	2.5% (2.0%, 3.0%)
Nelfinavir	47/1216	3.9% (2.9%, 5.1%)
Tenofovir (TDF)	126/4936	2.6% (2.2%, 3.0%)
Nevirapine	36/1179	3.1% (2.1%, 4.2%)
Lopinavir	30/1452	2.1% (1.4%, 2.9 %)
Atazanavir	37/1482	2.5% (1.8%, 3.4%)
Abacavir	47/1468	3.2% (2.4%, 4.2%)
Emtricitabine	141/4813	2.9% (2.5%.3.4%)
Efavirenz	28/1196	2.36% (1.6%, 3.4%)
Darunavir	27/753	3.6% (2.4%, 5.2%)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Raltegravir	22/581	3.8% (2.4%, 5.7%)
Didanosine	20/427	4.7% (2.9%, 7.1%)
Rilpivirine	14/711	2.0% (1.12%, 3.3%)
Dolutegravir	32/957	3.3% (2.3%, 4.7%)
Cobicistat	20/587	3.4% (2.1%, 5.2%)
Elvitegravir	13/450	2.9% (1.5%, 4.9%)
First trimester (Antiretroviral Pregnancy Register)	355/12047	2.9% (2.7%, 3.3%)
Any trimester (Antiretroviral Pregnancy Register)	643/22017	2.9% (2.7%, 3.2%)
Metropolitan Atlanta Congenital Defects Program		2.72% (2.68%, 2.76%)
Texas Birth Defects Registry		4.17% (4.15%, 4.19%)

Source: The Antiretroviral Pregnancy Registry (37) : <http://www.APRegistry.com>

Health-care providers caring for women with HIV infection and their infants with prenatal exposure are encouraged to report de-identified, observational, non-experimental pregnancy outcome data to the Antiretroviral Pregnancy Registry (APR) (www.APRegistry.com). The purpose of the APR is to detect any major teratogenic effects of the antiretroviral drugs to which pregnant women are exposed. Although the Registry is international, reports are predominantly from the USA (77.3%). Rates of reported defects are compared with rates from two external comparator populations, the Metropolitan Atlanta Congenital Defects Program (MACDP) and the Texas Birth Defects Registry (TBDR). The APR finds no apparent increases in the frequency of defects with first trimester antiretroviral drug exposures compared to exposures starting later in pregnancy and no pattern to suggest a common cause. However, the potential limitations of such registries should always be recognised.

Specific drug safety issues in pregnancy

The following section is included in detail to highlight the changing safety status of newly introduced antiretroviral drugs and how ART guidelines will reflect the currently available data as more women and infants are exposed in pregnancy.

Dolutegravir

Botswana embarked upon a birth outcome surveillance programme in 2014. In 2018, the Tsepamo Study in Botswana reported a potential safety issue with 4 neural tube defects (NTDs) being detected out of 426 pregnancies with dolutegravir exposure at the time of conception (incidence of 0.9% with a background rate of 0.1%). When dolutegravir was commenced during pregnancy, no NTD were detected in 2,824 pregnancies.

The US guidelines were quick to respond, initially recommending that dolutegravir not be used in pregnant women during the first trimester and in non-pregnant women trying to conceive due to concerns about a possible increased risk of NTDs (AIII). Previously it was recommended that pregnant women currently prescribed dolutegravir who present for care during the first trimester, be provided counselling regarding the risks and benefits of continuing dolutegravir or switching to another regimen.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Subsequent reports in 2018 from the APR relating to 246 live births and from the European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC) registry relating to 81 live births showed no CNS defects in either registry. The APR has reported one NTD being observed among the 834 integrase inhibitor periconception exposures through to 31 January 2019, including 1 bictegravir, 289 dolutegravir, 243 elvitegravir, and 310 raltegravir periconception exposures. In Brazil, the world's second largest surveillance cohort, 1,468 women were identified over the period Jan 2015-Mar 2018: 382 were exposed to dolutegravir, 78 to raltegravir and 1086 to efavirenz. No NTD were detected.

Combined with the Tsepamo data, there are now >14,000 births among women on dolutegravir at conception with 14 NTDs identified, giving a weighted NTD prevalence of 0.098%, which is not significantly different than nondolutegravir regimens at conception or women without HIV infection in either country. These data do not support an association of NTD and dolutegravir. There is a background risk of NTDs (0.05% to 0.1% for women not HIV-infected) regardless of ART regimen.

Dolutegravir is now a recommended integrase inhibitor in the guidelines. However, note that recent research has suggested that dolutegravir interferes with the binding of folate to its receptor. The availability of adequate folic acid supplements and folic acid fortified foods in pregnancy is essential.

Efavirenz

Efavirenz has long been classified as a Category D drug in pregnancy (for definitions of Australian categorisation system for prescribing medicines in pregnancy, see <https://www.tga.gov.au/australian-categorisation-system-prescribing-medicines-pregnancy>) following the initial reports of teratogenicity in the preclinical primate data and retrospective reports of an increased risk of neural tube defects in humans. However, a recent meta-analysis of 1437 women in 19 studies with first trimester efavirenz exposure found no increased risk of birth defects and only one neural tube defect (incidence: 0.07%).⁽³⁸⁾

Current British HIV Association guidelines and DHHS guidelines recommend that effective efavirenz-based ART be continued in a pregnant woman presenting in the first trimester. Pregnancy recognition often occurs after the critical time of organogenesis and the development and closure of the neural tube is usually complete by 28 days post-conception. Therefore, in theory, changes to efavirenz-based regimens after 4 weeks post-conception will not significantly reduce the risk of neural tube defects and after 8 weeks will have minimal effect on the risk for other structural defects.

Atazanavir

Atazanavir is associated with an increase in serum levels of bilirubin in the mother, which in theory might increase the risk of hyperbilirubinaemia-related disease in the neonate.

However, a number of studies have shown no pathologic clinical maternal or foetal effects to date.⁽³⁹⁾

Tenofovir

There have been some concerns in the past regarding bone and growth abnormalities in infants exposed to tenofovir in utero. However, the duration of treatment and clinical significance of any study findings thus far do not preclude the use of tenofovir in pregnancy.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Cabotegravir + Rilpivirine (Cabenuva)

Data are not currently available about the efficacy and safety of injectable cabotegravir (CAB) and rilpivirine (RPV) during pregnancy. Not recommended due to concerns regarding potential inferior virologic efficacy and low drug levels with risk of viral rebound. For those who are considering switching regimens prior to conception to prevent foetal exposure, it is recommended that the injections must be stopped at least one year before conception to ensure that these long-acting drugs are fully eliminated.

For women on long-acting injectable antiretroviral therapy who have a history of poor adherence to oral medications, switching from long-acting injectable CAB and RPV to oral ART to prepare for conception may be associated with increased risk of viral rebound and NNRTI resistance. Shared decision-making should be used when making decisions about changing to an oral regimen.

Preterm delivery

Early and more recent data are conflicting in regard to whether ART during pregnancy is associated with adverse pregnancy outcomes, specifically with preterm delivery (before 37 weeks). Multiple observational studies have detected small but significant increases in preterm birth with PI-based and non PI-based ART. (40, 41) Conflicting findings may be influenced by a number of factors, e.g. data variability available for analysis, the time when ART was commenced, HIV disease severity (an independent factor), maternal age and intravenous drug use.

These findings should not prevent the current drugs from being used as the benefits of effective ART in pregnancy currently outweigh any concerns about an increased risk of preterm delivery.

Monitoring of HIV-infected women during pregnancy

HIV viral load

More frequent HIV viral load monitoring is recommended in pregnant women with HIV infection to ensure rapid and sustained virological suppression has been achieved. HIV viral load should be assessed at the initial visit, 2 – 4 weeks after initiating or changing ART, monthly until undetectable, and at least 3 monthly thereafter. If adherence is a concern, more frequent monitoring is required. HIV viral load should also be assessed at 34 – 36 weeks gestation to inform decisions about the mode of delivery and optimal treatment of the newborn.

If adherence is a concern, especially during early pregnancy, more frequent monitoring is recommended because of the increased risk of perinatal HIV transmission associated with detectable HIV viremia during pregnancy. Also, as pregnancy may reduce the drug exposure levels or the efficacy of some drugs, patients who are taking these drugs may require a change in therapy or more frequent viral load monitoring.

CD4+ T cell count

In women with HIV infection, a CD4+ T cell count should be performed at the initial visit and at least 3 monthly during pregnancy. The CD4+ T cell count will often go down slightly during pregnancy but will return to pre-pregnancy levels after delivery.

Monitoring of other laboratory tests during pregnancy

Pregnancy increases the risk of hyperglycaemia and women will usually have an oral glucose tolerance test performed during pregnancy, usually at 24 – 28 weeks of gestation. The majority of studies in women with HIV infection have not shown an increased risk of glucose intolerance and insulin resistance in those taking a PI-based regimen in pregnancy. (42)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Diagnostic tests in pregnancy

Patients with HIV who desire or have indications for diagnostic testing during pregnancy (e.g., abnormal ultrasound or aneuploidy screening) should be counselled about the potential risk of perinatal HIV transmission, along with other risks of the procedure, so that they can make informed decisions about invasive testing. Although the data on women who are receiving current ARVs are limited, the risk of perinatal HIV transmission does not appear to increase with the use of amniocentesis or other invasive diagnostic procedures in women who have virologic suppression on ART. Prior to effective ART, invasive procedures, such as amniocentesis and chorionic villus sampling, were associated with a twofold to fourfold increase in the risk of perinatal transmission of HIV. Patients ideally should have undetectable HIV RNA levels at the time of the procedure.

Paediatric referral

It is vital to involve a paediatric multidisciplinary team before the birth of the infant. The team, consisting of a paediatrician, nursing staff, social worker, and dietitian, will support the mother and family in many ways, including the following:

- Counselling and support of the mother and her partner during pregnancy and after delivery of the baby
- Providing information on the strategies to prevent mother-to-child transmission
- Providing an outline of the necessary testing schedule of the infant, up to 18 months of age, and the tests to be undertaken – HIV antibody together with HIV DNA (proviral) PCR or HIV RNA PCR (43 – 44)
- Providing information and support regarding antiretroviral drug use for the baby after birth
- Recommendation regarding not breastfeeding. Not being able to breastfeed can be very confronting for many mothers in many cultures, and support by the paediatric team is invaluable in assisting with this issue
- Providing information regarding vaccination of the baby after birth. Routine vaccinations should be given to all babies according to the Australian Immunisation Schedule
- Developing a Care Plan of antenatal and postnatal management, always in consultation with the mother, to assist all health providers involved in care – HIV physician, obstetrician, general practitioner, and the delivery suite
- Providing ongoing care and support to the infants who are newly diagnosed with HIV infection. Paediatric care and support will continue into adolescence and will include, but not be limited to, Camp Goodtime and preparing the way for children to negotiate school commencement confidentially.

Reproductive options for HIV seroconcordant and serodiscordant couples

Consultations concerning HIV and pregnancy issues may involve serodiscordant couples or, less often, seroconcordant couples. For these couples, referral to an HIV Specialist for expert consultation is recommended.

In brief, recent studies have provided evidence of the effectiveness of ART in preventing sexual transmission of HIV, i.e., treatment as prevention (HPTN 052 and Partner Study). (45, 46) The reproductive health needs of seroconcordant and serodiscordant couples can, very briefly, be outlined as follows: (47)

- For couples in which both partners have HIV infection (extremely rarely, they might have different genotypes, one partner having HIV2), both partners should have attained optimal health before conception.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

They should have demonstrated sustained full suppression of HIV replication before attempting a pregnancy through unprotected intercourse.

- For serodiscordant couples where one partner has HIV infection and has sustained viral suppression, sexual intercourse without a condom allows conception without HIV transmission (now accepted paradigm of U=U, ie Undetectable = Untransmissible).
- For some serodiscordant couples, one partner may be very anxious to have unprotected intercourse to achieve a pregnancy. In this instance, pre-exposure prophylaxis (PrEP) can be offered, particularly when the male partner has HIV or has specific indications for PrEP. If PrEP is used by the HIV-negative partner, it should be continued for at least one month after conception is achieved and revisited throughout the pregnancy if there is any ongoing risk of seroconversion during pregnancy.
- Concerned couples can also be counselled that unprotected intercourse can ideally be limited to the 2-3 day window at the time of ovulation and counselled re strategies to identify the time of ovulation. (48, 49)
- For serodiscordant couples, if needed, an alternative safe option of donor sperm followed by artificial insemination or in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI) may be considered. In the past, sperm washing was available. However, this had very limited availability at the time and is no longer recommended.
- Finally, access to assisted reproductive technology (including IVF/ICSI) should be accessible for all couples as required, to address female and male infertility issues.

In conclusion, the current models of care for couples with HIV infection should encompass integrated HIV, obstetric and paediatric care, contraception when required, and integrated care for couples, which includes early access to treatment as prevention, PrEP if required, and access to interdisciplinary care.

Case studies

Case Study 1
Agnes is a 28-year-old woman from South Africa. She arrived in Australia 6 months ago and has no family supports. She is diagnosed as having HIV infection and she is also 10 weeks pregnant. She is non-Medicare eligible at this time. Initial investigations indicate a CD4+ T cell count of 190/μL and a plasma HIV RNA level of 43 000 copies/mL. <i>What are the key issues for this young woman that need to be considered and the possible solutions that are available?</i>
Case Study 2
Samuel was diagnosed as having HIV infection in 2005. He has been in a relationship with Sue for the past 7 years and they are now very keen to have a child. Sue has been engaged in long-term counselling regarding severe anxiety, including ongoing anxiety about acquiring HIV. Samuel is currently on Biktarvy and his HIV viral load has been undetectable for the past 10 years. <i>What are the key issues for this couple and the available solutions?</i>

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

In summary

- ART in pregnancy is the standard of care and is commenced regardless of CD4+ T cell count, HIV viral load or stage of disease.
- When all recommended strategies are implemented, the mother-to-child transmission risk is now considered to be below 1% in developed world settings.
- ART should be commenced as soon as possible if the woman is not already on therapy (but some women may prefer to wait until after the first trimester if ART-naïve).
- Choice of specific antiretroviral drug relates to demonstrated efficacy and safety.
- Two drug regimens are not recommended during pregnancy.
- ART is continued after delivery for all HIV infected women.
- Refer to guidelines and colleagues experienced in the management of both HIV infection and pregnancy.
- Women with HIV infection require more frequent monitoring during pregnancy.
- Management of pregnant woman with HIV infection requires a coordinated team approach – HIV physician, obstetrician, paediatric HIV specialist for the baby, midwives and allied health staff.

Resources

<http://www.APRegistry.com>

Antiretroviral Pregnancy Register maintains an up-to-date registry of antiretroviral drug exposure during pregnancy.

<https://clinicalinfo.hiv.gov/en/guidelines/perinatal/recommendations-arv-drugs-pregnancy-prevent-hiv-transmission-improve-health>

Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States.

Family Planning NSW: Contraception: an Australian clinical practice handbook. 4th edition; 2016.

MotherSafe

<https://www.seslhd.health.nsw.gov.au/royal-hospital-for-women/services-clinics/directory/mothersafe>
Counselling service for health providers and mothers regarding concerns about perinatal exposure.

WHO 2010

<https://www.who.int/teams/global-hiv-hepatitis-and-stis-programmes/hiv/prevention/mother-to-child-transmission-of-hiv>

WHO guidelines on prevention of mother-to-child transmission and breastfeeding.

<http://www.hiv-druginteractions.org>

University of Liverpool HIV Drug Interactions website.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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Nurses & Midwives

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

New HIV Diagnosis

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Last reviewed: 2024

Summary

This chapter discusses nurses' roles in caring for people, newly diagnosed with HIV.

- Introduction
- Engagement
- Ensuring engagement and a patient-centred approach
- Contact tracing

Introduction

In 2022, 555 Australians received a diagnosis of human immunodeficiency virus (HIV) infection, a 46% decline since 2019(1). For all of these people, this was a life-changing event. Pretest discussion may have been limited or may not have occurred at all. Newly diagnosed people with HIV (even those well-prepared during pretest discussion) may respond with a wide range of feelings and questions (Table 1).

Table 1: Some emotional responses and questions to testing HIV positive

• Shock • Disbelief • Puzzlement • Relief • Numbness • Fear • Panic • Guilt • Anger • Shame • Despair • Hopelessness • Feeling overwhelmed • Relief • Expression of self-harm (rare)	• How did this happen to me? • Will I die? • When did I get the infection? • What happens now? • What changes do I have to make in my life? • How can I help myself? • What should I avoid? • Can I have children? • Is there a cure? • Who do I have to tell? • Do I have to tell my employer? • How is HIV treated? • How much does treatment cost? • For patients without access to Medicare: • Will you tell the Department of Immigration? • Will I be deported? • How will I pay for tests and treatment?
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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Nurses are often involved at (or shortly after) the time of diagnosis. The initial (and subsequent) encounters present a unique opportunity to enable a healthy adjustment from being a person without HIV infection to being an HIV-positive person. All but a few newly diagnosed people make this adjustment, usually over a period of 6 months or less. Those who don't are often identifiable by one or more of the characteristics discussed under service engagement (Table 2). Commonly these may be:

- Alcohol and other drug use
- Significant mental health issues
- Younger age
- Heterosexual
- Belonging to a religious or ethnic group or culture where pre- or extramarital sex, injection drug use and homosexuality are taboo
- Denial.

The single most important nursing function at the initial encounter with a newly diagnosed patient is to foster engagement.

Engagement

Providing a person with HIV infection engages with specialist care and achieves sustained HIV suppression with antiretroviral therapy (ART), morbidity is greatly reduced, life expectancy approaches near normal and the chance of onward transmission of HIV is significantly decreased.(2) (3) (4) During 2013, an estimated 1212 people with diagnosed HIV in Australia were not engaged in care.(1)

Poor retention in care predicts poorer survival with HIV infection. A retrospective analysis of HIV positive outpatients in Europe found those who missed visits within the first year after initiating ART had more than twice the rate of long-term mortality, compared with those who attended all scheduled appointments (2.3 deaths per 100 person-years for patients who missed visits vs 1.0 death per 100 person-years $p = 0.02$ for those who didn't).(6)

Disengagement can happen at any point in the continuum of care but the time of diagnosis represents a particular time of danger.

Failure to engage with (or remain) in care is multidimensional and multifactorial (Table 2).

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Table 2: Failure to engage: patient characteristics (7)

• Non-White or predominantly European ethnicity • Member of a religious or cultural group with strong taboos around sex and sexuality and injection drug use • English as an additional language • Heterosexual – particularly if diagnosed in a setting that predominantly cares for gay men • Younger age • Distrust of mainstream medicine • Low level of education • Low literacy • Lower-income • Unemployment • No access to Medicare • Higher CD4 cell count • No acquired immune deficiency syndrome (AIDS) defining illness – the patient feels perfectly well • History of or current injecting drug use • Social isolation • Lower perceived social support • Low levels of self-efficacy • Psychiatric illness • Conflicting work schedules • Travelling for work • Homelessness • Secrecy and fear of disclosure • Feelings of no control – helplessness • Lack of childcare • Lack of transportation • Other concurrent crisis

Ensuring engagement and a person-centred approach

Promoting, nurturing and supporting engagement is best realised by providing:

- support
- education
- service coordination.

Importantly person-centred approaches need to be adopted to ensure the highest attainable standard of health for people living with HIV and people at risk of HIV acquisition. Person-centred approaches include:

- centre a person's autonomy, dignity and rights
- respect a person's decisions and experiences
- support a person to lead the dialogue about their health
- build relationships grounded in understanding and trust(7)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Tables 3, 4 and 5 outline some ways that nurses can facilitate each of these three key actions. Section 4 Key affected populations – how can nurses engage them in HIV care and prevention? provides more detail on issues faced by key affected populations.

Table 3: Providing support

- Identify those most at risk of poor service engagement (Table 2)
- Ask yourself (and the client) – ‘am I the right gender, age, sexuality to work with this person?’, ‘is there a feasible and accessible alternative?’
- Ask yourself (and the client) – ‘is this the right clinic setting for this person? ‘Is there an alternative for ongoing care?’ explain importance of right ‘fit’ for lifelong ongoing care. Facilitate engagement with an alternative and suitable clinic or service
- Is an interpreter appropriate and available? Sometimes clients will initially decline an interpreter because of concerns around confidentiality and cultural shame. Consider the use of phone interpreters and pseudonyms
- Make time
- Ensure privacy and confidentiality at all times
- Provide time-out – ‘do you want some time by yourself right now?’
- Pay attention to the client’s physical needs – is food or something to drink required?
- Pay attention to the client’s immediate needs – does he or she need to call an employer, child minder, cancel another appointment?
- Explore immediate support – ‘is there someone you trust that you’d like to call right now?’
- Listen, listen some more and listen again
- Let the person know they are being heard
- Anticipate and normalise the range of feelings the person expresses (Table 1)
- Let the client lead the conversation
- Correct misinformation and answer the common questions (Table 1) with simple, factual statements
- Provide hope – for the vast majority of people diagnosed with HIV infection the event is life-changing and not life-threatening
- Make sure the client will be safe. Consider:
 - Is there a history of mental illness?
 - Is the client expressing thoughts of self-harm?
 - Have you asked that question?
 - What supports does the client have?
 - Who might provide support outside of the clinic?
 - How does the client usually deal with a crisis?
- Where possible, if client agrees, involve a counsellor or social worker
- Provide written contact numbers for clinic assistance and include, if necessary, services such as Lifeline Australia: 13 11 14
- Provide ready access to the clinic – ‘drop in to see us or phone us whenever you want’, ‘these are our opening hours’
- Identify yourself or another person as the key individual to call or ask for – ‘this is how to get hold of me’
- Refer as appropriate to other internal or external service providers – follow-up and check the referral was received and actioned
- Arrange to see the client again within a week – be flexible with times
- Ask if it would be appropriate and acceptable to call or contact the client the day following a missed appointment
- Check you have the correct telephone number(s) and email address

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Table 4: Providing education

• Keep it simple • Don't attempt too much and avoid information overload • Do not overburden with referrals to other services • Be prepared to repeat information • Adjust the level of information to the client's ability to understand – avoid jargon • Use the client's questions and statements to raise key issues • Address the key issues of the initial encounter sensitively and respectfully • Prognosis – HIV is life-changing not life-threatening, near normal life expectancy for most • Treatment – effective, simple and usually well-tolerated • Modes of transmission and keeping others safe • Legal obligation relevant to where the diagnosis is made; • Who needs to know? (see contact tracing below) and importantly who doesn't? Once someone has been told, they can't be untold • Clients without access to Medicare have particular concerns around the cost of tests and treatment and immigration • Most HIV and sexual health clinics absorb the costs of further blood tests from their own budgets for this group • Free access to treatment may be available through enrolment in clinical trials or through pharmaceutical company compassionate access schemes • Low cost, generic, imported ART is available – see www.lpv.org.au • Printed and online resources: • Local AIDS councils: A list of local AIDS councils and other organisations can be found here • Health Equity Matters – www.healthequitymatters.org.au • National Association of People with HIV – www.napwha.org.au/ • Multicultural HIV and Hepatitis Service – www.mhahs.org.au/ www.aidsmap.com www.thebody.com

* Australia has transitioned from an industry-sponsored antiretroviral treatment (ART) compassionate access scheme to a Federation Funding Agreement (FFA) model that provides free or affordable access to ART for people with HIV who do not have Medicare. Information on how the scheme has been implemented in your state or territory can be found [here](#)

Table 5: Service coordination

• Assume a case management role: ◦ assessment of need ◦ care planning ◦ implementation ◦ care coordination ◦ regular review • Communicate throughout with the multidisciplinary team • Set up processes whereby clients who miss appointments are noted and called

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Contact tracing

Contact tracing is an essential part of the management of a person newly diagnosed with HIV but should rarely be the priority in the initial encounter. People with HIV can experience significant discrimination and rejection. There are implications for employment, relationships, insurance and immigration unless there is a possibility of providing post-exposure prophylaxis (PEP) to the partner. Confidentiality is usually a major concern and contact tracing can be difficult. Inexpert or insensitive handling of this issue can sometimes be enough to ensure immediate disengagement from health care. The newly diagnosed person will often raise the question of how the infection was acquired (and when) or can be gently led in this direction with questions about the timing of the last negative test or an illness suggestive of primary HIV infection. This conversation allows an opportunity to explore relationships and introduce the concept of contact tracing. Contact tracing should be seen as a process over time rather than an immediate concern.

See also [Contact tracing and partner notification](#)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Late presentation of new HIV diagnosis

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Last reviewed: 2024

Summary

- Introduction and definitions
- The importance of early diagnosis and linkage to care
- Barriers to testing and risk factors for late HIV diagnoses.
- Nursing implications – severe disease
- Immune reconstitution inflammatory syndrome

Introduction and definitions

Late diagnoses of HIV, delayed presentation to care, and people presenting late with severe disease are ongoing concerns globally (1). Late presentation of HIV, defined as a diagnosis with a CD4 T-lymphocyte (CD4) count of less than 350 cells/μL, accounted for an estimated 48% of human immunodeficiency virus (HIV) diagnoses in Australia in 2021 (2). This is the highest proportion reported in the last ten years. Approximately 34% of these were advanced infections, defined as having a CD4 count of less than 200 cells/μL (2). The proportion of people diagnosed late in Australia is higher amongst people born in Central or South America (44%), Sub-Saharan Africa (59%) and Southeast Asia (57%) than amongst those born in Australia. Late diagnoses are also higher amongst people who report heterosexual sex or injecting drug use as their HIV risk exposure (2).

People diagnosed late often learn of their HIV status only after being diagnosed with an opportunistic illness (OI) such as *Pneumocystis jirovecii* pneumonia or *Toxoplasmosis gondii* infection (3, 4) (see also [Clinical Manifestations of HIV disease](#)). These OIs occur with severe immunosuppression. They are at risk of serious morbidity and mortality, are more likely to require intensive care support if hospitalised and they have an increased risk of acquired immune deficiency syndrome (AIDS) or death, particularly in the first year after diagnosis (5-7). After starting ART, those who have been diagnosed late generally experience a longer time to immune reconstitution, may be at ongoing risk of OIs and experience immune reconstitution inflammatory syndrome (IRIS) (8).

The importance of early diagnosis and linkage to care

Early HIV diagnosis and treatment offer benefits including reduced morbidity and mortality, avoidance of hospital admission, prevention of HIV transmission and better quality of life through appropriate treatment, care, and support (9). Nurses working in a wide range of settings – sexual health, viral hepatitis and HIV, primary care, community health, custodial settings, the drug and alcohol sector and homelessness services – can play key roles in increasing awareness and access to HIV testing for vulnerable groups and in promoting HIV testing with appropriate pre-test education to avoid late diagnoses and their complications.

Strategies to promote early diagnosis and treatment initiation in Australia include HIV testing during antenatal

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

screening (10) and regular sexually transmissible infection (STI) screening for men who have sex with men (11). However, there are gaps in reaching those who may not perceive themselves as being at risk of HIV infection: for example, older adults, women, and heterosexual males. Nurses working in community health and primary care can assess risk and offer testing for HIV infection in individuals who present for general age-related medical examinations such as women attending for cervical screening tests or those seeking reproductive health services. Nurses involved in the development of Medicare-funded care plans can introduce questioning around relationships and sexual health, especially in older adults disclosing risk behaviours and those with unexplained illnesses. An [HIV Clinical Indicator Tool](#) can provide a useful guide to testing in all settings (12).

Barriers to testing and reasons for late diagnoses

In Australia, people who have engaged in an identifiable risk behaviour comprise the majority of those diagnosed with HIV, such as men who have sex with men (MSM). However, as noted above, significant numbers of infections are diagnosed in women, people from culturally and linguistically diverse (CALD) backgrounds and people in older age groups (13, 14). Personal and health-care provider ignorance about risk, social isolation, poor access to health care, language and cultural barriers, HIV-related stigma and fear of discrimination are some factors which prevent people from having timely HIV testing (13). A recent study in Europe highlights similar barriers, especially for migrant women (15).

Late presenters may have had limited contact with health services before their HIV diagnosis, but in some cases, a person may have attended primary health services with HIV-related indicator conditions e.g. seborrhoeic dermatitis, oral candidiasis (thrush) or unexplained weight loss, but the health care provider has not considered HIV. Healthcare workers may not have the knowledge to consider HIV or may not identify risk factors for HIV infection, resulting in missed or delayed diagnoses (16).

Nursing implications of late diagnosis – severe disease, treatment and prevention of opportunistic illnesses

Where people have been diagnosed late with HIV infection, skilled nursing is essential to their ability to follow through with treatments and remain engaged with the health system. The OIs (also referred to as AIDS-defining illnesses or AIDS-indicator diseases) with which those diagnosed late and with advanced disease may present are now relatively rare, due to effective treatments. Nurses in low HIV prevalence settings such as Australia and New Zealand may not have first-hand experience and knowledge of such illnesses. Thus, it remains important for nurses to understand the natural history and management of HIV and opportunistic illnesses.

Psychological and emotional reactions to a new HIV diagnosis can vary and can be serious (see Section 1 [New diagnosis of HIV](#)). The person may display signs of depression, appear withdrawn or become completely overwhelmed. Nurses can identify signs of difficulty with adjusting to and managing illness and can intervene and make appropriate referrals for counselling. They can support the person by listening, giving clients time to talk through their problems, providing empathy and care, and emphasising to the client that he or she is not alone. Utilising resources such as written information in the person's chosen language, audio-visual aids, and peer support (through meeting other PLHIV) can help ease the adjustment process. These interventions are all useful to promote engagement and retention in care (17, 18).

Nurses can educate clients, family members, and professional colleagues about specific issues to be aware of during this period; for example, signs of anxiety and depression; barriers to care, signs of disengagement;

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

indications of opportunistic illnesses; difficulty with adherence to medication and treatment toxicities or adverse reactions (see also Therapeutics and monitoring).

Clinical, primary health and community nursing services that are well integrated with peer support agencies (19, 20) and volunteer-based services can be fundamental to supporting the emotional and social adjustment of those diagnosed late and those with advanced disease (21).

Medication Support

People hospitalised following late HIV diagnosis and illness are often discharged with multiple medicines. In addition to antiretroviral therapy (ART) to reduce HIV viral load and improve immune function, they may require medicines to treat OIs and others to reduce the risk of other opportunistic infections developing while their CD4 count is low (below 200 cells/ μ L). This entails a significant pill burden, recognised as a barrier to adherence (22).

Managing multiple medicines can be difficult, especially for clients who have never taken tablets before. Nurses may assess, assist, administer and supervise medication management. High, sustained levels of adherence to ART (over 95% of all prescribed doses taken) maximise its effectiveness, reduce the chance of new or recurrent illness, reduce short- and long-term mortality and prevent the onward transmission of HIV (23). Of equal importance is adherence (doses taken and completion of the prescribed course) to medicines prescribed to treat OIs and those used to prevent new OIs (See [Clinical manifestations of HIV disease](#)).

Nurses can educate clients about their medicines and monitor for side-effects. (See [Adherence support](#) for more details). Nurses can also foster hope and optimism through educating people about U=U ([Undetectable=Untransmissible](#)) – that is, if people living with HIV achieve an undetectable viral load by adhering to their antiretroviral therapy, they cannot transmit the virus sexually.

Formulations of ART in single-tablet regimens can improve adherence (23).

Stigma

HIV-related stigma remains very real for many people, and disclosure of a person's HIV status can have serious consequences for the person with HIV. Respect for people's privacy and confidentiality is essential and should be actively communicated. Strategies such as providing a locked box to store medicines and medical documentation in the home can help maintain privacy and confidence in services.

Access to and retention in HIV specialist clinical care, and safe medicine administration delivered by qualified and competent professionals underpin increased survival for people with HIV (5). People diagnosed late should have access to the assistance of community nurses upon discharge from acute services and referrals should be made early, even where an obvious nursing clinical procedure is not needed. Close collaboration and liaison between hospital- or clinic-based nurses, nurses in primary care and community nursing services are essential and are a robust feature of the HIV sector in Australia and New Zealand (see also [Evolving roles of nurses in HIV care](#)).

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Late presenters and the risk of immune reconstitution inflammatory syndrome

Effective ART stimulates immune reconstitution, reducing the risk of opportunistic illnesses. However, some people commencing ART experience a phenomenon referred to as immune reconstitution inflammatory syndrome (IRIS) that can be life-threatening (24). IRIS affecting the central nervous system (CNS) has a high mortality.

Most people who develop IRIS will do so within 90 days of starting ART, though it can appear as early as 1 week and as late as 1 year after the person starts treatment (8). People are at greater risk with CD4 counts below 200 cells/μL (advanced immunosuppression) and high viral loads.

IRIS can manifest in two distinct ways:

- Paradoxical IRIS: ART initiation (in a patient who has never taken ART) in the presence of a known but treated opportunistic illness (OI) may worsen the OI. For example, a person may have been treated for cryptococcal meningitis, then commence ART and re-develop symptoms such as headache, necessitating re-treatment of the cryptococcal infection (8, 24).
- Unmasking IRIS: a previously unrecognised OI can become clinically evident as immune function improves. For example, a person may be discharged home from hospital feeling well after starting ART, then begin to have night sweats, joint pains and loss of weight and be diagnosed with an OI such as *Mycobacterium avium* complex infection 2 months later (8).

Treatment of IRIS depends on the clinical presentation and the OI involved, but generally entails optimal treatment of the OI, supportive management (such as intravenous fluids and oxygen), continuing ART, and the use of corticosteroids and/or non-steroidal anti-inflammatory medicines (8).

An IRIS event may be serious enough to require hospitalisation. Early referral to community-based or visiting nurses is useful as they can observe and identify symptoms of an IRIS event and expedite prompt medical attention. Nurses working in HIV can be an important link in the identification of IRIS and must have an awareness of IRIS as a possible complication of ART initiation (25) so that appropriate action can be taken. [Antiretroviral guidelines](#) suggest parameters regarding CD4 counts in the presence of an opportunistic infection to help prevent IRIS events. Nurses can educate and support people to remain on treatment if IRIS develops, and in the management of side-effects and symptoms of IRIS (25).

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

References

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Partner notification and contact tracing

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Last Reviewed: June 2024

Summary

Partner Notification is important to:

- alert partners of their risk of contracting HIV and encourage them to seek testing.
- provide an opportunity for prophylaxis, testing and treatment if required
- prevent unwanted long-term sequelae.
- prevent inadvertent onward transmission.

Partner Notification can be undertaken by:

- The index person (patient referral)
- The healthcare provider (provider referral)
- A combination of both (conditional referral)

What is partner notification?

Partner notification refers to the process of informing the sexual partners of a person living with human immunodeficiency virus (HIV) (or other sexually transmissible infections (STIs)) that they are at risk of acquiring HIV or an STI, and they should seek testing and, if infected, treatment. Partners sharing injecting equipment may also be at risk of contracting HIV or viral hepatitis and all partners can be offered the opportunity to take HIV post-exposure prophylaxis (PEP), if contacted within 72 hours of the exposure. Until the partner is assessed as not having the infection, or until they are adequately treated, they should take precautions not to transmit their potential infection to others. The main purpose of partner notification is to notify partners who may be unaware of their risk, assess eligibility for HIV PEP, encourage them to have testing, and if they have the infection, to have ongoing treatment (1, 2).

Why is partner notification important?

Healthcare providers who diagnose a person with HIV should ensure that they discuss the need for partner notification with that person. If a person is diagnosed with HIV, then they have acquired their infection from another person, and possibly transmitted it to subsequent partners. Consideration of transmission risk in people who have HIV infection should include those who may have acquired the infection through condomless sexual contact or sharing injecting equipment.

Partner notification is considered a cornerstone strategy in the public health management of HIV, and is undertaken for the following reasons: (3)

1. By contacting a partner who is asymptomatic but has undiagnosed HIV infection, you can encourage that person to consider HIV PEP if time permits or have an HIV test when they otherwise would not do so.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

2. Notifying partners with undiagnosed HIV infection will help them avoid potentially serious sequelae, because diagnosis and treatment will prevent HIV-related complications which can be serious and costly.
3. There is clear evidence that the earlier a person is diagnosed with HIV and commenced on treatment, the better their prognosis.
4. Notifying and arranging testing and treatment for partners exposed to HIV means that, if they are infected, they will substantially reduce the risk of inadvertently transmitting HIV to subsequent partners.
5. Contacting partners provides the healthcare provider an opportunity to deliver HIV testing, personalised education, and support to that partner; this will include prevention strategies aimed at reducing exposure to themselves (if they test HIV negative) and others (if they test positive) in the future.
6. Partner notification can also provide valuable data that inform policymakers and educators about an outbreak of an infection and will assist them to plan effective preventive and management campaigns and strategies.

What is the meaning of ‘index case’?

The index case is a person newly diagnosed with HIV. The healthcare provider must raise with this person the possibility of notifying their partners of their risk and encouraging the partner/s to test. Partner notification is completely dependent on the index person being prepared to discuss the matter and to identify partners who have been at risk of infection and require notifying. If the index person chooses not to provide any information about the partners at risk, then it is impossible for a healthcare provider to notify those partners. Therefore, in order to have this discussion with an index person, it is important that the healthcare provider create a non-threatening and non-judgmental environment in which the index person is comfortable to fully disclose their sexual history. The discussion should be confidential and private, and the language used must be appropriate and easily understood by the index person.

It is important to determine with the index person what sexual activities took place and, therefore, which of those activities could potentially transmit HIV. By having this discussion, the healthcare provider can also identify sexual activities that do not need to be followed up, such as those where the risk of transmission does not exist. In addition, it is important to understand the HIV testing window period and the past testing history of the patient, as this will determine how far back in time partners should be notified. For example, when considering partners of a person diagnosed with HIV, there is no need to notify partners where the sexual activity was protected (such as with a condom) or partners who were identified where the sexual activity took place more than 3 months prior to the last negative HIV test result of the index person.

It is important to ensure the index person understands that if a healthcare provider is to notify partners on their behalf, then the identity of the index person will remain strictly confidential and will not be divulged to the partner/s being notified.

The index person is more likely to provide information to a healthcare provider or carry out partner notification themselves if they understand why it is important to notify partners and what the potential benefits for partners could be (4). For example, partners who are notified within 72 hours of exposure are eligible to receive HIV PEP which may prevent the partner becoming infected. Partners whose exposure was longer than 72 hours ago will benefit enormously from being test and treated if infected.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Methods of partner notification

1. Patient referral: the index patient informs the partner/s of their risk and encourages them to undertake HIV testing and/or HIV prophylaxis, if appropriate.
2. Provider referral: a healthcare provider informs the partner/s of their risk of HIV whilst maintaining the confidentiality of the index person and encourages the partner/s to undertake HIV testing.
3. Conditional referral: a combination of the previous two strategies where the index person agrees to contact partner/s within a specific time period and if unable to complete this, the healthcare provider takes on the responsibility.

Patient referral: how does this work in the clinical setting?

Patient referral is by far the most used partner notification strategy in Australia. In this circumstance, it is important that healthcare providers discuss with the index person how they are going to carry out partner notification and determine the best time to do it. It is helpful to discuss different scenarios with the index person so that they can adopt a means of informing the partner that is comfortable for them. The index person should have an adequate understanding of transmission so they can answer any questions the partner may have. It is also helpful if the index person is equipped with information and resources; for example, where the partner may go to seek advice about HIV PEP, testing and if needed, treatment.

If the index person agrees to inform their partner/s, then their own HIV status will be known to those notified. Fear of others knowing about their infection is often the main reason why the index person will ask a healthcare provider to do this work on their behalf.

The healthcare provider's aim during discussion with the index person should be to motivate them to inform as many partners who were deemed to be at risk of transmission as possible. The question often arises about how the healthcare provider will know if the index person has completed the task. It is always a good idea to check with the index person that partner notification has been carried out. It may be reasonable to raise the topic with the index person a few weeks after the initial discussion to check with them on how the process is going. If the index person has been unsuccessful in completing it, the healthcare provider can offer encouragement or may take over the task on behalf of the index person.

Provider referral: how does this work in the clinical setting?

The index person may ask a healthcare provider to take on the responsibility of informing their sexual partner/s of the need for them to seek HIV testing.

Experienced healthcare providers with a good understanding of HIV and who use sensitivity and a person-centred approach in their practice should be able to discuss partner notification with their index patients.

Healthcare providers who do not have extensive experience in partner notification can request support, advice, and information from experts who work in this area. There are healthcare providers in each Australian state, as well as other countries, who undertake partner notification work on a full-time basis. Details of these workers can be obtained usually through a local public health unit of a government health department or via an internet search of local sexual health clinical services.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

The healthcare provider does not need to know the full name and contact details of every partner for partner notification to be carried out successfully. Partner notification can be completed with limited information, such as a first name and a mobile phone number of the partner. Sometimes, even just a first name and an address, or work location, or details of where the named person can be found is sufficient for experts to notify a partner.

However, the index person's healthcare provider may not feel comfortable undertaking partner notification on behalf of the index person or may not have enough time available to do the work themselves. In this case, partner notification experts can take on the task after referral from the index person's healthcare provider.

Conditional referral

This strategy is used when the index person agrees to contact their partners in the first instance but that they may also need to pass the task onto the healthcare provider after an agreed period if they have been unsuccessful.

Partner Notification Officers and Contact Tracers: who are they and what qualifications do they have?

Healthcare providers who undertake partner notification on a regular basis are often sexual health professionals who work in this specialty area. In Australia most of these are registered nurses who have the capacity to offer testing in the community when undertaking partner notification, which can be extremely beneficial particularly for those partners who may have difficulty accessing or attending clinical services. Aboriginal health workers can also assist in partner notification in communities where First Nations people reside and are particularly important in rural and remote communities where they have connections to the community, as well as health expertise.

Partner notification specialist nurses often have additional skills and qualifications, such as postgraduate training in mental health, psychology or psychiatric nursing that enable them to make psychological assessments of both index patients and their partners. This helps to ensure the physical safety and psychological well-being of all involved in the partner notification process. These skills also promote the rapid establishment of trust in a stressful situation, especially if a partner notified of an HIV exposure, is asymptomatic and unaware of their risk.

Conclusion

Partner notification is an important part of the public health management of HIV and nurses, and Aboriginal health workers often play a key role. Partner notification should be raised with all people who are newly diagnosed with HIV. The aim is to reduce transmission and to prevent unwanted sequelae in those who are found to have HIV infection but would not have sought testing without having been informed of the need to do so. (For more information on contact tracing see <http://contacttracing.ashm.org.au>)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Key Affected Populations

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1. HIV Nurse Practitioner, Bolton Clarke HIV Program/Homeless Persons Program, Melbourne
2. CNC Torres Sexual Health/ Men's and Women's Health
3. Torres Sexual Health/ Men's and Women's Health
4. Royal District Nursing Service, Melbourne (first edition)
5. Victorian Aboriginal Health Service (first edition)

Last Reviewed: June 2024

Summary

- Introduction to key populations
- First Nations Australians
- Health service considerations
- Nursing considerations
- Useful resources
- Asylum seekers, refugees, migrants, and international students
- Nursing considerations
- Privacy and confidentiality
- Men who have sex with men
- People who inject substances
- Nursing considerations
- Women
- People experiencing homelessness.
- Violence and key affected populations
- Self-care for nurses and midwives caring for key populations.
- Nursing strategies for working with key populations: summary.
- Resources

Introduction

Globally, members of key populations can be especially vulnerable to contracting human immunodeficiency virus (HIV) infection and, if already diagnosed with HIV, may experience poorer outcomes, mostly related to social determinants of health such as socio-economic circumstances, gender, migration status, or ethnicity (1,2). Typically, members of some groups are more likely to be diagnosed late, less likely to engage with health care, access treatment, adhere to treatment and achieve viral suppression, referred to as the HIV treatment cascade or care continuum (3). Lower rates of linkage and retention in HIV care lead to significantly poorer health outcomes and mortality risk, and ultimately greater healthcare costs (4,5).

International and national nursing standards of practice, codes of conduct, position statements and ethics research affirm that nurses have a special responsibility to those most vulnerable (6,7). It is therefore a

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

primary role of nurses, midwives, and community health workers to advocate for, and help members of key populations access HIV and mainstream health services and keep them engaged in health care.

This section draws from the practical experience of nurses in the Australian setting, and local and international literature. Key populations discussed include First Nations people, refugees and asylum seekers, women, people who inject drugs and men who have sex with men. All may belong to more than one group.

It is important to note that key populations differ in different Australian states and territories and this discussion is not exhaustive. Nurses and midwives must focus on those most affected/at risk in their local environment. However, the principles, strategies, guides, and resources discussed here can be helpful across settings.

First Nations people

There are relatively low rates of HIV among Aboriginal and Torres Strait Islander people in Australia. This can be attributed to the prevention work done by Aboriginal and Torres Strait Islander people in their communities, and to the development of dedicated sexual health worker and nursing roles in communities, under an inclusive policy and partnership approach (8).

Between 2012 and 2016, the HIV notification rate among Aboriginal and Torres Strait Islander peoples increased from 4.9 to 6.5 per 100 000, declined to 3.3 per 100 000 in 2019, and then declined further to 2.3 per 100 000 in 2021. By comparison, in 2021, the HIV notification rate was 2.2 per 100 000 among the nonIndigenous population. Trends in HIV notification rates in the Aboriginal and Torres Strait Islander population are based on small numbers and may reflect localised occurrences rather than national patterns (9).

Transmission modes differ, with higher rates of HIV among women, people who inject drugs and heterosexuals within indigenous populations (10,11).

Health Service Considerations

Aboriginal and Torres Strait Islander communities continue to be dramatically affected by systemic racism. Its lasting impact can make it hard for individuals to trust health services. It is the responsibility of health services to ensure that they have adequate systems to improve and ensure cultural safety for both staff and patients who are Aboriginal and/or Torres Strait Islander. Community involvement and local knowledge and awareness of customs are vital when developing prevention and care services. Increasing the number of Aboriginal and Torres Strait Islander staff employed, including nurses and doctors, is an important step in ensuring cultural safety whilst ensuring these staff are treated with respect.

In many communities, HIV prevention is best provided in a general setting and not targeted to minority groups within that community. It is important to be careful of language that may ostracise people further than what they may already feel. An example of good practice is to include HIV with all STIs, providing information for people of all genders and ages (though people may be in separate groups) during generalist health promotion and education.

Another strategy can be to include screening for HIV and other sexually transmitted infections in 'well persons and adult health checks' without asking personal questions that can seem intimidating. Community screening of young people is a successful strategy that has been used across Australia. This can be developed as a modified generalist check avoiding the stigma of specific STI screening (12).

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

An understanding of and access to PrEP may be limited for those not living in major cities (13). Ensure that local education materials are designed collaboratively with the community. Written material may not be the appropriate medium. Private discussion with individuals may be a better strategy in smaller communities.

Nursing Considerations

The National Aboriginal Community Controlled Health Organisation (NACCHO) and The Torres Model of Care specific to the Torres Strait Islands are two models of care that nurses should familiarise themselves with.

For optimal outcomes, care is provided in partnership with the PLHIV. Consideration must always be given to confidentiality, which is more difficult to manage in small communities. Unwanted disclosure may cause distress and deter people from seeking health care at all.

Continuity of staff is very important for all but is even more so if the person is isolated around their diagnosis and does not want to share their health information with family and friends.

Connecting people with peer support needs to be considered carefully. An individual may be concerned that if connected with an Indigenous support, group their confidentiality may be compromised – careful consideration and support are required. There are many positive benefits when this is managed well (see PATSIN).

It is important to clarify with the person with HIV exactly with whom he or she authorises information to be shared, and strongly adhere to this authorisation. Simply using someone's name in the wrong setting can breach their privacy or lead someone to perceive that his or her confidentiality is breached, even if it has not.

It is the individual's choice if the service provider is a mainstream service, a locally managed primary health centre or both. HIV, like other chronic conditions, needs to be managed by the person in a way that they can maintain over a long period. It can take time to work out what is best.

A strength-based approach with open communication and genuine enquiry is required. HIV is still a stigmatised condition. Regardless of whether stigmatisation is real or perceived, it needs to be considered when working with a person for their longer-term HIV management.

Basic enquiry about the person's social setting and home environment, including privacy for storage of medicines, and how medicines will be accessed is a key step to aid adherence. Likewise, nurses or midwives can offer to facilitate access to pathology and medical follow-up.

Other important questions include:

- Who are this person's best supports, and can these people be used to contact them?
- Are there any barriers for the person to access and remain engaged in care?
- Do they have strategies, and supports to overcome barriers that will make it easier to manage HIV?

In regional and remote communities, consideration to accessing some components of health care away from their community, for example, via telehealth may be beneficial. Plans for maintaining care, if they are travelling and alternative backup strategies for accessing treatments and other health services, are very useful.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Asylum seekers and refugees

An asylum seeker is a person who has fled their own country, applied for protection status, and is awaiting a decision on their refugee application (14). Depending on how they arrived in Australia, their date of arrival and their stage in the asylum claim process, asylum seekers may reside in immigration detention onshore or offshore, in community detention, or be living in the community on a temporary visa.

A refugee is a person who 'owing to a well-founded fear of being persecuted for reasons of race, religion, nationality, membership of a particular social group or political opinion is outside the country of his [sic] nationality and is unable or owing to such fear is unwilling to avail himself [sic] of the protection of that country' (15). The 1951 Refugee Convention aims to protect the human rights and treatment of people forced to flee their own countries.

Asylum seekers over the age of 15 years receive a health screen including HIV testing. Increasing numbers of asylum seekers with HIV were reported in Darwin, Northern Territory following the introduction of HIV screening for those arriving by boat without a visa (from 18 diagnoses in 2011-2012 to 30 in 2012-2013) (16).

Access to services including Medicare, medicines and work rights varies according to visa status. Importantly, asylum seekers and refugees are eligible for most health and community services in some states and are categorised as a Priority 1 group for community health services (17). Some states have arrangements in place to improve access to health services. People who are ineligible for Medicare can now access free antiretroviral treatment (18). However, it is important to note that there is a co-payment in some states/territories.

Nurses and midwives may be involved in the care of HIV-positive refugees and asylum seekers in any setting. While it is important to understand the legal situation around seeking asylum and eligibility, the nurse's role in keeping with the International Council of Nurses Code of Ethics for Nurses is to advocate and facilitate, support and promote health for all, especially those most vulnerable (19). In Australia, HIV specialist nurses are accessible to asylum seekers and refugees with HIV and early referral to nursing services is advisable, though often overlooked. Refugee health nurses are also involved in caring for people with HIV.

Refugees and asylum seekers in Australia come from a wide range of countries including, but not limited to, Iraq, Iran, China, Afghanistan, Sri Lanka, Sudan, Burma, and Sierra Leone. In recent years, greater numbers have arrived from Afghanistan, Iran, Iraq, Sri Lanka, Syria, Ukraine and Palestine (for current data, see Refugee Council of Australia).

They may experience specific clinical problems relating to epidemiology in their country of origin. For example, people with HIV from some countries may be prone to reactivation of latent infections not generally screened for in Australian populations such as schistosomiasis and strongyloidiasis (20). Recent reports from Germany indicate that tuberculosis and hepatitis B may be more common in Ukrainian refugees with HIV than in PLHIV in Germany (21).

Children from refugee backgrounds may be at greater risk of blood-borne viruses transmitted iatrogenically (through blood transfusions and contaminated injections and surrogate breastfeeding or milk banks) (22). There is a higher prevalence of HIV in children who have come from central Asia, Southeast Asia, and Sub-Saharan Africa for example (23).

Close collaboration with refugee health nurses, social workers, caseworkers and community health, housing and other services optimises the care of people with HIV who are refugees or asylum seekers. Refugee health clinics are available in most states and territories. See Refugee Health Australia

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Other migrants and international students

More recently, it has been recognised that Asian-born men who have sex with men are over-represented in new HIV diagnoses in Australia (24-26). Gay male Asian students face many challenges and opportunities when they come to Australia – they may find that they experience a far greater level of freedom to explore their sexuality (having come from countries where there may be legal discrimination etc), while at the same time facing challenges with language, accommodation, health care access (26).

It is important to note also, that overseas-born migrants living with HIV are more likely to be diagnosed late and with more advanced disease (27, 28) (see Section 2 Late presentation of new HIV diagnosis).

Privacy and confidentiality

Refugees and asylum seekers may have genuine fears of sharing their health information, especially where HIV is highly stigmatised in their country of origin, and about potential breaches of confidentiality. To gain trust and establish a relationship, it can be useful to provide reassurance about Australian nurses' and midwives' legal and ethical duties and responsibility to maintain privacy and reinforce that nurses only share information with the person's explicit consent (19).

The use of interpreters may be difficult to negotiate because asylum seekers and refugees with HIV may have extreme anxiety and concerns about privacy, especially in small communities. However, accurate health interpretation is important to ensure the person's comprehension of health- and treatment-related information. The use of phone interpreters (rather than face-to-face) and pseudonyms when using interpreter services can help overcome this problem (32). Having a conversation with an interpreter before meeting with them to emphasise their professional obligation to maintain privacy and confidentiality can be useful (32).

Stigma in their country of origin (relating to HIV, homosexuality or sexual transmission) can result in people feeling that any discussion of HIV is taboo and can lead to isolation. Using peer-led discussion and education around sexual health and HIV can be successful in helping break down taboos (32).

Despite many stressors, asylum seekers, refugees and migrants living with HIV demonstrate resilience (33-35). Nurses can support them to build upon their strengths as they navigate their new life and their HIV diagnosis and can assist them in accessing treatment and care.

Nursing considerations

Nurses can play an important role in helping people with HIV who inject substances engage in health care. Interventions include:

- Establishing trust through non-judgmental approaches, non-stigmatising language, and practices
- Supporting and educating them in harm reduction (45, 46) i.e. safe injecting techniques, access to clean injecting equipment and safe disposal of injecting equipment. This can help prevent complications that may arise from injecting as well as transmission of blood-borne viruses (46).
- Supporting and referring to services based on peer-led models (47).
- Providing care in supervised injecting rooms, providing a safe environment and opportunities for education, harm reduction, health promotion, and referral (48,49).
- Ensuring access to prevention, testing and treatment

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

- Facilitating adherence to antiretroviral therapy with the subsequent reduction of community viral load and reduction of the risk of HIV transmission, as well as preventing complications of untreated HIV infection
- Avoiding punitive approaches to substance use, including discriminatory institutional policies or behaviours towards people who use substances (50, 51).

Men who have sex with men

In Australia, sexual contact between men continues to be the most common mode of HIV transmission. In 2021, 68% of the total new HIV infections were among men who have sex with men (MSM) and 90% of all diagnoses were in men (36,37).

It is essential for the MSM population to access care and prevention and to remain engaged in care to reduce the community viral load and reduce the number of new infections and HIV-related comorbidities. (See [Adherence support](#))

The 2012 Global Men's Health and Rights Study found that men who have sex with men encounter barriers to access to treatment and prevention at different levels (38). At an institutional or systemic level, MSM often encounter stigma, criminalisation of homosexuality, and discrimination. In many cases, they do not disclose their sexual behaviour to healthcare providers, which leads them to delay HIV testing and accessing treatment. The follow-up recent Global Men's Health and Rights Study (2023) concluded that barriers to health services utilisation must be addressed at structural and community levels. The authors point out that interventions need to focus on reducing sexual stigma, training, and sensitising healthcare staff, and strengthening community interventions that bring gay and bisexual men together to develop comprehensive health services (39).

Nurses can facilitate access to care at health services that are welcoming to men who have sex with men (MSM-friendly and non-judgmental) and include safe spaces to meet other MSM. See [Becoming more gay-friendly in your practice](#)

People who inject substances

People who inject substances (PWIS), those who have done so in the past, or are perceived to inject, and are living with HIV experience severe stigmatisation and discrimination (28). Despite Australia's proactive stance in developing and implementing harm reduction policies (41), evidence suggests that people who inject drugs still experience reduced access to health care, and discrimination and poor treatment within healthcare services (41). PWIS are at greater risk of late HIV diagnosis than men who have sex with men or heterosexuals (42).

Without a firm commitment to the provision of harm minimisation and peer-based responses, HIV epidemics can develop and spread rapidly (41). The World Health Organization called for the decriminalisation of drug use in 2014 (43) in order to reduce the harms associated with criminalisation. WHO has reaffirmed this position in the WHO 2022 [Consolidated guidelines on HIV, viral hepatitis and STI prevention, diagnosis, treatment and care for key populations](#) (44).

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Nursing considerations

As for members of other key populations, trust is important to engagement in health care for refugees and asylum seekers, migrants, and international students. Members of these groups may mistrust health professionals because, in their country of origin, some health professionals have been involved in the administration of torture or may use instruments that remind people of traumatic experiences (29). Some have been subjected to sexual assault (which may also have been their source of HIV infection) and may be reluctant to undergo sexual health checks or examinations. Women living with HIV from refugee or asylum seeker backgrounds can experience additional vulnerabilities. Awareness of and sensitivity towards these matters is important and warrants a trauma-informed approach to service provision (30).

Furthermore, targeted prevention measures for gay Asian MSM are essential (31).

Women with HIV

Although women make up a small proportion of people with HIV in Australia, they suffer disproportionate levels of blame, ostracism, and stigmatisation, with assumptions being made about their sexual or drug-using behaviour (51, 52). In fact, most women with HIV have contracted HIV from a regular sexual partner (53).

An HIV diagnosis can raise complicated relationship issues for women and can leave them vulnerable to social isolation and violence (54-56). Peer support through state and territory-based groups for HIV-positive women can be helpful. Community nursing and volunteer-based HIV organisations can provide additional support for women with HIV (57).

With effective treatments, HIV-positive women can look forward to a hopeful future. Women who wish to have children can do so, with an extremely low risk of transmitting HIV to their babies or partners if both mother and baby receive appropriate treatment, care and support (see [Pregnancy & Midwifery Considerations in HIV](#))

See [Living well: Women with HIV](#)

People experiencing homelessness

Homelessness can be defined as:

- Primary homelessness – people without conventional accommodation, sleeping rough or in improvised dwellings.
- Secondary homelessness – people frequently moving from one temporary shelter to another.
- Tertiary homelessness – those staying in substandard accommodation (caravan parks, boarding houses) (58).

Internationally and within Australia, there are high rates of homelessness among people with HIV and relatively high rates of HIV among the homeless (59). It has been recognised that many people with HIV live without the support of family and friends that people can generally expect to receive, increasing their risk of disease progression (59). People experiencing homelessness are at risk of disengagement from medical and health care and are therefore less likely to be diagnosed with HIV, linked to specialist care, retained in care, prescribed ART, and achieve viral suppression (60, 61). With poor access to clean water, a bathroom, safe storage, money and transport, it can be difficult for homeless people to take ART and attend appointments (62).

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

A flexible, holistic nursing approach based on a social model of health, and incorporating assertive outreach, can help ensure people experiencing homelessness can attend appointments, maintain a continuous supply of antiretrovirals and maximise their adherence. These are important elements of engaging and retaining them in care and therefore improving their chances of achieving viral suppression and better long-term health outcomes (59).

Violence and key populations

People with HIV, and especially members of key populations, often experience gender-based and gender or sexual identity-based violence. Screening protocols should be in place within all sections of the health care system to assess for the risk of violence (63).

Nursing and midwifery strategies for working with key populations: summary

Nurses and midwives play important roles in providing and coordinating the care of individuals belonging to key populations and assisting them to navigate services. A holistic initial assessment can identify issues that affect an individual's care. A multidisciplinary approach is important to support the most vulnerable to remain engaged in care.

- At an individual level, assessment includes the following:
 - Educational needs regarding HIV treatment or prevention
 - Impact of the diagnosis or treatment on the life of the individual – including pregnancy, relationship issues
 - Sustainability of current accommodation settings and safety
 - Sustainability of income and access to financial assistance
 - Mental health and emotional needs
 - Access to tailored HIV services such as medical and nurse practitioners who are qualified to prescribe antiretroviral therapies and to treat PLHIV (in Australia, known as S100 prescribers)
 - Disclosure of HIV status and its impact.

At an interpersonal level, assessment includes identifying:

- Family and community connections
- Social isolation or social exclusion
- Access to peer support.

Strategies and systems that promote engagement include:

- No cost comprehensive and multidisciplinary services (64).
- Non-discriminatory policies and procedures
- Explicit commitment to confidentiality and support around HIV disclosure
- Regular staff education including reflection on attitudes, and consciousness-raising.
- Support for assertive outreach approaches.
- Professional (nursing and midwifery) involvement in community development interventions and projects
- Continuity of care by skilled and trusted providers (65).

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

- Integrated clinical and community-based care (such as through liaison and care coordination roles, partnerships with community-based AIDS organisations).

Strategies found to be helpful in the international context include:

- Strengths-based case management – clients are encouraged to identify their own abilities and skills to access resources and problem-solve. This provides strong evidence for retention in HIV care (66).
- Peer navigation – including peers as part of a healthcare team (64). This includes the use of First Nations liaison workers (68, 69).
- Reducing structural- and system-level barriers (64).
- Using community-based organisations as a setting for engaging persons with HIV
- Involving ‘significant others’ in retention in HIV care interventions
- ‘Differentiated service delivery’ – fewer clinic visits, ‘one-stop-shop’ clinics and community dispensing of antiretrovirals (70).

International research and guidelines suggest the following practices can improve linkage and retention in care:

- Routine viral load testing 6 months and 12 months after starting on treatment, and every 12 months thereafter, if stable on treatment (71)
- Less frequent clinic visits for those on stable ART – for example, every 3-6 months or even yearly.
- ART can be distributed by trained, supervised lay providers.
- Programs should include community support interventions and intensive outreach (71).
- Adolescent-friendly services (73, 74).

Self-care for nurses and midwives caring for key populations.

It is important to note that nurses, midwives and other health professionals working with members of key populations, especially those who have experienced trauma, need to look after their own mental health and well-being. The risks and mental health effects of vicarious trauma etc are real (75), highlighting the need for formal support for healthcare staff and a trauma-informed approach to care (76). [Clinical Supervision](#) section.

Summary

Members of the nursing and midwifery professions have a special responsibility to provide health care and to advocate for the groups most vulnerable in any health setting (19) and to ensure that key affected populations receive the best care.

In HIV nursing this responsibility is amplified, largely due to the long history of stigma associated with HIV, and with the marginalised groups most affected. Individually targeted and system-wide approaches are necessary to engage and retain people in HIV care (78).

ASHM has developed an online learning module to address systemic barriers to care, stigma, and discrimination (28) to increase access to the health system by people at risk of or living with HIV, hepatitis B, or hepatitis C.

To access this free education module, see [Removing Barriers](#)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Useful resources

- Nursing and midwifery care of Aboriginal and Torres Strait Islander people, see Best and Fredericks (2018) (79).
- The [NAPWHA-auspiced Positive Aboriginal Torres Strait Islander Network \(PAT SIN\)](#) is a national membership-based group for indigenous people with HIV.
- [EORA action plan](#) is an example of a Community-Controlled response to HIV prevention.
- [Cultural safety in practice](#)
- [NATSIHWA cultural safety framework](#)
- Kirby Institute Annual Surveillance Report 2022
- [Asylum seekers and refugees guide](#)
- [Australia refugee health practice guide](#)
- [NSW Health Refugee Health resources](#)
- [Harm Reduction Australia](#)
- [Medically supervised injecting room – Sydney](#)
- [Medically supervised injecting room – Melbourne](#)
- [National LGBTI Health Alliance](#)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Pregnancy and midwifery considerations in HIV

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Acknowledgment to Karen Blyth (first edition)

Last Reviewed: June 2024

Summary

- Introduction and global overview
- Pre-conception
- Pre-natal period
 - Emotional care and support during pregnancy
- Birth
- Mode of feeding
- Care of the infant in the first 18 months of life
 - PEP for the infant.
 - Infant testing
- Multidisciplinary care
- Education and stigma reduction
- Resources

Throughout this document, reference is made to 'women' based on the literature; however, where relevant, the information may apply to any pregnant person. Specific professional advice and support should be sought for all PLHIV who are pregnant regardless of their gender assigned at birth.

Introduction and global overview

Pregnancy and the post-natal period have been long recognised as potentially vulnerable times in a woman's life. When a woman is living with HIV (LWHIV), the potential for vulnerability is even greater.

Globally, approximately 1.3 million young women and girls LWHIV become pregnant each year. In the absence of intervention, the rate of transmission of HIV from a mother living with HIV to her child during pregnancy, labour, birthing, and breast or chest feeding ranges from 15% to 45% **(1)**.

In Australia, universal HIV testing is recommended for all pregnant women in the antenatal period **(2)**. This has been the case for approximately one decade and, as a result, perinatal HIV transmission has declined considerably. Throughout 2017 – 2021 inclusive, there have been 4 perinatal transmissions in Australia. This compares to 23 transmissions in the period from 2007-2011. **(3)**.

In terms of prevention of transmission strategies for WLWHIV, the most significant factors are knowing a woman's HIV status and the provision of ART. Effective ART suppresses the viral load (VL), significantly reducing the risk of perinatal transmission. **(4)** Duration of VL suppression is also a factor in reducing transmission, therefore early HIV detection and provision of ARVs is important **(5)**.

Nursing support, education, and care, in terms of access to, adherence to and provision of medication are important components of comprehensive care.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Preconception

For any person or couple planning to conceive, there should be opportunities to consider broad aspects of healthcare. This includes the importance of folate, healthy weight range, vaccinations, and lifestyle considerations, prior to conception (2). For PLHIV planning pregnancy, additional factors should be considered – appropriate anti-retroviral therapy (ART) as well as counselling and education around transmission risk and prevention strategies (6).

Pre-natal Period

The benefits of a woman knowing her HIV status during pregnancy include the opportunity for her to receive appropriate treatment and care for herself and to prevent transmission of the virus to her unborn baby. A further benefit is prevention of HIV transmission to partners or potential future children.

An HIV diagnosis in pregnancy requires a comprehensive multi-disciplinary approach. The development of a therapeutic relationship at this potentially vulnerable time in a woman's life is crucial and nurses and midwives must be skilled and qualified to enable this. *A therapeutic interpersonal relationship can be defined as one which is perceived by patients to encompass caring, and supportive non-judgmental behaviour, embedded in a safe environment during an often-stressful period* (7).

Fortunately, in Australia, with appropriate monitoring, treatment and support the risk of mother-to-child HIV transmission is currently approximately 1.9% (3).

It is best practice to introduce a woman who is pregnant and LWHIV with a midwife and paediatric nurse with appropriate skills and knowledge, while receiving ongoing care from their primary HIV provider and nurse specialist. Throughout the pregnancy, the midwife and paediatric nurse specialist can liaise, and provide expertise on the mode of birth, modes of feeding, and the expected HIV testing protocol for the infant.

Emotional care and support during pregnancy

During pregnancy and in the perinatal period, confusion, guilt, anxiety, fear of transmission to the unborn child may arise and require sensitive handling, negotiation, offers of referrals, support, and advocacy. The nurse may link the woman, and her partner/family, to appropriate counselling, peer support, and culturally specific care and provide education to help overcome practical or psychological problems around the time of diagnosis. The nurse can also act as the key worker in advocating for the woman and family when dealing with external agencies or health facilities.

In principle, the nurse should support the mother to:

- make informed choices about pregnancy care.
- make informed choices around the mode of birth and mode of feeding.
- ensure health information is dealt with sensitively and compassionately whilst maintaining confidentiality. This may include withholding information from other family members or contacts.
- support ongoing engagement with primary HIV care providers to help achieve HIV viral suppression (that her HIV VL is undetectable).
- receive the best information on care for herself and her baby through pregnancy and beyond.
- ensure optimal adherence to her prescribed ART.
- ensure attendance at appointments, avoid loss to follow-up after the birth.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Following these principles, the nurse may identify that the woman needs help to navigate the health system, as she may have competing priorities.

Birth

Current international guidelines recognise that if a pregnant woman LWHIV has an undetectable HIV VL, vaginal delivery does not increase the risk of HIV transmission to the infant (6).

Maintaining engagement in care is an important role of nursing and midwifery staff to ensure monitoring of women's VL throughout pregnancy, which will ultimately inform the mode of delivery and duration of Post Exposure Prophylaxis (PEP) for the infant (6). Risk assessment for and PEP for infants is outlined in the BHIVA guidelines on the management of HIV in pregnancy and the postpartum period 2025 (6).

For those women who are overseas-born or from Culturally and Linguistically Diverse backgrounds (CALD), navigating the Australian healthcare system may require enhanced support and education (11).

Mode of feeding

Providing opportunities for women to gather information and discuss infant feeding options during pregnancy is ideal, allowing women time to make informed decisions.

Provision of information on the topic of the mode of feeding in a supportive forum is a complex process. Nurses and midwives need to have expert knowledge of current evidence and guidelines, skills in collaborative communication and a holistic approach to addressing the WLHIV's needs (6,9,11).

In middle- and high-income settings, current guidelines recommend formula feeding to prevent HIV transmission through breast milk. However, international guidelines and the Australian ASHM guidance document (8) have more recently explored ways in which women LWHIV who do choose to breastfeed may be best supported, whilst minimising the risk of HIV transmission to the infant.

In the event of a woman choosing to breastfeed, engagement in care is vital. More frequent virological testing for both her and her infant is required, with a greater emphasis on access and adherence to ART. This is true for the duration of breast/chest feeding and some months after cessation of breastfeeding.

Infant feeding recommendations in high-income countries such as Australia differ entirely from those in low-resource countries. For instance, in resource-poor settings where breastfeeding remains the only option, infant PrEP may be used (6). Differing recommendations can confuse overseas-born women, particularly if they have experienced childbirth and infant feeding before their arrival in Australia. Nurses and midwives can support women in navigating the different approaches to care and explaining the reasons for differences, thus enhancing the therapeutic relationship and engagement in care.

Specialist nurses have a pivotal role in supporting weaning from the breast and the introduction of solid food in the context of minimising the risk of transmission. Furthermore, midwives and nurses can counsel women on appropriate strategies in the event of mastitis or gastrointestinal upset in the women or infant. Approaches to management of these situations are different to those for people who are not LWHIV (see 6 for more details). It is important to note that should a woman LWHIV not share her HIV diagnosis with a health professional due to lack of trust or fear of stigma, appropriate advice and care may not be provided, and the baby may be at increased risk of HIV transmission through breastfeeding.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

WLWHIV who choose to breastfeed will receive important counselling including the following information **(11)**:

- The importance of maintaining viral suppression through adherence to ART for the duration of breastfeeding
- The potential for maternal ART to be excreted in breastmilk and the potential for toxicity to the infant.
- The potential for increased risk of transmission in the event of:
 - maternal mastitis or cracked or bleeding nipples and how this should be managed
 - gastrointestinal disturbance in the infant, which can lead to gut inflammation, allowing HIV entry to the bloodstream.
 - GI disturbance in the mother, which may reduce ART absorption and efficacy, thereby increasing risk.
- Mixed feeding i.e. breastmilk and formula or breastmilk and solid food and how this may be managed to minimise risk **(6)**.
- The need for ongoing blood tests for both infant and mother, which are more frequent than a formula-fed infant and the occasional disparity between maternal serum HIV VL and maternal breastmilk VL.
- Who to contact and how to contact them should any of these situations arise, preferably provided to the woman in writing and in her chosen language.

If the woman chooses to formula-feed her infant, nurses and midwives teach safe preparation of formula, sanitising of teats and bottles, storage of formula and choice of formula. Many hospitals follow 'breastfeeding friendly' policies **(10)** which can mean that access to this information is not always readily available.

At the time of writing, free infant formula is not available to WLWHIV so the woman may require support and funding to access it.

Care of the infant in the first 18 months of life

Before hospital discharge following birth, nursing and midwifery staff can provide guidance for the parents/mother about:

- administration of PEP to the infant
- safe and private storage of ART
- ways to maintain confidentiality from visiting family members/friends.

Care coordination can ensure that the woman's paediatric HIV care team know of the birth, mode of feeding, PEP regimen, and details of blood collection. The Paediatric HIV nurse can follow up in:

- supporting the woman and infant.
- ensuring engagement in care
- facilitating future appointments
- identifying possible barriers to care such as access to Medicare and so on.

[Access to HIV treatment for people without Medicare | ASHM Health](#)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

PEP for the infant

PEP is given to the infant within 4 hours of birth and may be given orally, although it can also be given via a nasogastric tube or intravenously. In most cases, if the baby is categorised as 'very low risk' or 'low risk' of HIV transmission, PEP will be administered for 2 weeks, twice daily in a two-drug combination. If the risk of transmission is considered high, PEP may be given for 4-6 weeks and is usually in the form of triple combination therapy (6).

BHIVA guidelines on the management of HIV in pregnancy and the postpartum period 2025 (6).

Infant testing

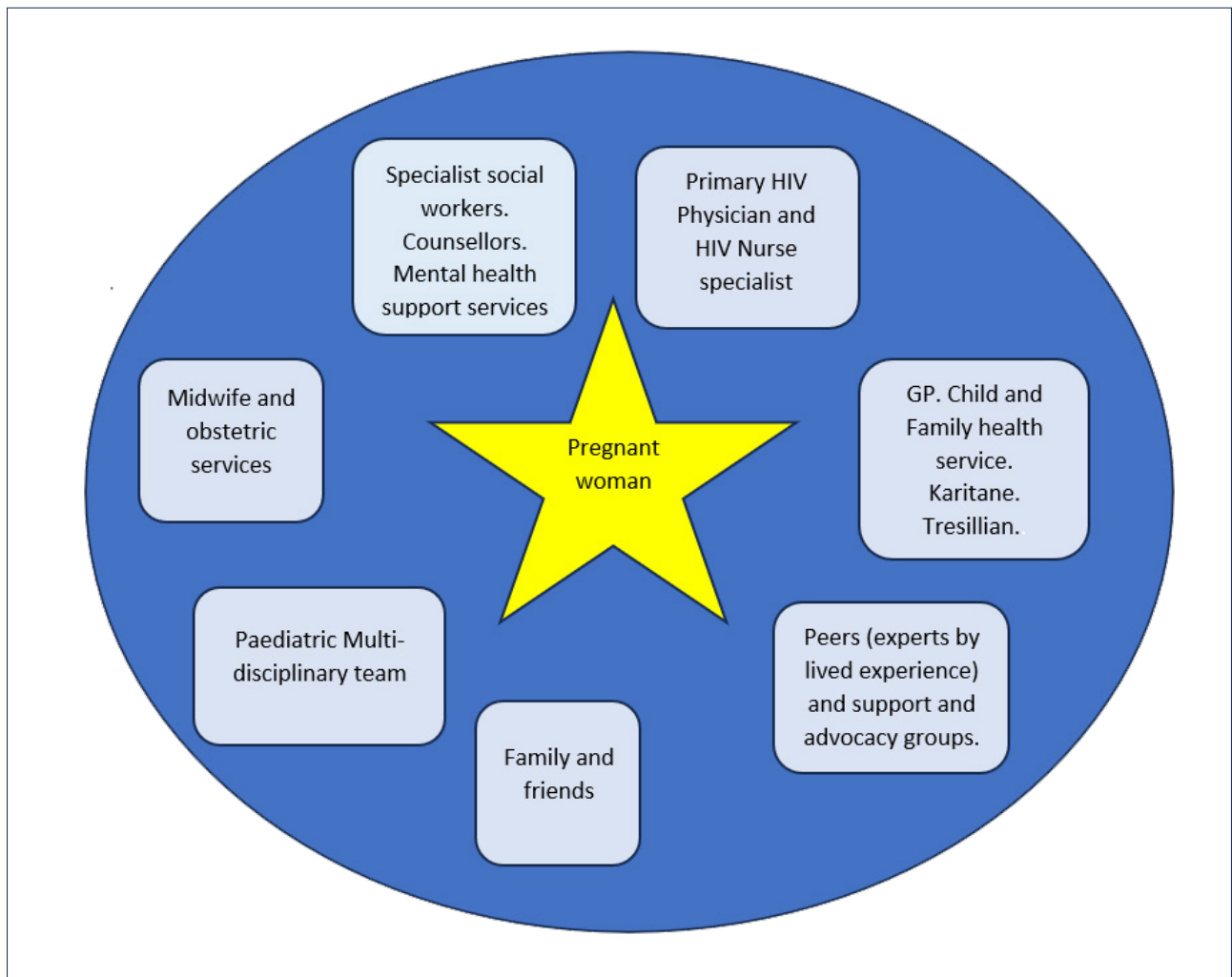
Testing for the infant is recommended at various intervals until 18 months of age (11), so the woman should feel safe and supported in a non-judgemental care setting. Maternal antibodies are usually present for at least the first 12 months of the infant's life, hence the need to delay an HIV antibody test until 18 months old, when the test is more reliable because the maternal antibodies will have cleared from the infants' bloodstream. Throughout this 18-month period, nurses can provide information about and referrals to other services such as Child and Family health centres and peer support programmes for WLWHIV, especially those with young babies. Ad hoc infant vaccinations may also be provided by Authorised Nurse Immunisers (ANI).

Multidisciplinary care

Effective care coordination for a WLWHIV is paramount. A coordinated, cohesive model enhances engagement in care and avoids difficulties in navigating a complex health system and the potential for loss of follow-up, suboptimal adherence to ART and risking transmission of the virus to the unborn child. (11). For these reasons, a multidisciplinary model is the ideal.

The multidisciplinary model (Figure 1) illustrates the range of specialist programs that may be involved in a woman's and infant's care, during birth and beyond. The woman is at the centre of the model; she may need all or only some of the available resources, depending on her age, ethnicity, religion, culture, overall health and medical history, migration experience or previous engagement with health services. Each woman and her situation are unique, and care is tailored to meet each woman's needs in a holistic and culturally sensitive manner.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		



Education and stigma reduction

The strength of a nurse-led model of care is paramount in the education arena. A nurse with experience in and knowledge of caring for women LHV in pregnancy and the perinatal period can provide support, counselling and education to the woman and her significant others, and to the wider health and allied health community caring for her. This must include the importance of confidentiality of health information.

Education to health professionals may be through formal education sessions, provision of written material and current expert resources, mentoring of less experienced staff, developing Nursing Care Plans, and serving as a resource for other nurses and midwives as required.

Stigma around PLHV within healthcare settings remains a serious barrier to engagement in care and to trusting relationships with health professionals. [\(13\)](#)

Education is important for breaking down preconceived, unhelpful, or ill-informed ideas that individuals may have about PLHV.

There are many valuable resources for use in education about HIV in pregnancy. Some useful and accessible resources are listed below.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Useful resources

[Recommendations for the Use of Antiretroviral Drugs During Pregnancy and Interventions to Reduce Perinatal HIV Transmission in the United States](#)

[The 2023 PENTA Guidelines for the use of antiretroviral therapy in paediatric HIV infection.](#)

[ASHM The Optimal Scenario & Context of Care ASHM Guidance for Healthcare Providers regarding Infant Feeding Options for People Living with HIV with highlights from Breastfeeding and Women Living with HIV in Australia August 2021](#)

[Pregnancy Care Guidelines | Australian Government Department of Health and Aged Care](#)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Considerations In the Nursing care of Children and Young People living with HIV

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Summary

- Children and young people (YP) LWHIV in Australia
- Children and HIV: is it different to adults?
- Treatment issues in children and YP living with HIV
- Keeping well: growing children into healthy adults
- Psychosocial context and considerations
- Sharing of HIV status and sharing of health information

Inclusivity

Within this document we strive to include everyone, regardless of cultural background, ethnicity, faith, gender, gender expression, gender identity, race, or sexual orientation.

Introduction

Worldwide, in 2023 it was estimated that approximately 1.5 million children (aged < 15 years) were living with HIV (1). Transmission is primarily perinatal.

In Australia, as of early 2024, there are approximately 60 children (aged under 18 years) LWHIV. As no national data is recorded, these numbers are estimates. Most of these infections are due to perinatal transmission, which changes the lived experience entirely. Fortunately, in Australia, due to universal antenatal screening for pregnant women, perinatal transmission rates have steadily declined over the last three decades to less than 2% in 2021 (2). Therefore, many children and YP LWHIV in Australia currently, are overseas born, acquiring HIV before they arrived in Australia. This means they face further challenges in navigating new and unfamiliar health and education systems in their new country.

What's different between children and adults LWHIV?

Children with HIV have higher mortality and morbidity rates in their first 2 years of life than adults if untreated. Approximately 80% of untreated infants, well at 6 weeks of age, will progress to AIDS-defining illnesses within 6 – 12 months (3).

The mechanism behind these concerning data remains unclear, however, it may be due to the 'normal' physiological immaturity of the infant's immune system (4). Tobin and Aldrovandi (2013) note that:

Regardless of the level of CD4+ T cells or plasma viremia, younger children are at greater risk of death or progression to AIDS compared to their older counterparts [...]. A 1-year-old child with 10% CD4+ T cells has a 40% risk of progression to AIDS and 20% risk of death within 12 months (4, p. 149).

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

These authors explain further that factors contributing to the high level of viraemia in young children might include 'an increased susceptibility of infant cells to HIV-1 infection and shared HLA alleles between mother and child, so that the virus is preselected for fitness in the infant' (4, p. 149).

Acute HIV infection in adults is characterised by high viraemia, which rapidly declines. In contrast, perinatally infected infants do not show the same fall in viraemia. HIV viral loads only start to decline beyond infancy, to reach an 'adult' set point by approximately 5 years of age (4).

Keeping well: growing children into healthy adults

Growth in children depends on multiple factors, some of them environmental such as nutrition, maternal health, and the psychosocial context in which they live. Growth also means a growing and developing brain. Factors such as lack of access to ARVs from an early age may lead to neurodevelopment impairment.

Nurses can ensure vaccination schedules are up to date and offer annual influenza vaccines where indicated.

School: Families are not required to disclose their health information to their child's school (5) however the nurse may counsel the family around the usefulness, in some situations, for specific personnel to be aware of a child's HIV diagnosis – for example during camp times/ or school trips, or where children may require supervision of their medications.

Nurses can educate school staff on Standard Precautions, which should be employed following blood or bodily fluid exposure or spill. This can be done without sharing information or identifying the child/YP LWHIV.

Treatment challenges in children

Due to the small population of children and YP LWHIV in Australia, paediatric formulations of antiretroviral medicines are not always readily available. Nurses may need to advocate for compassionate access to formulations not generally available in Australia.

Treatment adherence may be hampered by issues such as cumbersome liquid preparations which may require refrigeration. The child may need to consume large volumes of unpalatable medicines.

Nurses can assist both the child and the parent or carer in overcoming such barriers by providing acceptable and age-appropriate options.

Pill swallowing

Before initiation of treatment, nurses must assess and consider the child's ability to swallow pills. This is a fundamental skill required before treatment in pill form can start, and before the transition to tablets from liquid. Teaching pill swallowing may require several sessions and the use of placebo capsules or jelly sweets is often helpful. (6)

ARV dosages may need frequent adjustment due to age and weight recommendations; nurses can monitor growth and weight to help ensure correct dosages, by working within the multidisciplinary team. Further information on dosing can be found at PENTA (7).

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Psychosocial context and considerations

When children and YP are LWHIV, it is usually considered a ‘family condition’. The parents, one or both of whom are also usually LWHIV, often experience the psychosocial burden of having transmitted the virus to their child. This commonly influences the parents’ ability and willingness to allow the young person to learn of their own HIV status. This may be further complicated if siblings living in the same household, who may not be LWHIV, are not aware. Secrecy is a common theme and the development of a therapeutic relationship with both the child/YP, and the parents/carer is essential for the nurse to guide the family through the process of sharing health information. The aim is for the YPLWHIV to learn of their HIV status without affecting their trust in their parents (8, 9, 10, 11).

Parents commonly fear that the child/YP will unwittingly share their health information (and therefore the parents’ health information) and their concerns about disclosure should not be underestimated. The nurse needs to support the parents while simultaneously supporting the YPLWHIV.

As children move into adolescence, they experience changes just as their peers do, however, they are simultaneously learning about their HIV status and its impact on their lives. Activities such as school camps and sleepovers, and issues such as stigma, internalised stigma, feelings of abnormality, anxiety around romantic relationships, initiation of sexual activity and access to contraception are some complex challenges the nurse can support the young person through. (12)

As the demographic and epidemiological landscape of children and YPLWHIV has changed across Australia, the nurse must also care for children who were orphaned, who were adopted from overseas or are from asylum or refugee backgrounds. Being an orphan commonly leads to grief and a sense of loss which may also impact treatment adherence, particularly in the adolescent period (see 12, 13).

Transition to adult care

Transition to adult care may symbolise loss (as it does in many chronic conditions) however due to HIV-related stigma, this transition and associated sense of loss may be experienced more acutely.

Furthermore, since many YP moving to adult services are not yet sexually active, the nurse may need to facilitate referral to an appropriate service. For example, services such as Infectious diseases or Immunology Outpatient clinics in hospitals, or a young people’s sexual health clinic may be more appropriate than a sexual health clinic that caters predominantly for MSM.

Sharing of HIV status and health information

Informing a child or YP LWHIV of their HIV status can be a difficult task, best done as a gradual, family-centred process (8). Once a child/YP knows they are LWHIV, parents and health staff can support and educate them appropriately (9). Disclosure is best done in a planned, systematic way, rather than unplanned or forced (9) and nurses can support and educate the caregivers on how to do so.

The disclosure process ideally starts from a young age: 8 years or before, in an age- and developmentally appropriate manner. Nurses should address the family’s issues and concerns concurrently. Caregivers/ parental concerns may need to be explored and resolved before progressing with disclosure of the child’s HIV status. Referral to a psychologist may be useful and the nurse may collaborate with the parents’ adult HIV provider (with parental permission) to ensure that the parents are as well supported as the child. Before full

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

'naming' of the virus, the nurse can support caregivers in assessing the benefits and barriers to progressing. The rights of the child/YP should also be considered while balanced with concerns caregivers may have such as the impact of the child/YP sharing information independently (15).

The following case studies illustrate some of the complex issues that can arise in the care of children LWHIV, and the role of an HIV specialist nurse within a multidisciplinary setting. They also illustrate the importance of family-centred care and the multiple family members that the nurse may need to interact with to optimise the child's care.

All identifying details have been changed but the case studies depict actual events.

Case study 1

B. is a female age 9 years, diagnosed with HIV as a neonate. She was born in Australia to a woman LWHIV, whose HIV status was known before conception but who did not adhere to ART throughout pregnancy. The father's HIV status was unknown. The mother reported a history of family violence. Furthermore, she experienced prolonged rupture of membranes during labour.

The infant commenced ARV at age 1. Starting ART had been delayed due to complex psychosocial issues impacting the family's capacity to adhere to the regimen. After initiating ART, the family administered it to B. sporadically. As a result, she developed resistance to some agents, and therefore ARVs were ceased.

B. developed severe thrombocytopenia and intravenous Immunoglobulin (Ig) was administered. There were challenges accessing Ig from Life Blood as B. did not meet the usual criteria for this treatment. The medical team continued to promote adherence to the new ART regimen, but unsuccessfully.

As B. grew, she demonstrated developmental and speech delays. She was eventually diagnosed with Attention Deficit Hyperactive Disorder (ADHD), which impacted negatively on her school and learning experiences. She had behaviour problems at school and was at risk of suspension. She was referred to a speech therapist.

The HIV nurse specialist engaged with the Child Protection Unit, and other support organisations became involved. With the support of the Child Protection Unit, a hospital admission was arranged to observe her taking her treatment directly. The nurse specialist taught B. pill swallowing.

B. experienced recurrent skin and ear infections. She had regularly been given food as a way of managing her challenging behaviour, resulting in obesity and insulin resistance.

B's mother was in poor physical and mental health. The parents separated and the mother became B's principal carer.

ART was successfully re-initiated when B. was age 7. She achieved viral suppression.

Disclosure of her HIV status will be carefully addressed as B. moves towards puberty.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Case study 2

S. is a 17-year-old female from Sierra Leone. Her mother died suddenly of an unknown illness. Her father died in a motor vehicle accident one month later, before her move to Australia at age 7.

S's older sibling is her official guardian and carer. S. became unwell after arriving in Australia and was diagnosed with HIV. No other family members are LWHIV.

ART was commenced soon after diagnosis once her pill-swallowing ability had been assessed by the HIV nurse specialist.

S. has been adherent to ART, is healthy and growing and developing in line with her peers. Throughout her care, the nurse specialist linked her with services such as a Child Life Therapist (formally known as a Play therapist) and clown doctors, with the aim of enhancing her hospital experiences.

Throughout her care, the nurse specialist spoke with her at age-appropriate stages about her health, however at age 14 years, she was still not aware of her HIV status. This was due to her sibling/carer's reluctance to allow progress in the disclosure process.

The nurse specialist engaged in intensive education and counselling of the sibling guardian over a long period. Despite this, the sibling remained very concerned about disclosure and felt the best course of action was to protect her by avoiding it. During this prolonged period, the nurse specialist continued to work with the young person, discussing general aspects of health.

Although the young person had been told rudimentary information about her health, she was not aware of any details until she searched the name of her medicines on the web and discovered they were for the treatment of HIV. The nurse specialist worked hard with the young person and family to restore trust and build their relationships. This work will continue.

Useful resources

- [Antiretroviral / HIV Drug Dosing for Children and Adolescents 2022-2023 Imperial College Healthcare NHS Trust](#)
- [HEEADSSS 3.0: The psychosocial interview for adolescents updated for a new century fueled by media](#)
- [Supporting young people in moving to adult services: Who we are: Trapeze](#)
- [Sydney Children's Hospitals Network](#)
- [CHIVA](#)
- [The Royal Children's Hospital](#)
- [Elizabeth Glaser Pediatric AIDS Foundation](#)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Client education

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Last Reviewed: June 2024

Nurses play a pivotal role in diagnosing and managing human immunodeficiency virus (HIV). In particular, nurses have a fundamental role in providing clients with evidence-based education, so that they can make informed choices, evaluate decisions, and choose the best options to maintain and improve their health. The scope of this work may vary both in the role of the nurse according to their clinical practice and the needs of the client. How to prevent future infections (including sexually transmitted infections [STIs] and blood-borne viruses [BBVs]), empowering patients to take an active role in their health care and preventing onward transmission of HIV, are some examples. People differ in their health needs and being aware of their level of health literacy is critical to tailor the information and ensure their understanding, giving them the ability to make informed health decisions.

Educational strategies

Educational strategies in HIV and sexual health take into account individual values, knowledge and situations, and ensuring regardless the approach is 'person-centred'. Nursing input into the sexual health of individual clients, couples, partners and cultural groups, needs to take into consideration diverse issues: sexuality, gender identity, and gender equality, sex, fertility and reproductive health rights, relationships and STIs including HIV. (1) Should a nurse not feel comfortable discussing these issues, it is important that they refer the client to a specialist HIV or sexual health service.

To gain trust, a non-judgmental approach and reassurance of the clients confidentiality when discussing sexual health and sexual practices is imperative. Providing basic information such as that available on quality internet sites; utilising the full scope of a nurses practice and their experience and skills as a patient advocate (2) to gain an understanding of the individual's values. It is important to dispel misperceptions or internalised (or societal) phobia surrounding sexual health and STIs.(3) (4)

Strategies and tools that can be used to engage and assess clients' needs and values include HEADSS assessment (Home and Environment, Education and Employment, Activities, Drugs, Sexuality, Suicide, Depression) (5) or the PLISSIT model (Permission, Limited Information, Specific Suggestions, Intensive Therapy)(6) or a specific sexual health history and risk assessment: See, for example, <https://www.health.qld.gov.au/clinical-practice/guidelines-procedures/sex-health/guidelines>

Client education for HIV prevention

Sex and sexuality involve complex human dynamics. The aim of patient education is to develop positive and protective factors to assist the client in achieving optimal sexual health.(7)

Sex is foremost about pleasure; whether it is masturbating alone, or with a companion; or physical, psychosocial or emotional intimacy in partnerships and relationships. Example discussion points for nurses when addressing HIV/STI prevention with clients include:

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

- The earlier an individual is diagnosed with an STI, the earlier it can be treated and transmission prevented. Recognising symptoms of STIs (dysuria, urethral discharge; genital pain) early may prompt an individual to access clinical services(8)
- Factors that contribute to STI transmission are dependent on the type of sexual activity people engage in.(9) The use of condoms is protective against most STIs, especially HIV. However, other STIs such as human papillomavirus (HPV) and herpes simplex virus (HSV) only require close genital skin-to-skin contact for transmission to occur(10)
- While condoms are considered the gold standard for prevention, there are alternative methods, referred to as biomedical prevention methods. These methods can involve the client taking antiretroviral drugs prophylactically following a high-risk exposure (post-exposure prophylaxis [PEP]) or before and ongoing, in the case of repeated high-risk exposures (pre-exposure prophylaxis [PrEP])(11) See [HIV pre-exposure prophylaxis](#) or [HIV post-exposure prophylaxis](#) for more information.
- Concurrency in partnerships (having more than one partner at any one time) may occur throughout life. Factors that may contribute to concurrency may vary. However, ensuring that clients know the HIV status of their partner/s and the importance of open communication around what HIV/STI prevention strategies will be used with each type of partner is critical, i.e. regular partner/s versus casual partner/s.(12)

Client education at the point of diagnosis

To establish the education needs of a client at the point of diagnosis, acknowledge that each person is different in how they respond to their diagnosis and what questions they may have. People's level of health literacy is variable and responses to open-ended questions may help target information to levels that will be understood and assist in prioritising the individual's concerns. It is important to remember at the point of diagnosis, people are often overwhelmed. The nurse can provide written material, direct clients to suitable internet sites (if appropriate), acknowledge that the diagnosis may be overwhelming and allow clients to ask and repeat any questions they may have. (See Section 1 New diagnosis of HIV for further information.)

After clarifying the client's main concerns, other critical points to discuss include:

- HIV is a treatable and manageable chronic disease
- Treatment is safe, highly effective and most beneficial if started as soon as possible after diagnosis
- There are many supports available (including psychosocial, community and peer supports) – see [Health Equity Matters](#) locate services in the relevant state or territory
- Contact tracing and partner notification are important, and the nurse can explain ways this can be done (see also [Partner notification and contact tracing](#))
- There are effective ways to prevent onward transmission. Nurses can educate clients that if they achieve an undetectable viral load by adhering to their antiretroviral therapy, they will not transmit the virus sexually - [Undetectable = Untransmissible](#).
- How to disclose their status in the future (Note: the legal framework around HIV disclosure varies in each state and territory. More information regarding the disclosure of HIV status can be found [here](#)).

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Ongoing client education

Following diagnosis, the role of ongoing education and maintaining a rapport with a client can be critical in them remaining linked into clinical care. Just as during other times throughout the continuum of care, people's ongoing education needs will vary. Ensuring a holistic approach is taken is key in ensuring that all aspects of client care are considered and addressed. The following is not an exhaustive list but provides guidance on topic areas that should be addressed with people living with HIV:

- Assessing their understanding of adherence once they commence treatment and in particular their comprehension of Undetectable = Untransmissible. (See also Section 11 Adherence support)
- Ways of preventing other STIs and BBVs in terms of preventing onward transmission
- The importance and role of maintaining a healthy lifestyle (diet, exercise, limiting the use of alcohol and other drugs)
- What being HIV positive will mean in terms of how often they will need to attend medical appointments (such as monitoring, annual check-ups, vaccinations, STI checks, prescriptions.)
- Fertility choices and options
- Referrals available for support services and counselling (may include those relating to drug use, potential self-harm, family violence)
- Encourage questions or concerns when you meet at follow-up appointments.

Other useful resources

Preparing a client for treatment

<https://www.health.nsw.gov.au/endinghiv/Documents/preparing-for-treatment.pdf>

Supporting adherence

<https://www.health.nsw.gov.au/endinghiv/Documents/supporting-adherence.pdf>

Brief Interventions for the Prevention of HIV and Sexually Transmitted Infections (STIs)

<https://www.health.nsw.gov.au/endinghiv/Documents/intervention-for-prevention.pdf>

Motivational Interviewing Techniques

<http://www.racgp.org.au/afp/2012/september/motivational-interviewing-techniques/>

Sexuality and coming out

Rainbow Network

<https://www.rainbownetwork.com.au/resources>

QLife – Support and Referrals

<https://qlife.org.au>

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Building up relationships

Love is Respect

<https://www.loveisrespect.org/everyone-deserves-a-healthy-relationship/>

Genital anatomy and variances

Normal genital anatomical variances; penile sizes; vulval appearances; body image

<http://www.stiatlas.org/SearchAtlas.aspx>

Labia Library

[www://labialibrary.org.au/](http://www.labialibrary.org.au/)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

References

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Nursing considerations of major clinical issues

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Last Reviewed: June 2024

This section explores key issues for nurses in relation to ageing and long-term survival with HIV.

- Ageing with HIV
- Accelerated or accentuated ageing
- Long term survival
- Multiple losses and grief
- Mental health and resilience
- Multimorbidities
- Disability, respite, and long-term care
- Advance care planning
- Ageing with HIV (See also [HIV and Ageing](#))

As the life expectancy of people with human immunodeficiency virus (HIV) increases due to successful treatment, more people with HIV are ageing. The average age of people with HIV in Australia is over 45 and the number of people over 60 has been increasing at 12% per year since 1995 (1). The proportion of people over 55 years with HIV was 25.7% in 2010, with a predicted increase to over 44% by 2020 (2, 3).

Older people living with HIV may be long-term survivors of HIV. However, there are also significant numbers of older people newly diagnosed with HIV. Between 2018 and 2021, 22% of new HIV diagnoses in Australia occurred in people 50 years and over (3). People diagnosed with HIV when they are over 50 years of age tend to have more advanced disease and experience greater HIV-related illness (4). Older people who are newly diagnosed with advanced HIV disease can have very different needs to those who are long-term survivors (see [Nursing implications of late diagnosis – severe disease, treatment, and prevention of opportunistic illnesses](#)).

Accelerated or accentuated ageing

An important concern in HIV care is the concept of premature, accelerated, or accentuated ageing. People with HIV may experience some problems associated with ageing at earlier ages than people who do not have HIV, such as frailty, neurocognitive impairment, and osteoporosis. These concerns have been attributed to the effects of the virus, risk factors (such as smoking, drug use and viral hepatitis) which can confound study interpretations (5) but also to the effects of some antiretroviral medications (6, 7).

The implications of accelerated or accentuated ageing can be that PLHIV may need additional supports such as home nursing, personal care, respite, and rehabilitation much sooner than is generally the case and when funding arrangements allow (for example, before becoming eligible for aged care services – 65 years in Australia, and 50 years for Aboriginal and Torres Strait Islander peoples). This is discussed further at the end of this section.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Long-term survivors

People who have survived many years with HIV, some from the mid-1980s, are considered long-term survivors. Key predictors of long-term survival include early diagnosis, engagement and retention in HIV care, and timely initiation of ART (8).

Specific needs of long-term survivors of HIV include psychological and emotional concerns relating to grief and loss, particularly for gay men. Older gay men with HIV may struggle with issues such as the interruption of their life plans, maintaining good health and managing HIV treatments. Ageism, homophobia, and stigma can also affect this group (9). Although the HIV population in Australia is diverse, it affects gay men disproportionately, especially those who have lived with the virus long term.

There is global and Australian literature documenting that lesbian, gay, transgender, and intersex people (LGBTI) experience systemic discrimination within healthcare systems (10). Now that many require aged-care services, they fear discrimination and a lack of knowledge about their needs at a vulnerable time (11).

Along with clinical and biological factors, psychosocial and spiritual factors can contribute to long-term survival (12). Having a hopeful attitude, being an active participant in health care and having excellent relationships with their healthcare team have long been associated with long-term HIV survival (13, 12). Nevertheless, the following concerns can be significant for long-term HIV survivors.

Experiencing multiple losses and grief

In the 1980s, gay men in Australia, New Zealand and internationally had their social networks decimated, and their lives shaped by the HIV epidemic (14). Many long-term survivors have suffered the loss of lovers, partners, friends, and their community. For some, in the early days of the HIV epidemic in particular, the grief of gay men who lost their partners was often not acknowledged by families and the broader society. In many cases, this group was told they would not survive for long; now they are ageing, having spent their youth expecting to die, and witnessing many of their friends and supporters die.

In the late 1990s, US author Eric Rofes wrote that the 'mass psychic numbing, fragmentation and suffering experienced by gay men is analogous to that suffered by survivors of genocide and wars' and suggested that methods that aid such survivors may be more adaptable to people with HIV than traditional models of grieving (15). It is increasingly recognised that some long-term survivors experience symptoms usually associated with post-traumatic stress disorder (referred to by some as 'AIDS survivor syndrome') (16). HIV-related 'post-traumatic growth has also been examined (17-19).

Knowledge of and awareness of these contextual issues highlight the need for trauma-informed approaches to assessment and care planning for long-term survivors (20).

Mental health and resilience

Depression and anxiety

Depression and anxiety are the most common mental health problems among people with HIV (21). Depression may be related to the cumulative losses of friends and relationships, lack of social support, loss of employment, career prospects or earning capacity and a sense of hope for the future. Lesbian, gay, bisexual transgender and intersex people experience depression and anxiety at higher rates than the wider population and can be at a greater risk of suicide and self-harm.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

See: [Beyond Blue](#)

Despite a higher prevalence of anxiety and depression among PLHIV, many have developed resilience, defined as positive psychological, behavioural, and/or social adaptation in the face of stressors and adversities (22). Resilience is a protective factor for longer-term mental health. Some studies have shown that nurses can promote resilience through modelling social skills and assisting the client in developing coping skills (23).

Bletzer notes that resilient people with HIV tend to have a higher level of knowledge of their illness, demonstrate self-responsibility, and persistence (24). Others have noted better quality of life, 'post-traumatic growth', less psychological distress, positive beliefs, and the ability to relinquish control over the uncertainty of life with HIV among those who demonstrate resilience (19, 25).

Multimorbidities

People with HIV are at greater risk of comorbidities including heart disease, cancers, osteoporosis, and neurocognitive impairment, often manifested at younger ages. It is thought that HIV contributes to more rapid ageing due to prolonged immunodeficiency, chronic inflammation, and immune activation. Side effects of treatments are also believed to contribute to earlier ageing in those with HIV (26).

One large international case-control study showed that, compared with HIV-negative controls, HIV-positive people have a higher rate of comorbidities at all ages; however, the most significant rate was among those over 60 years, where the rate of comorbidities in people with HIV was 63% compared with 12% for HIV-negative controls (27). In addition, comorbidities may appear from 10 to 20 years earlier than they do among HIV-negative people (28, 29). Non-acquired immune deficiency syndrome (AIDS)-related conditions or comorbidities that disproportionately affect people with HIV include cardiovascular disease, diabetes, osteoporosis, liver and kidney disease, mental health issues, cognitive problems, drug, and alcohol problems (30). Cardiovascular disease can be related to untreated HIV infection and certain antiretroviral therapies that can cause metabolic changes (31).

The nursing literature on ageing people with HIV also emphasises comorbidities, long-term medication toxicities and drug interactions, erectile dysfunction, diabetes, peripheral neuropathy, hepatitis C and renal disease (30, 32). Concerns about medicines for older people include polypharmacy, treatment burden, the need for adherence support and stigma, highlighting the need to develop medicine optimisation strategies (33).

Frailty affects a significant minority of older PLHIV, and can have an impact on their mobility, overall health, and quality of life (34). Screening for frailty is an important component of the nursing assessment of older PLHIV, informing appropriate nursing interventions, referral, and support.

Cancers

People with HIV are at a higher risk of some types of cancers. This is believed to be due to several factors, including immune deficiency, co-infection with other viruses such as human papillomavirus (HPV) or hepatitis viruses (35) and higher rates of smoking (36-38).

Certain cancers – Kaposi sarcoma, non-Hodgkin's lymphoma, and invasive cervical cancer are classified as AIDS-defining illnesses. HIV-associated cancers that are mostly infection-related occur at relatively high rates in people with HIV – anal cancer, vulvovaginal cancer, penile cancer, and liver cancers (35).

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Many cancers can be prevented. Nurses' roles in preventing both HIV-related and other cancers focus on health promotion and client education (advice and referrals for smoking cessation, safety in the sun to minimise the risk of skin cancers, vaccination against Human Papillomavirus or hepatitis viruses as required), promotion of cancer screening (39), and antiretroviral adherence support to maintain optimal immune health. The START study results indicate that the risk of some cancers is reduced with early treatment initiation (40).

While AIDS-defining cancers remain the most common cancers in people with HIV, both HIV-related and non-AIDS-defining cancers are increasing and are more prevalent among people with HIV than within the general population. Hospitalisation rates for people with HIV have been reported as 50–300% higher in a cohort of HIV patients in Australia than in comparable groups (by age and sex) in the general population, with age being significantly associated with hospitalisation. Mortality rates among people with HIV are still around 10-fold higher than in the general population (41).

As can be seen, as people with HIV live longer, the prevalence of comorbidities increases significantly and can affect health-related quality of life. This can mean that older people with HIV require enhanced community and social supports (42).

Sars-CoV-2 infection – COVID-19

While evidence does not suggest higher rates of COVID-19 infections amongst people living with HIV, once they contract COVID-19, PLHIV can be at greater risk of severe illness and poorer outcomes (43). Risk factors for severe COVID-19 amongst PLHIV include older age, comorbidities such as diabetes and chronic renal failure, but also HIV-specific factors such as immunosuppression, high viral load (44) and other opportunistic infections (44). Those who are on ART, have normal CD4 counts and are virally suppressed have a lower risk of poor outcomes (44), but a large WHO study found that HIV infection remained an independent risk factor for severe disease and mortality regardless of viral load suppression and use of ART (46).

Nurses need to consider that immunosuppressed PLHIV will not respond as effectively to vaccination against COVID-19 (47) and seek expert advice on targeted vaccination for this group (48). Check the latest edition of the [Australian Immunisation Handbook](#) for current recommendations.

Advance care planning

While PLHIV are generally living longer and healthier lives, end-of-life issues, and advance care planning (ACP) are often underutilised and overlooked (49, 50). Advance care planning is a form of communication between individuals and their proxies to help plan for future healthcare decisions (51). Factors affecting ACP can include low socio-economic status, lower severity of illness, social isolation and practitioners' resources and training (26). Nurses can often initiate these discussions and support people through the process with the multidisciplinary team.

Advance Care Planning

Palliative care expertise remains an important component of the care continuum for PLHIV (50). Referral to palliative care services and collaborative care between HIV specialist teams and palliative care services can ensure quality care at the end of life.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Voluntary assisted dying

Voluntary assisted dying (VAD) involves medical assistance to end a person's life because they have an advanced medical condition causing intolerable suffering and voluntarily request it. VAD is available in New South Wales, Victoria, Queensland, Western Australia, and South Australia, with strict and variable criteria. More information can be obtained via the health department in the relevant state. See further information below under Resources and links.

Disability, respite, and long-term care

If people with HIV are under 65 and experience disabilities, they may be eligible for the National Disability Insurance Scheme (NDIS). If they are 65 years old or older, or over 50 if they are Aboriginal or Torres Strait Islander people, they may be eligible for Aged Care services.

Some older PLHIV may be concerned about accessing services due to fear of stigmatisation and discrimination when their HIV status is disclosed, and to a perceived lack of knowledge and experience of carers and care workers in caring for this group (51).

Nurses can support PLHIV through advocating for and navigating services including the National Disability Insurance Scheme, My Aged Care, residential, respite or community care. Outreach programs, community-based and district nurses, peer and carer support agencies in various states and territories and general practitioners can advise on options for people with HIV in their local areas, as well as services that can support carers.

The Commonwealth Home Support Program helps facilitate respite in a person's or their family member's home, in community centres or aged-care facilities. Home care packages are now consumer-directed: that is, people and carers can choose how their home care package of services is provided. Assessment for respite and for home care packages are obtained via [My Aged Care](#).

Resources and links

[National Disability Insurance Scheme](#)

Guide for carers of older people with HIV – [Positive Caring](#)

[Advance Care Planning](#)

[Aged care workers and HIV ageing](#)

[PCA-Guiding-Principles-Voluntary-Assisted-Dying.pdf \(palliativecare.org.au\)](#)

[Voluntary assisted dying](#)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

HIV associated neurocognitive disorder

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Last Reviewed: June 2024

Summary

This section explores key issues for nurses in relation to cognitive impairment and people living with HIV (PLHIV):

- Background
- Examples of dementia
- HIV associated neurocognitive disorder (HAND)
- Screening, diagnosis, and predictors of HAND
- Signs and symptoms of HAND
- Treatment of HAND
- Strategies for support of cognitive changes
- Advice for caregivers

Introduction

People living with HIV (PLHIV) may be susceptible to cognitive changes which could be related to HIV, vascular cognitive impairment or they may develop conditions such as Alzheimer's disease as they age, all of which can have a profound effect on a person's daily function and quality of life. Cognitive impairment for PLHIV is frequently multifactorial (1).

This chapter briefly describes a range of dementias but will focus on HIV associated neurocognitive disorder, or HAND. More importantly for the PLHIV is recognition and validation of cognitive symptoms, to enable early intervention and treatment.

Background

The complexities around neurological health for PLHIV may be increasing. Ageing is seen as a factor in cognitive impairment for PLHIV because they may be more vulnerable to cognitive impairment than the general populations (2,3). However, the Charter Study (2023) noted there was little difference between age groups unless the person had significant co-morbidities and was not virally suppressed (4). Additionally, those with baseline cognitive decline showed significant deterioration which could be a predictor of future cognitive ability (5). Continued research is required in this space to provide guidance for clinicians to support PLHIV experiencing signs and symptoms (S&S) of cognitive change.

The International HIV-Cognition Working Group (2023) (6) suggests a new approach to cognitive changes for PLHIV towards an emphasis on the clinical context, suggesting that HIV-associated brain injury may encompass any potential cause of brain injury caused by HIV which may represent changes to the clinical burden of disease. Recommendations state that cognitive symptoms should refer to any change in cognition noticed by the person or others regardless of the impact on daily function. Cognitive symptoms are now generally milder in PLHIV due to improved HIV treatments which can affect quality of life but may not have a great impact on activities of daily living (4).

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Comorbidities which are more prevalent in PLHIV (7,8) can increase the risk of developing vascular impairment, such as cardiovascular disease (especially midlife), a recognised risk for vascular dementia, Alzheimer's disease, and mixed dementia (9). Risk factors for vascular cognitive impairment include ageing, mild HAND, socioeconomic and ethnicity factors, mental health, alcohol, and substance use, smoking and antiretrovirals (10).

Additionally, chronic viral infection in neurodegeneration and brain amyloid accumulation is a key neurodegenerative pathway (11). Studies have recognised that Stroke is becoming another complex health issue for long-term treated PLHIV (12). Cystique and Brew (2023) suggest that there may be a cumulative risk of dementia in ageing PLHIV from multimorbidity and disease burden perspectives (13). This is due to the effects of chronic immune activation, immune senescence, and cardiovascular disease, noting that PLHIV should be assessed for vascular S&S. Strategies should be developed to prevent or reduce risk of vascular disease (e.g. treating hypertension and diabetes), as mild vascular cognitive impairment contributes to neurodegeneration (13).

Examples of dementia

In addition to HAND, PLHIV may be at risk of developing other forms of dementia. Dementia is a term used to describe a group of conditions characterised by gradual impairment of brain function, which may impact cognition, memory, mobility, speech, personality, and behaviour. The most common form of dementia is Alzheimer's disease; it is also common for an individual to have multiple types of dementia, known as 'mixed dementia'.

Examples of dementia include:

- Alzheimer's disease, the most common dementia diagnosis among older adults. It is caused by changes in the brain, including abnormal build-ups of proteins (amyloid plaques and tau tangles).
- Vascular dementia is caused by conditions that damage blood vessels in the brain or interrupt the flow of blood and oxygen to the brain.
- Lewy body dementia is caused by abnormal deposits of the protein alpha-synuclein, called Lewy bodies.
- Alcohol-related dementia, from drinking excessive alcohol (Korsakoff's syndrome and Wernicke-Korsakoff syndrome are forms of alcohol-related brain injury which may be related to alcohol-related dementia).
- Frontotemporal dementia, a rare form of dementia that tends to occur in people under 60 years. It is associated with abnormal amounts or forms of the protein's tau and TDP-43.
- Mixed dementia, a combination of two or more types of dementia, often seen only on autopsy.

Source: Dementia Australia (14).

First Nations Populations

First Nations people experience dementia at a rate 3 to 5 times higher than the general population and are more likely to develop dementia at a younger age (15).

Many First Nations people view dementia as a natural part of the life cycle rather than an illness, as long as the person with dementia, their family and community, are safe. That is, if it doesn't affect the connection to family, community, and culture. First Nations people require integrated services to be culturally safe and community-controlled so families and communities can care for people with dementia on Country. Use of culturally

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

appropriate and co-designed screening tools for dementia and quality of life and creating culturally safe care plans such as the Kimberley Indigenous cognitive assessment (KICA) tool (15).

More information is available at [Dementia Australia](#) and the [Australian Institute of Health and Welfare](#).

HIV-associated neurocognitive disorder

HIV-associated neurocognitive disorder (HAND) is an umbrella term used to describe neurodegenerative disease caused by human immunodeficiency virus (HIV)-1 infection and may affect more than 30% of PLHIV (16) regardless of virological suppression (17).

The central nervous system acts as a reservoir for HIV with neuronal damage occurring both at the time of initial HIV infection and throughout the chronic phase (18). Although there is a decreasing incidence of HIV-associated dementia, milder forms of cognitive impairment have increased amongst PLHIV, regardless of their HIV virological suppression and immune recovery. Cognitive impairment is the most common central nervous system complication in PLHIV (19).

There are three categories of HAND, each associated with an increasing level of impairment:

1. *Asymptomatic neurocognitive impairment* (ANI) shows HIV-associated impairment in cognitive function, but everyday functioning is not affected.
2. *Mild neurocognitive disorder* (MND) is characterised by HIV-associated impairment in cognitive function with interference in everyday functioning (20,21).
3. *HIV-associated dementia* (HAD) shows marked impairment in cognitive function, especially in learning of new information, information processing, and attention or concentration (19).

Prevalence rates: ANI 30%, MND 20-30% and HAD 2-8% (19,12).

Screening and diagnosis for HAND

It is recommended that PLHIV be questioned and screened annually about any changes to cognition or memory decline (23). If any symptoms are identified, HIV neurology review should be considered. In the short-term strategies should be discussed with the person to treat symptoms. If the person is then diagnosed with cognitive impairment the person should be provided with a clear pathway for supports (23).

There are several screening tools for HAND, such as the Montreal Cognitive Assessment, Cogstate (24) and the International Dementia Scale (25). but there is no one tool which can be used across all settings (26). Some tests are sensitive to moderate but not to mild cognitive decline (27). Additionally, performance on these tests can be culture bound/based and may vary between groups with different sociodemographic and educational backgrounds (28). The Mini Mental Status Exam (MMSE) (28) is not useful in this context as HIV cognitive impairment affects the sub-cortex of the brain, but the MMSE can be used to screen for other forms of cognitive impairment such as Alzheimer's disease. If clinical neurological examination is not freely available, asking PLHIV and their caregivers about changes to their activities of daily living and mood is a useful starting point.

No known biological markers have been identified to support a definitive diagnosis of HAND. (27) The gold standard for HAND diagnosis is formal neuropsychological tests completed by a specially trained clinical neuropsychologist with or without radiological tests such as magnetic resonance imaging (MRI) (29). Therefore, multiple detection methods such as clinical review, functional review and neurological imaging are necessary.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

The diagnosis of HAND is also often made through a process of excluding other conditions (e.g. excluding new opportunistic infections such as progressive multifocal leukoencephalopathy, and cryptococcal meningitis (18). This approach presents challenges for clinicians as there are several confounding and comorbid conditions such as depression or alcohol-related brain damage that may complicate the diagnosis. Further, PLHIV may downplay their signs and symptoms, or their caregivers may attribute behaviours to other causes such as ageing or poor mental health.

Predictors of HAND

Studies suggest predictors of HAND include history of AIDS-defining central nervous system (CNS) disease (14), other CNS disease (14), low T cell nadir (30), longer duration of HIV infection (31), drug and alcohol use (31), and hepatitis C infection (32). Additionally, the risk of HAND increases as CD4+ counts decline below 350cells/uL and with higher plasma viral load (33).

General (non-HAND) cognitive impairment risk factors

Comorbidities often appear earlier and progress faster in PLHIV. Vascular risk factors such as smoking, hypertension, diabetes, hypercholesterolaemia and hyperlipidaemia should be considered, as they would in the non-HIV population. Other considerations include impaired renal function, cytomegalovirus, frailty, chronic pulmonary disease; the gut biome may also be involved (4,35).

Signs and symptoms of HAND

Signs and symptoms (S&S) of HAND experienced by PLHIV that can indicate changes in cognition may be a new behaviour (e.g. poorer memory). S&S may be so subtle that they are missed or the PLHIV may attribute the changes to something else, such as being tired, stressed, or busy. If the person has always misplaced keys, this is considered their usual behaviour. It is more important to take note of new changes in behaviour.

The person's usual behaviour may be different, which could indicate that they are experiencing some cognitive change, for example, change affecting the person's ability to perform activities of daily living (preparing meals, managing finances, remembering doctor's appointments, and driving ability). Cognitive changes may also impact social relationships and the ability to retain employment or work at a higher level.

Key areas affected are motor skills, memory, concentration, and social engagement. In addition, executive function can also be affected whereby the person may experience changes in their ability to plan, organise and to solve complex or new problems (see Table 1). The person may also experience less language fluency.

Nurses working in a wide range of settings – sexual health, viral hepatitis and HIV, primary care, community health, custodial settings, the drug and alcohol sector and homelessness services can play key roles in increasing awareness of cognitive impairment and assisting PLHIV with developing individual strategies and discussing and validating the person's experience.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Table 1: Areas affected by HIV-associated neurocognitive disorder (HAND) and nursing strategies.

*Source Dementia Australia (14) and HAND Poslife NSW Resources (35, 44).

Area affected	Signs and Symptoms	Strategies
Motor Skills	Increasing fatigue Unsteady gait Increased clumsiness Fine motor coordination Slowed motor speed. Driving deficits Difficulty typing, texting	Provide information slowly. Give ample opportunity for response. May need assistance to complete activities
Memory	Forgetting dates (e.g. birthdays), where placed keys, phone Memory affecting cooking and shopping. Missing appointments and medications Forgetting to send emails and issues for meetings.	Write down instructions relating to important information and check understanding. Encourage use of memory aids (e.g. diaries, calendars, Post-it notes) Repeat and write down new information. Provide reminders of appointments Encourage a routine. Pay more deliberate attention to what the person is trying to remember
Concentration	How the person becomes receptive to stimuli and how he or she begins to process information Problems include: Difficulty taking simple information and following directions. Difficulty keeping track of conversations. Short attention span May have to re-read things. Difficulty completing activities. Difficulty following plots of movies and books. Becoming mentally fatigued easily	Present information in small amounts at a time Present information in a manner that is clear, simple, and concrete. Limit distractions (e.g. TV) Provide prompts and reorient to task if distracted. Determine the time of day at which the person is most alert and encourage completion of difficult tasks at that point

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Behavioural (social) changes	The person can experience one of two areas of behaviour change: 1: Apathy and listlessness Withdrawal Lack of motivation Impulsivity and disinhibition 2: Hypomania Change in personality. Increased agitation, aggression, and irritability (e.g. stealing, swearing, overfamiliarity) Emotional lability	Identify the person's change of mood, ask if he or she is aware of changes; are there any reasons for becoming withdrawn. Arrange a psychiatric assessment to exclude depression. If not, depression assist the person to have small achievable goals. Check in with the person frequently to encourage engagement with the service. Identify changes in mood Ask the person what he or she has noticed whether there are any specific reasons for increased irritability for example. Arrange a psychiatric review (possible prescription of medications) Develop strategies to reduce elevated mood or irritability. Refer to other services to support changes in mood outcomes to life
Executive function	The person may experience difficulty in: Initiation of a task Planning Problem-solving Cognitive flexibility Decision-making Concept formation and abstraction Judgment- (poor judgement and assessment of situations etc) Feedback utilisation and monitoring behaviour	Encourage client to work through problems with a trusted person and to write down alternative solutions for later referral. Try to break complex tasks down into smaller components. Provide a structure or plan where possible. Guide the client through complex decisions step-by-step

Consider the clinical picture and how it impacts on the person:

Which S&S are the PLHIV experiencing? Are there recent changes in behaviour or mood? Has there been an impact on their quality of life (QoL)?

It is important to ask the person (and caregiver, if they have one) questions relating to changes they may have noticed.

A question to start the conversation can simply be: **"Have you noticed any changes?"** acknowledge any concerns whilst not creating fear and try to normalise the next steps. This may also validate what they are feeling.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Questions to ask PLHIV

- Ask the person to tell you about any changes they have noticed in themselves.
- Are you slower in your thinking than you used to be?
- Are you more forgetful than you used to be?
- Do you have any difficulty paying attention (e.g. following conversations or the plot of a TV show or movie)?
- Is it harder to organise things?
- Have you noticed you are having difficulty when you try to solve problems or plan things?
- Are you able to find pleasure in the things you used to enjoy?
- Have you become clumsier; have you been tripping or falling?

Questions to ask their caregivers:

Caregivers and loved ones can provide unique insight and collateral history into the person's behaviour and, if available, are important to include in the discussion. Ask them if they have noticed any changes.

- Have you noticed any changes in the person's behaviour?
- Is the person more forgetful?
- Has his or her personality changed?
- Is the person finding it harder to organise his or her life?
- Does the person become more irritable generally or with you?

Treatment of HAND

HIV antiretroviral medication is the cornerstone to treat cognitive impairment (17). Early and continuous viral suppression with ART is associated with improved performance on neuropsychological testing (37). But medication adherence can be difficult for someone experiencing S&S of HAND. When treatment fails and virologic rebound occurs, cognitive function deteriorates. More than 30% of PLHIV may develop cognitive impairment regardless of optimal therapy and virological suppression (16).

Historically, prior to availability of combination antiretroviral therapy, those PLHIV with diagnosis of AIDS and dementia had a median survival time of 6 months. With access to ART there has been a decrease in neuropsychiatric diagnosis and the incidence of dementia has halved, with survival time increasing to 48 months for those with 'AIDS dementia complex' (as it was known then) (19).

Following initiation of ART or changes in ART regimen, PLHIV may experience improvements; however, for various reasons some people may be left with some form of deficit, or their deficit may worsen. The reasons for this result are varied: ART can cross the blood-brain barrier to varying degrees, and some drugs have increased anti-HIV activity in the central nervous system (CNS) which result in clinical improvement in the PLHIV. Regardless of whether the person is treatment-naïve or experienced with ART, the option of adding an additional antiretroviral medication that will have enhanced coverage in the CNS could be considered in the choice of medications (38). Once diagnosed and treated, improvement in HAND may be seen within 12 weeks, continuing up to 18 months (39).

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Some PLHIV, however, may notice increased deficits. Reasons for this may include poor penetration across the blood-brain barrier; a legacy effect (damage before initiation of ART) which may cause continuing neurocognitive decline; potential for resistance with reseeding of systematic compartment (10% escaped to cerebrospinal fluid [CSF]). Some PLHIV, although viral load is controlled in the plasma, will still have detectable virus in the CSF, and this, over time, may be linked to less effective control by ART in CSF, affecting the brain, and additionally affecting immune activation in the CSF with cognitive dysfunction); toxicity from ART and inadequacy of antiretroviral agents with low level replication occurring (40). There are trials to evaluate whether treating the virus focusing on restoring metabolic and immune homeostasis can be neuroprotective (35).

Furthermore, HIV and ART cause changes in mitochondrial structure and function which can alter pathways in neuronal and glial cells which may impair brain health. With ageing, the brain is exposed to higher levels of the drugs as pharmacodynamics change and the blood brain barrier may weaken (35).

Some ART medications have poor CSF fluid to plasma ratio indicating poor drug penetration to the CNS (38). It remains unclear whether this translates into poor drug levels in the CNS and if drug penetration is clinically important. Currently, in the absence of data, no general recommendation exists to change a patients' ART regimen to agents with a higher CSF penetration based on cognitive status (35).

The one significant thing that PLHIV can do is to maintain adherence to ART.

Maintaining 100% medication adherence can be difficult for someone experiencing signs and symptoms of cognitive impairment and may indeed indicate there is an underlying cognitive impairment (41). Strategies should be developed with the person and a caregiver, if available, to maintain or improve medication adherence. Signs and symptoms of HAND may fluctuate over months with some people improving, some deteriorating and the majority remaining stable (42).

Strategies for medication adherence:

Developing an individualised plan with the PLHIV is essential. Consider a pharmacist and a medical review of medications to reduce pill burden wherever possible, arrange dosage administration containers such as Webster packs or dosette boxes, establish a medication routine, set reminders for example on mobile phones and monitor adherence regularly.

Adherence Support section by Danielle Collins.

Significance of early recognition of HAND

There are several reasons why early recognition of cognitive impairment is important:

People with HIV with cognitive impairment have been shown to be less adherent to HIV medication regimes (33-34). This may lead to drug-resistant HIV, resulting in their current medication regime becoming ineffective (20-21). Morbidity and mortality can then be affected as the person experiences poor health outcomes secondary to impaired adherence. For those who can maintain a single-dose daily regimen, this could help adherence.

- As PLHIV are ageing and may have a longer duration of HIV infection the overall prevalence of neurocognitive impairment has increased especially in its milder forms (19).
- Increased potential for many PLHIV who are otherwise controlled to become disabled through neurological impairment.
- The interval between initial infection of CNS and the development of HAD represents a window of opportunity to detect early and treat, therefore reducing potential clinical progression.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Impacts of cognitive impairment

Changes in cognition may have an impact on daily function and the PLHIV may experience a level of disability related to their cognitive impairment as previously discussed. Cognitive difficulties can also lead to decreased socialising and increased social withdrawal. PLHIV need to be supported to maintain social connectedness and relationships.

Providing information to the PLHIV and their caregiver may provide a better understanding of what they are experiencing and can help the person deal with any difficulty (1). This may help to reduce stigma and self-stigma the person may be experiencing related to cognitive impairment which can also affects a person's self-worth, confidence, and independence (1,43).

What to do

Regularly review the PLHIV – annual assessment is recommended. Ask the PLHIV questions about changes they may have noticed.

- Be aware of risk factors for HAND and other general cognitive impairment.
- Identify, reduce, and treat preventable cognitive risk factors including:
 - smoking
 - reduce cholesterol and triglycerides.
 - treat hypertension, diabetes, HCV.
 - reduce alcohol intake,
 - reduce or cease substance use.
- Encourage healthy eating strategies in combination with physical activity and sleep to restore metabolic normalcy and stimulate neuronal growth. Encourage weight loss if the person is above their optimum weight (30).
- Improve physical exercise. Aerobic exercise has a moderate favourable effect on cognitive function. Recommend activities to increase the heart rate (gardening, fast walking, dancing) for 30 minutes 4-5 times a week. Exercise can also have the added benefit of improving mood and general health (42).
- Assist the PLHIV who has S&S of cognition change to develop personal strategies such as using reminder notes and lists, using a diary (hard copy or on a device), have someone attend important appointments with them, use a visual prompt for appointments such as a whiteboard.
- It may be useful with the PLHIV's permission to send letter to important or new medical appointments to explain any deficit so that the person learns about the PLHIV deficit and can adjust how they communicate with the person if necessary.
- Consider a referral to a local memory group, social groups, and exercise group. If the person feels apprehensive arrange for someone to escort them to the group initially.
- Develop a local guide for referral pathways for access to supportive care, such as occupational therapist, physiotherapist, dietitian, the [National Disability Insurance Scheme \(NDIS\)](#) and [MyAged Care](#).
- Encourage the PLHIV to stay socially active; this may include joining groups or starting a new hobby (which can all be online) which will keep their brain active (puzzles, quizzes, art classes, learning new skills anything to stimulate the mind) (14).
- Consider legal issues when a person becomes diagnosed with cognitive impairment such as power of attorney, last will and testament and advanced care directives.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Advice for caregivers

Caring for someone with cognitive impairment may at times be stressful. Assisting someone with practical activities such as medication adherence, help with cooking, shopping, and attending appointments, may all increase a caregiver's exhaustion.

Caregivers may be concerned about the person's deterioration and what that means to their relationship; grief for the change in relationship – thinking about the potential loss of aspects of the partnership which may increase as the PLHIV's cognition changes. The caregiver can assist the person by encouraging them to have a medical review of S&S.

The caregiver can take steps to make the situation manageable relevant to the PLHIV's needs. Making the environment familiar; using memory prompts such as notes, calendar reminders, webster packs can be helpful in reducing frustration. Limit the number of tasks to be done and break them down into smaller steps, develop a routine. Making changes may alleviate the caregiver's stress.

Caregivers need to care for themselves. If the need arises, when the PLHIV's S&S of cognitive impairment increase, accessing additional support such as for practical activities can be helpful. The caregiver needs to take some time for themselves keeping connected to their social network, joining a support group, doing things that bring them pleasure to maintain their own mental health wellbeing.

Caregivers can access information and support. Dementia Australia is a useful website for information (including LGBTI guide). Both Dementia Australia and Poslife NSW have resources for the individual and for caregivers such as *HIV associated neurocognitive disorder: Booklet for partners, families, and friends* (14, 44).

Conclusion

Cognitive impairment continues to represent substantial personal, societal, and economic burdens and may place an increasing burden on Australian resources, especially as PLHIV age. Early recognition and treatment are paramount and can have a positive impact on quality of life and health outcomes for those living with HIV.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Adherence support

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Last Reviewed: June 2024

Summary

In this section, the author discusses the important issue of adherence to antiretroviral therapy from a nursing perspective and provides practical evidence-informed recommendations and additional resources.

- The importance of adherence to antiretroviral therapy
- Factors affecting adherence and nursing interventions used to promote adherence.
- Conclusion and future directions
- Resources

The importance of adherence to antiretroviral therapy

Adherence to a medication regimen can be defined as ‘the extent to which patients take medication as prescribed by health care providers’.(1) Continuous adherence to combination antiretroviral therapy (ART) is paramount to its success in effectively treating human immunodeficiency virus (HIV), achieving virological suppression, preserving immune function, avoiding drug resistance and preventing opportunistic infections. (2) More broadly, it can confer a public health benefit by reducing what is referred to as community viral load (CVL). Community viral load can be defined as ‘an aggregation of individual viral loads of HIV-infected persons within a defined community. (3) A decrease in community viral load will considerably reduce the likelihood of HIV transmission in that community. (4-6)

Missed doses, treatment breaks or interruptions, drug holidays, non-use, or reluctance to commence antiretroviral therapy pose considerable challenges for clinicians. The consequences of inadequate adherence to antiretroviral therapy to the individual can include the development of drug resistance which may limit the person’s later choice of effective antiretroviral therapy regimen, development of opportunistic illnesses and increased risk of morbidity and mortality. (7)

Many factors contribute to successful antiretroviral therapy adherence, and these include thorough assessment both at treatment initiation and at ongoing clinical encounters, clinical care whereby the patient is engaged and feels comfortable with their clinician of choice, and ongoing adherence counselling, education and assessment of side effects, early toxicities, psychosocial complexities, and other factors which may impact on continuous adherence.(8, 9) The World Health Organization (WHO) advises assessing adherence with each patient interaction.(10) Nurses are integral to this process given the dynamic role they play in patient care.

The START Study findings (May 2015) demonstrated that starting antiretroviral therapy regardless of CD4 count for all individuals diagnosed with HIV is preferable to delaying treatment commencement as previously recommended, and as such changed both national and international guidelines on ART initiation.(11) Following this came the findings from the HPTN 052, PARTNER and Opposites Attract studies, demonstrating

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

amongst both heterosexual and men who have sex with men (MSM) populations that where the partner living with HIV has a sustained suppressed HIV viral load (<200 copies/mL), no linked HIV transmission occurred across either of these three landmark clinical trials, leading to the concept of “U=U” (Undetectable Equals Untransmittable). (12, 13) With strong evidence to support early treatment initiation and the rationale behind strict adherence, adherence support must remain a component of care from the outset for every person living with HIV.

Factors affecting adherence and nursing interventions used to promote adherence

Factors influencing antiretroviral adherence are multifactorial. They can be internal – pertaining to the person, and external – pertaining to those providing the care and to the medicines themselves. (14) External factors affecting an individual's adherence can also be structural and systemic.

The advent of the COVID-19 pandemic in 2020 brought with it a multitude of unforeseen challenges for People Living with HIV (PLHIV). Aside from the impacts on daily life caused directly by the pandemic and associated restrictions, many health services limited face-to-face appointments and converted to telehealth. Despite this, HIV care continued albeit in a new hybrid model, with access to ART and adherence largely uninterrupted. (15, 16)

Nursing interventions depend on the setting and the patient population. There is no single guideline or recommendation that will prove beneficial for all patient groups; therefore, a variety of strategies may need to be trialled until one or more are successfully adopted by the patient.

Nursing strategies to encourage, improve and maintain adherence include discussing potential antiretroviral regimens with consideration to lifestyle, comorbidities, family history, evidence surrounding early treatment and continuing therapy once commenced. (17-19)

Long-acting injectable antiviral therapy (LA ART) provides another avenue for nurses to work with and support patients around adherence, whilst providing an alternative to taking a daily oral tablet for those reluctant to do so. Given the frequency of injections and the role of nurses in primary care and hospital outpatient departments already in administering immunisations and other injectable medication to PLHIV, there is a strong argument that nurses lead the delivery of LA ART and associated adherence education and support within their health services.

Table 8 summarises internal or individual factors affecting adherence and nursing interventions. **Table 9** summarises external factors relating to the medication affecting adherence and nursing interventions and **Table 10** summarises external factors relating to health-care providers and the broader system.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Table 8: Individual factors affecting adherence and nursing interventions (20)

Individual -related factors influencing adherence	Comments and evidence	Nursing interventions
Younger age at HIV diagnosis	Shown to predict poorer antiretroviral adherence. (21)	• Empower the client by including them in all decision-making processes. • Link with age-appropriate counselling and support services. • Involve friends and family members where appropriate.
Ambivalence around commitment to life-long treatment	Regardless of age, starting a medication that requires life-long commitment can be daunting.	Explore the concerns behind ambivalence. • Provide pragmatic suggestions such as planning the best time of day to take medication, or a practice run with a multivitamin before commencing antiretroviral therapy. • Allow the person to select their own start date. • Provide adherence aids such as dosette box or suggest a phone app as a reminder. • Provide evidence-based literature and information about the long-term effects of the regimen. • Provide future options such as LA ART.
Alternative or poorly informed health beliefs	There are many myths surrounding both HIV and antiretroviral therapy. These may contribute to an individual's reluctance to start and adhere to therapy. (22-24)	• Explore health beliefs and provide education with non-biased evidence-based information specific to needs and level of understanding. • Use a non-judgmental, non-coercive approach to foster engagement, taking into account the choices made by the person living with HIV and acknowledging the beliefs behind their decision. • Linking the person to an HIV specialist who will listen and nurture a respectful relationship. • Providing non-didactic education and empowering health promotion about HIV and related health issues. For example, encouraging immunisation, teaching people to recognise signs and symptoms of disease progression and assisting them to access medical care when needed. • Support and encouragement in health maintenance. For example, encouraging the person to agree to take prophylaxis to prevent opportunistic infections, despite choosing not to take antiretroviral therapy. • Health monitoring and crisis intervention including specialist referral if the client becomes unwell. • Linking with mental health services, community-based support, and other HIV-specific services such as housing and counselling.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Stigma related to taking antiretroviral therapy	HIV-related stigma can affect a person's willingness to start and adhere to antiretroviral therapy. (25)	- Identify specific concerns around stigma. - Counteract myths around taking antiretroviral therapy and living with HIV. - Suggest counselling. - Normalise ART in the context of Pre-Exposure Prophylaxis (PrEP), Treatment as Prevention (TasP) and U=U - Refer to peer support group and networks. - Assist the person to develop strategies to minimise unwanted disclosure e.g. locked medication cabinet. - Explore multiple levels of influence – intrapersonal, interpersonal, structural. (26)
Occupational	Shift work or regular travel may make daily adherence to medication difficult.	- Suggest the client switches or simplifies regimens if possible. - Consider dosing requirements and pill burden, or if LA ART is a better option. - Devise a back-up plan with the client to manage a missed or delayed dose. - Assist client to manage side-effects if changing regimens is not possible.
Lack of support network and poor engagement in health care	Social isolation and poor engagement in health care have been identified as a predictor of poor medication adherence.	- Ensure clinical support is adequate to meet the client's needs. - Consider a team care approach involving pharmacist, social worker, peer support service, community nursing service and GP. - Encourage client to attend peer support group. - Consider case conferences at structured intervals.
Financial barriers	Despite universal health care and subsidised antiretroviral therapy in Australia, evidence shows that 3% of Australians cease antiretroviral therapy each year. (27) Cost of living crisis in Australia at time of update to guideline (2024) may also impact access to care and ART.	- For eligible Indigenous clients with chronic illness, antiretroviral therapy and all medicines are available free of charge through the Closing the Gap Pharmaceutical Benefits Scheme (PBS) Co-payment measure. (28) - Ensure financial support is provided in other areas of life where possible such as a subsidised taxi card if eligible, access to free or subsidised food. - Simplify antiretroviral therapy regimen to reduce pharmacy dispensing fee. - Refer for financial counselling and support.
Mental illness	Depression and mental illness are predictors of poor adherence. (29-31)	- Engage the client's mental health-care team. - Adopt a team care approach. - Explore adherence aids. - Develop a plan of care with the client, and a plan of action in the event of an exacerbation of their mental illness.
Psychosocial factors	Family violence, unstable housing, food insecurity contributes to suboptimal adherence.	Explore the client's priorities which may be different from assumed or caregiver priorities. - Engage social work and other allied health support. - Assess support to access and maintain stable housing. - Provide dietary education and linkage to community agencies that provide subsidised or free food and meals.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Alcohol and other drug use	The use of amphetamine-type stimulants (ATS: such as methamphetamine) has been identified as playing an important role in difficulties with adherence to antiretroviral therapy. ATS use has been described as a barrier to adherence among gay and bisexual men. This may be both planned and unplanned non-adherence. (32)	• With client's consent, engage with pharmacotherapy provider and pharmacist to provide additional support. • Consider a planned treatment break with increased health monitoring in consultation with the client's physician as this may reduce the risk of developing medication resistance if unable to maintain adherence and all other avenues of support have been exhausted.
Cognitive impairment and ageing	As Australia's population ages, so too are PLHIV, many of whom have been living with HIV in the pre-antiretroviral therapy era. (33)	• Referral and assessment for HAND and other organic causes of cognitive impairment, which may include the recommendation of changing ART regimen. • Use of reminders i.e. use the smart phone calendar, set an alarm clock, leave notes in a visible place, involve carer or significant others to remind the person or to administer if required. • Refer to a community-based nursing service to support and promote adherence, to coordinate medication management and administer medication regularly if required.
Level of health literacy	Poor health literacy is a strong predictor of poor health and negative treatment outcomes, and as such needs to be explored with the client and accounted for during adherence counselling sessions.(34, 35) It is important to help the person understand the need to continue taking treatment when they feel well, and to understand health jargon terminology and meaning e.g. undetectable viral load does not mean the virus has gone. (36)	• Ensure education is appropriate to the client's level of comprehension. • Engage pharmacist, other clinical or allied health-care providers involved in client's care to provide a team care approach. • Introduce supportive strategies such as keeping a diary of dosing and any questions for the next appointment with the physician or nurse.
Ethnicity and cultural influences	People from different cultures hold varying beliefs around ill health and medication and may influence a person's acceptance of their HIV diagnosis and willingness to accept treatment.	• Explore cultural beliefs around health, illness, and medication and incorporate into adherence counselling sessions. • Engage community members or elders if appropriate. • Ensure CALD resources are available. • Use an interpreter service ensuring appropriate confidentiality provisions are in place beforehand. • Consider cultural implications regarding pregnancy and breastfeeding.

CALD: culturally and linguistically diverse; CNS: central nervous system; HAND: HIV-associated neurocognitive disorder

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Table 9: Medication-related factors affecting adherence and nursing interventions.

Medication-related factors	Comments and evidence	Nursing interventions
Pill burden	As the HIV population ages, concomitant medication use accumulates and can lead to suboptimal antiretroviral therapy adherence.	• Introduce a dosette box or other dosage administration device. • Engage the pharmacist and a team care approach. • Arrange Home Medicine Review through client's GP. • Simplify antiretroviral therapy regimen where possible.
Adverse effects/ Toxicities	Undesirable effects attributed to ART can have a negative effect on the capacity of the individual to maintain daily activities and life events. Poorly managed symptoms or early toxicities can lead to poor adherence and influence people's decisions to seek and remain engaged in care. (37)	• Support through initial side-effects post- antiretroviral therapy commencement by providing anti-emetic, anti-diarrhoeal and temporary dietary restrictions as required. • Ask the client to keep a diary of adverse effects, noting pattern, frequency, any relieving or exacerbating factors, and if any were present before commencing antiretroviral therapy. • Consider changing regimens or the time of dosing i.e. before bed if sedating side-effects are being experienced.
Drug-drug interactions	Actual or potential drug-drug interactions can introduce complexity affecting adherence.	• Liaise with all members of the care team from all disciplines to stay abreast of medication changes. • Educate client about drug-drug interactions with an emphasis on over-the-counter remedies such as antacids and herbal medicine. • Suggest Liverpool drug interactions website or phone app.
Food requirements	The food requirements associated with some antiretroviral therapy regimens may act as a barrier to optimal adherence.	• Client education about food, vitamin, and supplement interactions with antiretroviral therapy. • Review drug regimen, change antiretroviral therapy or time of dosing. • Dietitian referral. • Ensure the client has access to food and basic amenities.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Table 10: Provider, health system and socio-political factors affecting adherence and nursing interventions.

Provider, health system and socio-political factors	Comments and evidence	Nursing interventions
Service access	Access to health services may provide a barrier for clients living in remote and rural regions. Physical access to a service may also pose a barrier for an individual living with a disability. Specific settings such as prison, immigration detention or other institutional settings may thwart or support adherence. (38)	- Consider referral to a local provider or telehealth conferences. - Consider using the local pharmacy for medication collection. - Ensure the health services the client is accessing are aware of specific needs. - Outreach of HIV specialist teams to custodial settings.
Cost	See Financial barriers	
Provider attitude	Institutionalised stigma may prevent people with HIV engaging in their care. (39)	- Educate and dispel myths about HIV among clinicians. - Ethical consciousness-raising. (40, 41)
Incorrect prescribing, dispensing or administration. (42)	Prescriber errors can contribute to suboptimal adherence as can incorrectly dispensing from a pharmacy, dosing errors and drug interactions. (43) Consequences can include: - o Drug resistance - o Treatment failure - o Toxicities - o Loss of trust - o Increased costs - o Legal implications. (44)	- Enhanced medication reconciliation upon admission or discharge from hospital or other transitions or settings (respite, aged care). (45) - Nursing consultation with HIV specialist pharmacists. - HIV nurses supporting, educating, and mentoring general nursing staff. - Improved data collection, analysis of medication errors. - Attention to factors contributing to errors: interruptions, communication, lack of adequate medication reconciliation processes and procedures. (46)
Fragmented or uncoordinated care	Poor continuity of care may contribute to poor adherence.	- Referral to community nursing services with expertise in HIV can be an important early intervention for those identified as at risk of poor adherence. - Involvement of community sector (e.g. HIV organisations, Peer Services, local services) to provide supports such as transport. - Professional and industrial nursing advocacy for appropriate staffing levels, skill mix.
Other psychosocial and socio-political factors	Examples: • Family dysfunction • Criminalisation of drug use • Homelessness • Poverty • Cost shifting	- Refer for social work and counselling. - Support in accessing legal, housing, and financial services. - Structural advocacy.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Conclusion and future directions

The ability of people with HIV to adhere to treatment can be a complex matter, influenced by a wide range of individual, system-related, psychosocial, and socio-political factors potentially compounded by the life-long nature of antiretroviral therapy for HIV treatment.

Nursing strategies to encourage, improve and maintain adherence include discussing potential antiretroviral therapy regimens with consideration to side effects and potential toxicities, simplification, mode of administration, lifestyle, comorbidities, and family history; and evidence surrounding early treatment and continuing therapy once commenced. (47-49) Addressing social stigma related to revealing HIV status during adherence counselling sessions can be effective in helping to improve adherence.

Given the impetus towards TasP and evidence supporting U=U, (50) as well as the massive scale up of PrEP for HIV prevention and more recent introduction of LA ART, the role of nurses at all levels of practice in supporting adherence to antiretroviral therapy extends not just to ongoing support to those living with HIV but to a greater role in biomedical HIV prevention as well. (51) (See [Biomedical HIV prevention for more information](#))

At the systemic and socio-political level, nurses can contribute through research, policy development and structural advocacy to the development of systems that support health promotion, and access to and equity within health care, so that all PLHIV will have equitable chances of optimising their adherence to antiretroviral therapy and thereby maximising their health outcomes.

Adherence – Case example

Bert is a 43-year-old gay man who was diagnosed with HIV seven years ago. He had held a firm belief that HIV medications were 'toxic' and preferred to use complementary therapies, vitamin supplements, and meditation. He was lost to follow up for some time during the COVID-19 pandemic. He became unwell following a psychotic episode and was hospitalised and diagnosed with cerebral toxoplasmosis. He started antiretroviral therapy in the hospital and was discharged home with a referral to an HIV community nursing service.

Bert accepted visits reluctantly and suspiciously, anticipating that the HIV community- nursing team would 'lecture' him and seek to impose a biomedical model of care on him and intrude upon his life. The HIV community nurses slowly gained his trust, allowed him the time to express his concerns and discuss his preferences, and helped him develop strategies to incorporate his desired lifestyle changes and wishes into his health regimen. The nurses filled a dose administration container for him each week and helped him to organise his prescriptions to ensure a continuous supply of antiretrovirals and other medicines. He was incapable of doing this himself effectively initially due to memory loss and planning difficulties but gradually improved and gained independence with managing his medicines. At each visit, he discussed his wish to stop antiretroviral therapy and return to his complementary therapies. The nurses liaised with his GP over side effects he experienced on antiretroviral therapy and helped him tailor his medication times to suit his dietary preferences, lifestyle, and tolerances. They encouraged him to remain on antiretroviral therapy without imposing home visits upon him. They provided a supportive environment where he felt confident that his concerns were heard and taken seriously.

Over time, Bert has stopped antiretroviral therapy on a few occasions for brief periods, when he felt that side-effects affected his functioning. He recently requested a change in antiretroviral therapy due to joint pain, and this change has been successful. Bert still has reservations about antiretroviral therapy but is adherent to it and remains well. He lives a healthy lifestyle, eats as well as he can, exercises and meditates. He maintains a strong relationship with his GP and the community nurses have discharged him from their service. He occasionally calls with questions or concerns.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Additional resources

- [Initiation of Antiretroviral Therapy – ARV Guidelines \(ASHM\)](#)
- [Australian Commission on Safety and Quality in Health Care. National Medication Management Plan – User Guide. 2021.](#)
- [Find a Prescriber – ASHM Health](#)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Health promotion

Karyn Gellie: Community Health Nurse

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Last Reviewed: June 2024

This section examines health promotion in the HIV nursing context.

- What is health promotion?
- Health promotion in HIV nursing practice in Australia
- Health promotion into the future in HIV nursing
- Additional resources

What is health promotion?

Health promotion is “the process of enabling people to increase control over, and to improve, their health” (1). The Ottawa Charter for Health Promotion (2) provides guidance with the use of three key strategies; advocate, enable and mediate; across five priority action areas:

1. Build health public policy.
2. Create supportive environments for health.
3. Strengthen community action for health.
4. Develop personal skills.
5. Re-orient health services.

Individual and community health education is an important component of health promotion; however, the Ottawa Charter identifies the need for greater empowerment of communities involving building skills, relationships and creating supportive conditions for health (3).

In recent decades, our understanding of the underlying influences on health outcomes has grown with increased recognition of inequality as a key driver of poor health (3). Health inequality results from systemic factors and the broader social determinants of health (SDH), “the conditions in which people are born, grow, work, live and age”, including social norms, policies, political and other systems (4).

The social determinants of health can contribute in positive and negative ways to health outcomes and include, among others; income, education, employment, food security, housing, social inclusion, and non-discrimination (4). The influence of the SDH can be larger than other factors such as access to health care and lifestyle choices, accounting for as much as 30-55% of health outcomes (4).

With the emergence of the human immunodeficiency virus (HIV) in the 1980s, the subsequent response was one of the first health promotion approaches to utilise the Ottawa Charter principles from the outset in Australia (5). Affected communities and activists were at the forefront of a rights-based movement, developing partnerships between impacted communities, governments, and health care providers (5). There was recognition that SDH such as discrimination, violence and access to health services were impacting on both prevention of HIV and the health of people living with HIV (5). Community and peer strategies have been

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

critical in Australia's response to HIV, but they required the removal of structural barriers such legal and policy frameworks and access to health care to enable health gains (5).

In recognition that health inequalities are mostly due to factors outside of the health sector, such as politics, economies, digital transformation and planetary ecology, there has been a shift to broader well-being frameworks (6). The World Health Organisation (WHO) has developed 'Achieving Well-being: a Global Framework for Integrating Well-being into Public Health Utilizing a Health Promotion Approach' (6). The framework continues to support health promotion as a key to well-being but establishes the roles and actions beyond the health sector in achieving health gains (6).

In Australia, some states have created or are working toward well-being frameworks. For example, in the Victorian Well-being plan, improving sexual and reproductive health is a priority (7). In 2023, the Australian Government launched 'Measuring What Matters', the first Commonwealth National Well-being Framework (8). The framework is underpinned by inclusion, equity and fairness across five themes: healthy, secure, sustainable, cohesive, and prosperous. It uses well-being measures as an addition to traditional economic measures and includes a 'dashboard' for interactive monitoring of outcomes (8).

Quality of life, empowerment of communities, equitable distribution of resources and recognition of the concept of well-being and knowledge systems within Indigenous peoples are key concepts outlined in the WHO global framework (6). This is congruent with Australian Aboriginal and Torres Strait Islander concepts of well-being including social, cultural and community wellness that enable the health of the individual (9). The Australian well-being framework is a broad approach across the population and is intended to work in partnership with the National Aboriginal and Torres Strait Islander Health Plan 2021-2031 (8).

Health promotion in HIV nursing practice in Australia

Promoting health is a significant component of HIV nursing. Nursing 'contributes to almost all of the foundations of well-being' including the equitable distribution of resources and capacity building (10). The Australasian Sexual Health and HIV Nurses Association (ASHHNA) identify enabling equitable and culturally appropriate access to health care, acting to eliminate stigma and discrimination, and educating others on the determinants of health as key practice standards (11). Nurses have a professional responsibility to advocate for the elimination of health inequities (10,11).

Nurses work in a variety of settings including acute and community health care, schools, justice systems and across the lifespan of people, enabling significant opportunity to initiate and participate in health promotion. Nurses are experienced health educators in areas such as healthy lifestyles, chronic conditions and risk behaviours. However, it is imperative to consider the impact of SDH and review the efficacy and evidence for strategies as they relate to different population groups (3). An overemphasis on individual behaviour can further increase inequality by not creating the conditions for individuals to have greater ability to manage their health (3). For example, without change to laws in Australia to allow needle and syringe programs, access to clean injecting equipment, non-judgemental health care and harm reduction and education could not have been enabled.

Whilst there are other health promotion models, the Ottawa Charter for Health Promotion (3) can be a useful guide due to its emphasis on recognising underlying factors outside of individual behaviour and potential for the use of multiple strategies across multiple action areas to address the SDH (3):

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

1. Build healthy public policy:

Healthy public policy is at the core of health promotion (12). Forming health policy involves awareness, advocacy and sometimes activism (5,12). Nurses have strong advocacy skills and should work to put health on the agenda at all levels and across other sectors (10,11). Nurses can achieve this through participation in professional organizations, committees and initiating processes, projects and research. Social and political activism is an extension of professional advocacy with an aim to influence systems, funding and public policy (12). A recent example is nurses' involvement in advocating for 'Medicare ineligible' people to have access the care and treatment through ASHM resulting in a change in policy.

2. Create supportive environments:

Nurses should monitor the impacts on health of the environments we in which we live and work (1). In a local context, ensuring services are accessible through consultation with impacted communities and developing strategies to overcome structural barriers such as opening hours and financial constraints, developing referral pathways to other services and creating a non-judgmental environment. Nurses can establish and foster partnerships between individuals, services, peer-based organisations and community groups for accessible health care and health promoting strategies.

3. Strengthen community action for health

Empowerment of communities is a central process for health outcomes (1). Nurses can raise awareness and develop training within the health sector and community about the SDH (13). For example, nurses can raise public awareness of discrimination and stigma by initiating and participating in community events and social marketing such as World AIDS Day. Nurses can advocate for funding, initiate and support community action in specific settings such as schools, prisons, hospitals to prevent blood borne virus transmission, enable access to blood borne virus treatments, development of referral pathways and to address other SDH relevant to the setting (14).

4. Develop personal skills

Nurses can support, build capacity and harness community strengths, for example, training volunteers in caring for people with HIV through HIV organisations and peer support networks (15). When providing health education, nurses can act to improve health literacy that avoids lifestyle blame and understands that drivers for behaviour can be complex and arise from social, economic, environment and cultural factors (3).

Nurses can build capacity within health care to respond to health inequality and social determinants of health through role modelling, sharing skills and knowledge in providing equitable care, developing and disseminating research and implementing training.

5. Re-orient health services:

To improve health outcomes, health care needs to continue to evolve beyond 'clinical and curative' services (1). This can be achieved by strengthening primary health care and accessibility for vulnerable groups (6,12). Taking a holistic view of people and communities is essential including cultural sensitivity and empowerment of culturally diverse and marginalised populations (1). Nurses can instigate and support organisational change and health care models to improve health access to vulnerable groups for example, outreach and the use of peer workers and navigators. For example, nurses can outreach and partner with community and peer-based organizations to facilitate health promotion activities such as addressing food security, harm reduction, education and health literacy (15).

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Health promotion into the future in HIV nursing

Some health promotion experts have called for approaches with increased focus on enhancing health more broadly than the risk factor approach or disease focus (3,6). The more recent focus on well-being frameworks exemplifies this (3). This does not equate to the 'rejection' of prevention, public health or bio-medical approaches but rather creating a balance and re-orientation to value equity, empowerment and positive SDH (3).

A re-orientation of resources is required to ensure *equity* (not necessarily the same but what is needed) (6). Nurses can continue to research and advocate for models of care and health policy that are evidence-based and incorporate strategies to address the SDH (11).

Nurses can increase our efforts in improve health equity and well-being through holistic, empowering, person centred and culturally safe practice. Nurses can utilise every contact as opportunity for health promotion (10). Nurses can use holistic tools for assessment and referral pathways for individuals and communities that incorporate broader determinants of health.

The Joint United Nations Programme on HIV/AIDS (UNAIDS) in its 2022 report, 'Dangerous Inequalities' asserts "Inequalities are blocking the end of the AIDS pandemic" (16). Whilst low-income countries primarily experience the burden of HIV/AIDS (17), inequity still exists among vulnerable populations in high income countries (18). Globally, it is clear that if health is treated in isolation (according to a solely biomedical model), the HIV epidemic will continue to affect some groups disproportionately.

Additional resources

Health Equity Matters (2022) [Health Workforce Toolkit: HIV and Sexual Health for Aboriginal and Torres Strait Islander people](#)

[National Aboriginal and Torres Strait Islander Health Plan 2021-2031](#)

[NSW Government STI Programs Unit](#)

[Queensland Health \(2021\) Health Equity Toolkit](#)

[Reducing stigma and discrimination associated with blood-borne viruses and sexually transmissible infections: A stigma reduction toolkit for the Victorian healthcare workforce \(2022\). Australian Research Centre in Sex, Health and Society, La Trobe University](#)

[VicHealth \(2015\) Health Equity Summary Report: Promoting Health Equity Through Addressing Social Determinants of Health in Healthy Settings Approach. An Evidence Summary.](#)

World Health Organization (1986). [The Ottawa Charter for Health Promotion 1986](#). First International Conference on Health promotion, Ottawa, 21 October.

World Health Organization (2023) [Integrating the social determinants of health into health workforce education and training.](#)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Clinical supervision for nurses in the HIV sector

Judith Gorst

Family Therapist, Victoria

Last Reviewed: June 2024

- Introduction
- What is clinical supervision for?
- Confidentiality
- Why should nurses working in the HIV sector be provided with routine clinical supervision?
- Remote and indigenous communities
- The impact of COVID-19
- Conclusion
- Resources

Introduction

Clinical supervision is not the norm for people working in nursing and midwifery, though it is well established in mental health nursing (1). There is a general assumption that nurses and midwives, doctors and other health professionals must push on through, regardless of what they may endure at work. This notion may have developed because health workers' traditional working environments have been in acute settings, with a constant flow of patients; this is the first, formative environment to which all health-care professionals are exposed. The provision of a time and space to discuss, reflect on and question the care being provided as well as the personal impact of the work, may seem unrealistic and is certainly not part of the cultural norm. Healthcare professionals frequently conduct conversations about patient management, but the nature of these discussions tends to be linear, direct and solution focused. Conversations that are more reflective and expansive in nature are less frequently engaged in.

People with human immunodeficiency virus (HIV) who need nursing or midwifery care often present with an enormous range of clinical, psychosocial, cultural, and ethical challenges. The clients in this group, whether they are being cared for in community or hospital settings, may often be unwell and present with more than one complex, clinical issue. Nurses and midwives may need to use skills more frequently utilised by social workers, community, alcohol and other drug workers, mental health practitioners and pastoral care workers.

It is worth noting that social workers and healthcare workers in the mental health and drug and alcohol sectors are routinely provided with clinical supervision by their employers. There is also a requirement to access supervision as part of their registration with their professional bodies.

What is clinical supervision for?

The Australian Clinical Supervision Association (ACSA) defines supervision as:

'A formal professional relationship between two or more people in designated roles, which facilitates reflective practice, explores ethical issues, and develops skills (2). The ACSA emphasises that it is not based on a hierarchical relationship or culture, and that the power lies with the supervisee.

The chief purpose of clinical supervision is to provide a space for the supervisees to discuss and reflect on the nursing work they are doing with their clients. This can take place one on one or in a group setting. Trust and confidentiality are essential components of good supervision.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Ideally a qualified, external supervisor, with specific knowledge of the human immunodeficiency virus (HIV) sector, who is not the nurse's line manager, is best positioned to provide clinical supervision. Supervision is not about performance appraisal. Good supervision allows for a discussion to unfold and grow and for themes to develop. It allows the supervisees to expand their understanding of their client's clinical and psychosocial condition as well as their own life situation and potential triggers. It also provides an opportunity for the supervisees to reflect on their strengths, deficits, and needs. It encourages them to examine their practice and the rationale for their approach. This in turn promotes professional growth and a greater therapeutic awareness (1,2).

An equally important consideration is the opportunity supervision provides for a conversation to develop about the emotional impact of the work. Supervision provides a forum for the supervisee to talk about the toll the work might be taking on them as clinicians. As trust and confidence builds within the group, or for the individual, participants feel more able to share some of their concerns as well as identify strategies to deal with complex situations. One of the roles of the supervisor is to provide support as well as a critical and positive endorsement of the supervisee's work.

Confidentiality

Central to all supervision is confidentiality. All supervisees must be aware of the meaning and the limits of this principle. The supervisor must maintain a clear boundary between the supervisees and the employer/organisation. They will only report any concerns to the employer if they sense that the supervisee is at risk or is placing clients at risk. It is important for the employer and the supervisees to understand the importance and necessity of this boundary.

Why should nurses and midwives working in the HIV sector be provided with routine clinical supervision?

There are a variety of reasons why clinical supervision is relevant for nurses caring for people with HIV. Since HIV has become a chronic condition rather than a life-threatening, terminal illness there is now a far greater emphasis on care in the community. Working in the community or general practice requires the nurse to work more autonomously than within the acute sector. This is an attractive aspect of the job for many nurses. However, it potentially poses challenges that warrant the provision of supervision on account of the complexity of clients' health issues, and the resultant risks to which the supervisee, clients and the employer might be exposed.

There are numerous potential risks, for example, ethical dilemmas, clinical, psychosocial and cultural challenges and, with the emergence of the SARS-CoV 2 virus (COVID-19), actual physical risks for the healthcare worker and/or potentially immunosuppressed, or unvaccinated clients.

For example, a nurse may be asked by their client for advice on an ethical dilemma around the sharing of information about their blood-borne virus status or safer sexual or injecting practices. It is, at the best of times, difficult to answer queries of this sort briefly, without the opportunity to explore the context and reason behind the question. In the context of a nursing appointment, this may be even harder, because it is important to provide a response delivered in a respectful and non-discriminatory manner whilst also being clinically accurate. Of equal importance, if the nurse were to provide misinformation in this situation, the client (and others) may, inadvertently, be harmed.

Apart from the potential for harm, there is also a risk that the organisation may be held responsible for the information offered. The organisation's reputation might be affected and the potential for litigation increased.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

With regular clinical supervision, issues such as these can be discussed, and skills developed to address them safely.

Remote and Indigenous communities

As mentioned previously, clinical supervision has not been regarded as an essential part of a nurse's professional development. Factors such as workplace culture, organisational factors, time, an appropriate location, and the availability of technology, for instance Wi-Fi and computers, all act as potential barriers. For nurses working in remote settings and with indigenous communities, this is particularly relevant. However, themes of an increase in skills, knowledge, professional enthusiasm, commitment, and confidence, combined with a reduced sense of isolation, all point to the potential benefits of supervision (3, 7).

The impact of COVID-19

COVID-19 added a new layer of complexity for health care workers. At times it might be hard to recall the level of fear, anger and distrust that accompanied the pandemic. The risks of exposure to COVID-19 were very real. Everyone operates within a system and COVID-19 added another element to this system (4-6).

Nurses and midwives had to manage their own families, including aging family members or those who required home-schooling, but also their clients who were facing similar struggles.

Some people chose not to be immunised and this group presented their own challenges particularly when the evidence pointed to the advantages gained through vaccination. Having the opportunity to talk about and address some of these issues in supervision, albeit via telehealth, proved helpful.

Conclusion

Clinical supervision, through its restorative or supportive function, can address the mental health and well-being of frontline health workers through facilitated reflective practice, debriefing, and strengthening the supervisee's stress management and coping mechanisms (8).

The COVID-19 pandemic has highlighted the importance for healthcare workers of support (8). We cannot foresee what the future holds nor predict what challenges a new pandemic might bring. MPox (formerly known as Monkeypox) is an example of an infection that may affect specific groups disproportionately [see section on MPox]; other emerging infections may have no immediate treatment or vaccine.

Clinical supervision holds a mirror up to the work that the nurse is doing with their clients.

Recognition that it is not possible to 'pour from an empty cup' has never been more relevant for a profession that traditionally puts its own needs last.

On an aeroplane, people are advised to put their own oxygen mask on before they help the infant they are accompanying. Similarly, if healthcare workers attend to their own needs and well-being, they are better placed to provide optimum care to their clients and others who rely on them.

Clinical supervision is just one of the ways this can be achieved.

Resources

[Australian Clinical Supervision Association](#)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Biomedical HIV prevention

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Last reviewed: 2024

More recent Australian clinical guidelines on HIV PrEP are available.

Read the guidelines: <https://hiv.guidelines.org.au/prep-guidelines/introduction/>

More recent Australian clinical guidelines on HIV PEP are available.

Read the guidelines: <https://hiv.guidelines.org.au/pep-guidelines/introduction/>

Summary

This chapter describes biomedical HIV prevention technologies in the Australian setting, evidence for their effectiveness, and the settings in which they can be used. It discusses nurses' roles in the implementation of biomedical prevention, guidelines and education.

- Introduction
- Non-occupational Post-exposure prophylaxis (PEP)
- Time to first dose
- Incomplete adherence
- Continued risk
- HIV Pre-exposure prophylaxis (PrEP)
- Potential risks of PrEP
- Nurses' roles in PrEP

Introduction

The most effective way to prevent the sexual transmission of human immunodeficiency virus (HIV) is to prevent HIV exposure. The consistent use of condoms is the mainstay of any personal, or population level, sexual risk reduction strategy. However, in an analysis of two large studies of condom use and HIV incidence in men who have sex with men, the overall effectiveness of condoms in preventing HIV infection during anal sex was estimated at 70%.⁽¹⁾ Ineffectiveness was related to condom failure e.g. breakage, slippage, leakage, and delayed and intermittent application during sex.⁽²⁾ Men who have sex with men represent the Australian population at most risk of HIV infection and while condom use should continue to be promoted, alone it is unlikely to reduce HIV incidence.

Antiretroviral drugs can be used to treat and prevent HIV infection. The final two decades of the 20th century saw not only the evolution of antiretroviral therapy (ART) used to effectively treat HIV infection but also the increased use of ART to prevent HIV acquisition in occupational, non-occupational, antenatal and postnatal settings. The first 15 years of the 21st century have advanced the use of ART as prevention in HIV-positive and

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

HIV-negative populations; most notably in serodiscordant relationships and other groups of men and women at risk of HIV infection. Table 11 describes the various uses of ART as prevention. This section will focus primarily on HIV post-exposure prophylaxis (PEP) and HIV pre-exposure prophylaxis (PrEP) and describe the ways that a nurse might contribute to the assessment and care of HIV-negative men and women using ART.

Table 11: Antiretroviral therapy as prevention

Antiretroviral therapy as prevention	Acronym	Description	Efficacy
Postexposure prophylaxis	PEP OPEP: occupational PEP NPEP: non-occupational PEP	28 days of antiretroviral drugs taken as soon after, and within 72 hours of, an occupational or non-occupational (sexual or injecting drug use) actual or potential HIV exposure event	OPEP: 81% risk reduction ⁽³⁾ NPEP: no empirical data, strongly supported by non-human primate and the prevention of mother-to-child HIV transmission studies ^{(4) (5)}
Prevention of mother-to-child HIV transmission	PMTCT	Universal antenatal HIV screening, maternal ART, caesarean section, #short-course postnatal ART for the newborn and avoidance of breast feeding	< 1% risk of vertical transmission (from a 13-40% risk without intervention) ⁽⁶⁾
Treatment as prevention	TasP	ART to men or women with HIV infection in serodiscordant relationships	≥ 96% ⁽⁷⁾
*Pre-exposure prophylaxis	PrEP	Daily ART (usually coformulated tenofovir disoproxil fumarate and emtricitabine – Truvada) in HIV negative men and women	Men who have sex with men: 44 – 92% ⁽⁸⁾ Heterosexual men and women: 75 – 90% ⁽⁹⁾ IDU: 49 – 74% ⁽¹⁰⁾

ART: antiretroviral therapy; HIV: human immunodeficiency virus; IDU: injection drug user

Additional benefit of caesarean section in women on antiretroviral therapy with an undetectable viral load is unknown

*Maximum efficiency is dependent on high levels of adherence and detectable drug in plasma. The range represents the overall efficacy and, in those participants with detectable drug, best efficacy. The study in injection drug users used tenofovir disoproxil fumarate alone.

Non-occupational postexposure prophylaxis (NPEP)

NPEP has been in wide-spread use in Australia since 1999 and is recommended by the Australian Government's Department of Health and Ageing.⁽¹¹⁾ The Australian National NPEP guidelines recommend 28 days of ART (at prescriber's discretion) with two or three drugs for an HIV transmission risk event of ≥ 1: 15,000. Australian men who have sex with men and, to a lesser extent, people who inject drugs, are the principal target groups. Nurses have diverse roles in the assessment and provision of PEP (see Table 12). Any nurse working in HIV and sexual health, family planning, an emergency department or in a general practice requires a minimum of PEP literacy (see Table 13).

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Table 12: Nursing roles in non-occupational postexposure prophylaxis (NPEP)

• Management of statewide services • NPEP assessment, initiation and care in emergency departments and sexual health and HIV care settings • NPEP hotlines • NPEP research • Participating in development of state and national guidelines • Providing education and support

Table 13: Minimum post-exposure prophylaxis (PEP) literacy

• What constitutes a risk event – how to assess risk • How to access help (PEP hotlines, emergency departments, sexual health clinics, HIV care providers, overseas) • The importance of timing – NPEP should be started as soon as possible after a risk event • The duration of therapy • Adherence education and support • The need for a high level of adherence to the regimen • Choosing the optimum dosing time based on the patient's routine work and leisure patterns including discussion about the dosing window – a rigid, fixed time to dose sets patients up to miss a dose and fail • Strategies to assist adherence – teaching cueing (the act of associating pill taking with a habitual behaviour), visual and electronic reminders, pill boxes, preparing for the unexpected: for example, keeping a supply at work, in the car, in a bag, at a friend's house. • What to do if a dose is missed • Likely regimen related side-effects • What to do and how to access help if side-effects occur • The nurse can provide the first port of call and access to help by encouraging re-presentation and providing telephone access and support

Of the 170 (49%) that occurred during a week day, 10% were between the hours of 08:30 and 17:00; the usual operating hours of clinics that provide NPEP. Thus, emergency departments assess the majority of presentation for NPEP and nurses who work in emergency departments are a particular group who need to be PEP literate.

In addition to a minimum PEP skill set, nurses provided with adequate training, support and resources are also capable of independently assessing and managing patients requiring ART as PEP.

The National NPEP Guidelines provide comprehensive information about risk assessment, in brief:

- an HIV risk event needs to have occurred
- the person with whom the event occurred needs to be HIV positive or from a population likely to have HIV
- the patient needs to present for assessment within 72 hours of the event

Table 14 presents a simple flow-chart which can be used as a NPEP risk assessment tool.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Table 14: Non-occupational post-exposure prophylaxis (NPEP) risk assessment#

Consider NPEP if conditions 1, 2 and 3 are met
1 High-risk exposure • Condomless receptive intercourse (anal or vaginal)ⁱ • Condomless insertive intercourse (anal or vaginal) ⁱ • Use of contaminated injecting equipment ⁱ Condomless means no condom used or condom slippage or breakage Notes: Condomless receptive oral intercourse with ejaculation MAY BE CONSIDERED as a high-risk exposure providing the source is known to be HIV positive with a detectable HIV viral load and there is oral mucosal disease or an open lesion in the mouth or throat. Significant exposure of non-intact skin with blood, sperm or vaginal fluids MAY ALSO BE CONSIDERED as a high-risk exposure providing the source is known to be HIV positive with a detectable HIV viral load.
2 Source is known to have HIV infectionⁱⁱ OR Source is likely to be at increased risk of HIV • Men who have sex with men • Heterosexual person who injects drugs • A person from a high HIV prevalence country (HIV prevalence > 1.0%)ⁱⁱⁱ • A sex worker OUTSIDE of Australia ⁱⁱ NPEP is NOT RECOMMENDED following insertive or receptive anal, vaginal or oral sex, sharing of needles or other injecting equipment, and mucous membrane and non-intact skin exposure when the source's viral load is KNOWN to be undetectable – this is provided the source is known to be compliant with medication, attends regular follow-up and has no intercurrent sexually transmissible infection (STI). ⁱⁱⁱData available at: http://aidsinfo.unaids.org/
3 The client presents within 72 hours of exposure
1 + 2 + 3 = NPEP

For a comprehensive guide to risk assessment see the Australian National NPEP guidelines available at: <https://pep.guidelines.org.au/>

NPEP does not always prevent HIV acquisition. The time to first NPEP dose, incomplete NPEP adherence, continued HIV risk behaviour and primary ART resistance have each been linked to NPEP failure.^{(12) (13)}

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Time to first dose

NPEP appears to be most effective when administered as soon as possible after exposure. In macaque monkeys, tenofovir initiated within 24 hours of a simian immunodeficiency virus (SIV) challenge provided 100% protection from infection vs 50% and 25% when initiated at 48 and 72 hours, respectively.(14) In seven human cases of seroconversion following NPEP, the median time from exposure to first dose of NPEP medication was 45.5 hours (range 14 – 72.4 hours) and three of the seroconversions to HIV in this series initiated NPEP after 48 hours post exposure although this difference was not statistically significant.(12) Nurses should be aware of the critical nature of time with regard to PEP, educate accordingly, facilitate rapid referral if required and, in emergency departments, allocate a high triage priority to patients who present for PEP.

Incomplete adherence

Intolerable side-effects result in many clients failing to complete the prescribed course of NPEP. In a meta-analysis of PEP adherence, completion rates were 57% overall and 67% in MSM.(15) Toxicity driven discontinuation was commoner with three-drug regimens than with two-drug regimens (2% vs 9% respectively).(16) The World Health Organization (WHO) recommends that three antiretroviral drugs be universally used(17).

Given that between one half and one third of clients do not complete the prescribed course principally because of side-effects, the choice of safe, tolerable drugs for use in NPEP is paramount and nurses have an important role in supporting clients on PEP who experience side-effects (see Table 12). In Australia, Truvada (emtricitabine and tenofovir disoproxil fumarate) with the integrase inhibitor raltegravir is widely used as three-drug NPEP. In men who have sex with men, it has been shown to be well tolerated with high rates of on-drug adherence, treatment completion and, were a protease inhibitor the third drug, a low risk of potentially dangerous drug reactions.(18) More recently, Truvada with the non-nucleoside reverse transcriptase inhibitor (NNRTI) rilpivirine and Truvada with the integrase inhibitor dolutegravir have both been evaluated as three-drug HIV postexposure prophylaxis in men who have sex with men; both have also demonstrated low toxicity, high adherence, high completion rates and the added convenience of once-daily dosing.(19) (20)

Continued risk

NPEP use is a good indicator of future HIV risk and acquisition. Australian men who have sex with men who have ever used NPEP are around three times more likely to eventually acquire HIV infection when compared to men who had never used NPEP.(22) This heightened risk is less about drug failure and more about inability to modify risk or indeed a negative past experience while on NPEP. The importance of carefully evaluating and choosing the best agents to use as NPEP has been discussed. By employing a variety of behavioural interventions, sexual risk (as measured by condomless anal sex) in men who have sex with men can be reduced, at least in the short term, by about third.(23) So referral to appropriate services of men who have sex with men interested in addressing risk behaviour remains important in the new era of ART as prevention. NPEP initiation after a risk event is usually a stressful time and clients often reflect on their risk behaviours thus presenting an opportunity for brief intervention and referral. While behavioural interventions in men who have sex with men interested in change are effective, referral of men who have sex with men uninterested or ambivalent about change is not. Lecturing and scare tactics are equally unproductive. Nurses have an important role in providing a positive, non-judgmental and enabling environment. 'I'm really glad you've presented for assessment', 'I'm really pleased you've started (re-started) PEP' are positive and affirming ways to start a client PEP encounter. An HIV-negative man who has sex with men who has difficulty consistently

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

using condoms who is deterred from using NPEP because of health-care provider attitude or censure may become an HIV-positive man who has sex with men who has difficulty consistently using condoms.

- NPEP has been the predominant use of ART as prevention in HIV-negative Australian men who have sex with men and others at high risk of HIV infection, however pre-exposure prophylaxis (PrEP) (see below) has the potential to change this situation. NPEP will still, however, have a place as:
 - a gateway to PrEP
 - an adjunct to PrEP in the context of poor adherence and a high-risk HIV event
 - an option for men who have sex with men who are not at high or imminent risk of HIV acquisition (should use PrEP) but who still have intermittent risk events
 - a risk reduction strategy for men who have sex with men who choose not to use PrEP
 - a risk reduction strategy for men who have sex with men unable to use continuous PrEP because of the potential for toxicity (bones/kidneys) related to long-term use.

HIV pre-exposure prophylaxis (PrEP)

More recent Australian clinical guidelines on PrEP are available.

Read the PrEP guidelines: <https://unifiedhiv.wpenginepowered.com/prep-guidelines/introduction/>

Up to 1:8 Australian men who have sex with men has HIV infection.(23) High levels of adherence to daily co-formulated TDF/FTC has been shown to be highly effective at preventing HIV infection in populations at high risk of HIV acquisition (Table 11).(24)

It is estimated that 20% of gay men in Sydney are now taking PrEP the vast majority gaining access through 'The expanded PrEP Implementation in Communities in NSW study' (EPIC-NSW); an open-label implementation study of the use of co-formulated TDF/FTC to prevent HIV. The study ran from March 2016 and closed to recruitment in April 2018. Pre-exposure prophylaxis for HIV was then listed on the Pharmaceutical Benefits Scheme (PBS) on 1 April 2018. Pharmaceutical Benefits Scheme (PBS) subsidised PrEP prescription data outlined that between 1 April 2018 and 31 December 2023, 74,597 people (97.5% male) were dispensed PBS-subsidised PrEP at least once.(25)

PrEP using daily co-formulated TDF/FTC is approved by the Australian Therapeutic Goods Administration (TGA) and available through the Pharmaceutical Benefits Scheme (PBS). National PrEP Guidelines have been published.(26) In addition to access via implementation projects and the PBS, generic co-formulated TDF/FTC PrEP can be legally imported for personal use in Australia and is currently cheaper than the cost of a PBS prescription at \$39.50/30 days for non concession card holders). Various websites offer access to PrEP via self-importation and some offer free access for those unable to afford PrEP via a coupon system e.g. PAN (PrEPaccessNOW) at: <https://www.pan.org.au> As with any on-line purchase, caveat emptor applies. Only reputable sites verified and recommended by AIDS organisations or established Australian PrEP providers should be used for on-line purchases.

Potential risks of PrEP

Daily co-formulated TDF/FTC used as part of an HIV risk-reduction strategy is not itself without risk, mainly to the kidneys and bones. Decreases in renal function have been documented, and occasional cases of acute renal failure, including Fanconi syndrome, have occurred among people with HIV infection using tenofovir (TDF) containing regimens.(27) An estimated glomerular filtration rate (eGFR) less than 60 mL/

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

min/1.73m² precludes daily use of co-formulated TDF/FTC as PrEP and 3-monthly check of renal function is recommended. People on daily co-formulated TDF/FTC should be advised against concurrent use nephrotoxic drugs for example, regular use of non-steroidal anti-inflammatory drugs.

Creatine supplements (thought to improve strength, increase lean muscle mass, and help the muscles recover more quickly during exercise) are commonly used by gay men and can cause an artefactual increase in serum creatinine with the commensurate drop in eGFR. Creatine supplementation use should be explored when assessing decreasing renal function in gay men on PrEP.

Decreases in bone mineral density (BMD) in the region of 3-4% have been observed in people with HIV infection treated with ART including tenofovir disoproxil fumarate-containing regimens.(28) Serial dual-emission X-ray absorptiometry (DEXA) scans on a subset of men who have sex with men in a randomised, placebo-controlled trial of Truvada PrEP trials determined that when comparing those persons randomised to receive PrEP medication and those randomised to receive placebo a small but statistically significant (approximately 1%) decline in BMD can occur during the first few months of PrEP which either stabilises or returns to normal. (8) There was no increase in fragility (atraumatic) fractures over the 1-2 years of observation in these studies. In contrast, in a small study of 34 men who have sex with men on daily Truvada as PrEP, about 50% had more than a 5% loss in BMD at one or more bone sites through 12 months of follow-up.(29) A lack of a control or placebo group and no data on other causes for low BMD mean that these data should be interpreted with caution but the results do raise the need for further investigation and education for those taking PrEP about maintaining good bone health.

Nurses' roles in PrEP

PrEP use in Australia as part of an individual and population HIV risk reduction strategy is now wide-spread. Nurses have an important role to play (Table 15).

Access to PrEP is crucial to realising its benefits. Nurses should be aware of those not currently benefiting from PrEP (younger men and those born overseas and without access to Medicare) and assess their barriers to and options for access.

Adherence to the PrEP dosing schedule is also crucial to realising its benefits. Those who most need PrEP may well be those who most struggle to maintain these high levels of adherence. They will be men who have sex with men (or others) with significant alcohol or other drug issues or significant mental health problems. Rather than exclude these vulnerable groups from PrEP access, because of fears about poor engagement and adherence, ways should be found to support the adherence required. In the IDU Bangkok PrEP study, participants received Truvada by directly observed therapy (DOT) 86% (SD 25%) of the time and were compensated for travel and the time required by the study procedures.(30)

Nurses can and ought to have a pivotal role in exploring and providing innovative methods of PrEP medication adherence support in marginalised, vulnerable populations which could include DOT, other forms of highly supported therapy and the provision of financial incentives.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Table 15: The nurse's role in pre-exposure prophylaxis (PrEP)

• Providing a nurse-led PrEP service • Ensuring that those at risk know about PrEP and current pathways to access in Australia • Referring onwards to providers who can facilitate PrEP access • Adherence education and support ◦ The need for a high level of adherence to the regimen and dosing schedule ◦ Choosing the optimum dosing time based on the client's routine work and leisure patterns including discussion around the dosing window – a rigid, fixed time to dose sets clients up to miss a dose and fail ◦ Strategies to assist adherence – teaching cueing (the act of associating pill taking with a habitual behaviour), visual and electronic reminders, pill boxes, preparing for the unexpected: keeping a supply at work, in the car, in a bag, at a friend's house, borrowing from a friend ◦ What to do if a dose(s) is/are missed ◦ For vulnerable groups, intensive support, case management, directly administered or observed therapy (DOT), partial-DOT, financial incentives. • Education about maintaining healthy bones • How to access help if unexpected side-effects occur ◦ The nurse can provide the first port of call and access to help by encouraging re-presentation and providing telephone access and support
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Conclusion

Antiretroviral therapy as prevention is currently front and centre stage. Nurses have a key role in service provision, education, support, and innovative research as NPEP and now PrEP assume a more prominent role in HIV prevention.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Evolving roles of nurses in HIV care

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Acknowledgement: Emily Wheeler: Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine (ASHM) co-authored the first edition of this section.

Last Reviewed: June 2024

Nurses have been involved in varying capacities in supporting people with human immunodeficiency virus (HIV) since the beginning of the HIV epidemic in the 1980s. As the epidemic has evolved from one of the greatest public health crises of the twentieth century along the chronic disease trajectory to a largely treatable and preventable chronic condition, so too has the nursing response. **(1)(2)** This section seeks to explore the evolving models of nursing care and roles within the HIV sector in Australia and internationally.

National context

Nurses, alongside doctors, allied health professionals and peer workers, working at the forefront of HIV care in Australia in the early years of the epidemic, faced a highly politicised and stigmatising landscape given the nature of the illness and the already marginalised affected population. **(1)** With no precedents, the HIV nursing models that emerged were shaped by the response the crisis demanded, creating a diverse range of nursing roles and a strong, flexible professional specialty. **(2)** This challenging working environment has been attributed to the strong alliances formed between health professionals, creating the cohesive and resilient sector that still exists today. **(1)(2)**

In this largely collegial working environment, nurses across all areas work collaboratively with HIV specialist general practitioners, infectious disease or immunology physicians, HIV specialist pharmacists, social workers and other allied health professionals and peer workers to provide holistic, equitable HIV care. HIV specialist nurses work across a range of areas including:

- Community and domiciliary nursing services such as Bolton Clarke, Silver Chain, Sydney District Nursing Service
- General practice and community health
- Acute and subacute hospital in-patient and out-patient care; Hospital Admission Risk Programs
- Youth, maternal and child health
- Refugee health.
- Custodial settings
- Sexual health services
- Clinical trial research

Given the differing levels of complexity among patients, nursing roles vary considerably between settings. Nurses across the sector can experience differing levels of acuity for the same patient based on the setting from which they are providing care, whether it be seeing that patient at a routine GP follow-up appointment or undertaking a home visit through a community nursing program. A strength in the collegial working environment of the HIV sector is the ability for nurses across the spectrum of roles to support and educate one another to ensure the best patient outcomes. The experiences of nurses in the HIV sector in a well-resourced

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

metropolitan tertiary setting will for example, be entirely different to that of a nurse providing HIV care in a remote or rural setting, however each have much to offer the other in terms of collaboration and collegiate partnerships. This approach can be conferred to other sectors not traditionally involved in HIV care who may now be involved in HIV prevention and subsequent new HIV diagnosis or ongoing management.

The Pharmaceutical Benefits Scheme (PBS) approval for both nurse practitioner and general medical prescribing of Pre- Exposure Prophylaxis (PrEP) for the purposes of HIV prevention in 2018 resulted in a rapid up-take of the latest tool in the HIV prevention tool kit. (3) This shifted what was once a specialty medication accessed through a clinical trial setting, to any setting appropriate, dramatically upscaling accessibility for patients, as well as opportunities for nurses outside the traditional HIV sector to upskill and expand their HIV knowledge around prevention, new diagnosis, and concepts such as undetectable equals untransmissible. (4)

The Aged Care sector is a worthy consideration for the expansion of HIV education and collaborative cross-sector partnerships among nurses given the ageing population of People Living with HIV (PLHIV). Many long-term survivors have now lived with HIV for close to forty years, a testament to the success of antiretroviral therapy (ART) among other interventions and are transitioning towards aged care services and residential aged care facilities (RACFs). A local protocol to support nurses and staff in RACFs to deliver considered, appropriate care for PLHIV was developed with this in mind by Murray et al in 2014. (5)

Since the first edition of this publication in 2016, Australian nurse practitioners were granted approval to prescribe PBS subsidised antiretroviral therapy for HIV management under the s100 program (April 1, 2020). This greatly expands access and opportunities for patients, and nurse practitioners in this area (6)(7).

Since HIV in Australia is increasingly being managed as a chronic disease, nurses have a significant role in care delivery, comparable with chronic disease management care for other conditions. The role of nurses in leading chronic disease management approaches has been shown to be feasible and acceptable to both clients and fellow health professionals (8). Nurses are the largest health profession in Australia and are effective in managing chronic diseases, including HIV. With increasing healthcare costs demanding reform, there is a need to continue to support nurses to care for those affected by HIV across all healthcare settings and all levels of nursing practice to prevent avoidable hospital admissions and improve patient outcomes.

Principles

The principles underpinning nursing in this specialty sector have been translated into practice standards by the Australasian Sexual Health and HIV Nurses Association (ASHHNA). (9) These standards were developed and updated, by referencing current national and international sexual health and HIV nursing competency and practice standards. The standards account for differences in practice for both the registered nurse and advanced practice registered nurse and seek to clarify key areas under seven domains. (9) The domains incorporate the Nursing and Midwifery Board's registered nurse standard for practice and were designed to be utilised alongside these standards 'to provide a platform for practice development and advancement in sexual and reproductive health and HIV nursing' for both existing and new members to the sector. (9) While these standards differ from the Nursing and Midwifery Board of Australia (NMBA) nurse practitioner standards for practice, the underlying principles can be applied to nurse practitioner practice across the sector. The domains in the ASHHNA Competency Standards are:

Standard 1: Thinks Critically and Analyses Nursing Practice

Standard 2: Engages in Therapeutic and Professional Relationships

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Standard 3: Maintains the Capability for Practice

Standard 4: Comprehensively Conducts Assessments

Standard 5: Develops a Plan for Nursing Practice

Standard 6: Provides Safe, Appropriate and Responsive Quality Nursing Practice

Standard 7: Evaluates Outcomes to Inform Nursing Practice (9)

The values that guided the development of the practice standards were born out of the turbulent medical, social, and political history of HIV and the complexities that faced those affected. (2) A hybrid model of care was identified by combining a social and medical model approach, one that acknowledges the social determinants of health while also addressing disease specific requirements. This model is grounded in the principles of primary health care and champions social justice by seeking to provide advocacy, health promotion and accessible, equitable and holistic health care for all.

International context

There are vast differences between HIV nursing models nationally and internationally due to epidemiological variability, differences in health system infrastructure including the scope of nursing practice and access to resources worldwide. The models of care that exist reflect the need of the population they were developed for and change according to the needs of that population.

International models of HIV nursing care are similar in resource rich settings to the models existing in Australia, as demonstrated by the translation of HIV and sexual health guidelines from the United Kingdom into an Australian context. (9) These include similarities in access to care through hospital, outreach and collaborative care models and an emphasis on holistic HIV treatment and prevention with the contribution of nurses from all levels of practice highly valued (10-12). Nurse practitioners and nurse prescribers are well established in the HIV sector in Canada, the United States of America, and the United Kingdom, with pioneering HIV nurse practitioners from the UK first practising during the height of the AIDS crisis in the 1990's (13). Advanced practice roles have taken longer to develop in the Australian context, and this may perhaps be more reflective of barriers imposed by State- based nursing legislation and the structural barriers to nurse practitioner expansion more broadly, such as perceptions around cost-effectiveness and fit within the existing healthcare framework, rather than the HIV sector itself. (14)

Just as in resource-rich settings, resource-poor settings typically operate in collaborative care models, although the nuances between the models vary and appear largely driven by workforce shortages and a corresponding focus on task-shifting, and an economic imperative in resource-poor settings. This, coupled with the challenges associated with patients lost to follow-up, political instability, food insecurity, co-infection with malaria, tuberculosis and other infectious diseases, and limited access to HIV treatment and prevention strategies equate to a vastly different and challenging nursing environment. (15) Task shifting, or the up-skilling of non-physician healthcare workers, has been identified as an effective and economically viable way to manage the human resources crisis affecting HIV care in resource-poor countries in sub-Saharan Africa. (16) (17) This practice extends to up-skilling nurses to nurse practitioner-type roles, and community health workers to undertake nursing duties to increase access to HIV treatment, care, and prevention strategies. (18)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

With the human resources crisis affecting health care in resource-poor settings only further exacerbated by the advent of the COVID-19 pandemic, and ever ever-more present reality of global warming and the subsequent threat of mass population displacement, there will surely be a role for Australasian nurses to develop and strengthen relationships with nurses in resource-poor settings to support the HIV treatment and prevention scale-up efforts already in place. (19-22).

Summary

Uniting these differing models of health care is the underlying commitment to reduce the burden of HIV-related disease on those affected and continue to scale up the response. Despite a vastly different landscape in HIV nursing in Australia today compared to when the sector developed forty years ago, the same guiding philosophy and commitment to primary healthcare principles exist in a sector that remains as bonded as ever.

Australasian HIV nursing organisations

[Australian Sexual Health and HIV Nurses Association \(ASHHNA\) Inc](#)

[Australian and New Zealand Association of Nurses in AIDS Care \(ANZANAC\)](#) via Facebook

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Nursing ethics in the care of people with HIV

Elizabeth Crock: Bolton Clarke HIV Program, Melbourne

Acknowledgements:

Donna Tilley: Western Sydney Local Health District, Sydney (first edition)

Last Reviewed: June 2024

This chapter introduces ethical principles and decision-making in practice and highlights key ethical issues that can arise in the care of people living with HIV.

- Introduction and background
 - What is the purpose of nursing and midwifery ethics?
- Stigmatisation and discrimination in healthcare
 - Impact of HIV-related stigma and discrimination
 - Strategies for nurses to address discrimination.
- Disclosure of HIV status in health care and the perceived 'right to know'.
- Confidentiality
- Informed consent
- Quality of life, advance care planning and end-of-life decision-making
- Emerging issues and their ethical implications – Pre-exposure prophylaxis
- HIV and ethics – case example

Introduction and background

Nurses and midwives work along the continuum of HIV care, from prevention and testing, engagement in care, sexual and reproductive health, and long-term management to palliative care. They work in a wide range of environments, caring for people with HIV across the lifespan. Regardless of the setting, ethical issues arise in clinical practice every day, and can often be relatively simple to deal with (1). In HIV nursing and midwifery practice, ethical issues may be extremely complex and difficult to resolve (1). It is therefore imperative that both professions 'have the knowledge, skills, and 'right attitude' to be able to respond to the issues in an appropriate, ethically warranted and just manner' (1, p. 147).

Ethics is the branch of knowledge that deals with moral principles, or ways of thinking about, understanding, and examining 'how best to live a moral life' (1). The word 'ethics' is derived from the Greek *ethikos*, meaning custom or habit (2, 3). The equivalent Latin term is 'mores' (custom or habit) from which the term 'moral' derives, despite popular usage being somewhat confusing; that is, some people interpret the word 'morality' as relating to personal or private values (3). In this section, the terms 'ethics and 'morality' are used interchangeably, there being no philosophically significant difference between the two (3).

In 1991, ethicist Fredrick Reamer observed that the HIV epidemic has tested 'the moral mettle of [health] professionals in a way perhaps that no prior public health crisis has' (4). Despite much progress since then, this statement remains true. HIV as a disease and as a social phenomenon has challenged health professionals to examine their ethical/moral values and to uphold those of their professions in the face of profound stigmatisation of those affected (4).

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Ethical issues such as those relating to privacy and confidentiality, access to new or experimental treatments, reproductive rights, and the rights of Lesbian Gay Bisexual Transgender Intersex and Queer (LGBTIQ) people have taken on a heightened emphasis throughout the HIV epidemic. Moreover, the inextricable link between human rights violations and the spread and impact of HIV on individuals and communities is now well understood (5).

What is the purpose of nursing ethics?

Ethical frameworks for nursing and midwifery practice provide guidance on identifying ethical issues, making ethical decisions, and taking action.

The International Council of Nurses (ICN) Code of Ethics for Nurses is the guiding document for ethical decision-making for nurses in Australia (6). The code identifies ethical standards and values agreed to by the profession. It is a tool for nurses to reflect on how to apply ethics within their domains of practice. The elements within the code describe the human rights standards and ethical values nurses are expected to uphold. Similarly, The International Confederacy of Midwives Code of Ethics for Midwives guides the ethical practice of Midwives in Australia (7).

The ICN Code of Ethics contains four principal elements that provide a framework for ethical conduct:

1. Nurses and patients or others requiring nursing care/services.
2. Nurses and practice
3. Nurses and the profession
4. Nurses and global health

Under each element, standards and values guide practice.

The standards include:

- promotion of an environment in which the human rights, values, customs and spiritual beliefs of the individual, family, and community are acknowledged and respected.
- advocating for equity and social justice in resource allocation, access to health care and other social and economic services.
- holding in confidence personal information and respecting the privacy and confidentiality and interest of patients in the lawful collection, transmission storage and disclosure of personal information.
- using judgment regarding individual competence when accepting and delegating responsibility
- ensuring that the provision of care and use of technology is compatible with the safety, dignity, and rights of people.
- active participating in developing research-based professional knowledge that supports evidence-informed practice.
- contributes to an ethical organisational environment and challenges unethical practices and settings.
- sustaining collaborative and respectful relationships with co-workers (6)

Ethics is framed by the principles and standards of human rights and 'the inherent dignity of all members of the human family', recognised as 'the foundation of freedom, justice and peace in the world' (8, p.1). The Universal Declaration of Human Rights includes civil and political rights, such as the rights to life, liberty, free speech, and privacy. It also includes economic, social, and cultural rights – the rights to social security, health, and education (8).

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Alongside the concept of human rights, nursing ethics appeals to the principles of justice, autonomy, beneficence (doing good) and non-maleficence (avoiding harm) when justifying ethical decision-making (3, p. 12). Midwifery ethics also appeals to these principles, acknowledges women as persons with human rights, and seeks justice for all people and equity in access to health care (7).

Stigmatisation and discrimination

The most profound ethical problem that arises in the field of HIV is stigma and its repercussions, and it therefore warrants addressing first.

The word *stigma* comes from the Greek word meaning a mark of disgrace or shame (9).

Stigmatisation can lead to discrimination resulting in unequal or unjust outcomes (10).

HIV-related stigma is defined by the Joint United Nations Programme on HIV/AIDS (UNAIDS) as 'negative beliefs, feelings and attitudes toward people living with HIV, groups associated with PLHIV and other key populations at higher risk of HIV' (11).

HIV-related discrimination has been defined as:

Unfavourable treatment on the basis of known or imputed HIV status; action or inaction that results in people being denied full or partial access to otherwise generally available services or opportunities because of known or imputed HIV status (12).

Discrimination can be further described as direct and active (intentional and planned) – such as the placing of alerts on an HIV-positive person's clinical file or refusing to treat or care for a person with HIV. Alternatively, discrimination may be indirect and passive – such as the establishment of rules, policies, or conditions that in themselves do not appear discriminatory but result in discrimination against those who are unable to meet the required conditions (13). For example, generic intake practices where a person is asked about their diagnosis over the phone can indirectly discriminate by reducing access for people with HIV who are reluctant to disclose their HIV diagnosis to strangers and who may, therefore, avoid contacting a service.

Internationally and within Australia, numerous studies have found that people with HIV experience discrimination by nurses and other health workers, ranging from prejudicial attitudes, lack of eye contact, brusque speech, the use of excessive infection control precautions or inconsistencies around the use of standard precautions, denial of care, modifying care (for example, not taking blood, not touching patients) (14).

Women with HIV who are pregnant or trying to become pregnant have been judged more harshly than others and have been frequently labelled drug users or sex workers, with assumptions being made about their lives (14). In some countries, women living with HIV have been forcibly sterilised or coerced to terminate their pregnancy and undergo other coercive reproductive practices in health care (15, 16). Human rights abuses such as these derive from entrenched HIV-related stigma.

The 2022 Australian HIV Futures Survey indicated that more than one-third (36.6%) of the respondents living with HIV reported at least one experience of HIV-related stigma or discrimination in the past 12 months. 29.8% of those surveyed reported they had been treated differently by a healthcare worker due to their HIV in the past 12 months (17). Common forms of stigma and discrimination include avoidance, confidentiality breaches, and the use of excessive infection control measures.

Experiences of stigma and discrimination against PLHIV are common within health settings; thus, the care and treatment of people living with HIV remains an important area of concern for nursing and midwifery ethics.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Impact of HIV-related stigma and discrimination

Stigmatisation and discrimination are barriers to people accessing HIV testing and treatment and are associated with poor mental and physical health outcomes (18). Fear of discrimination due to negative past experiences can deter people with HIV from accessing services. Stigma can also be internalised – a person feels shame about themselves (based on the stigma), expects or fears discrimination to occur, and may avoid services (14).

The health consequences of HIV-related stigma include increased rates of depression, diminished self-esteem, mental health problems, and poor physical health. Ultimately, stigmatisation and discrimination affect people's access to health care (14). As such, stigmatisation itself is a breach of ethics: it leads to unjust discrimination in reducing people's access to healthcare, which is a basic human right.

Strategies for nurses to address discrimination

There is a lack of high-quality evidence on reducing HIV-related stigma in healthcare, and a need for randomised controlled trials using validated instruments that can measure stigma and discrimination (18). Nyblade et al note that interventions to address HIV-related stigma in nursing and midwifery practice need to focus on individual, environmental and policy levels (19).

- Nevertheless, there are numerous documented strategies that can help change prejudicial attitudes and promote ethical care of PLHIV:
- Role modelling and demonstrating kindness, core actions to support care that upholds human rights (20)
- Educating other healthcare workers and the community about HIV, including training popular opinion leaders (18)
- Providing education about standard precautions; educational interventions to address HIV-related fear, dispel myths and clarify misunderstandings about transmission risks (21, 22)
- Leading discussions about ethical issues and providing an open forum for questions and clarification of concerns.
- Moral consciousness-raising among colleagues about the effects of stigma and discrimination (23)
- Using HIV-positive speakers in healthcare worker education (24-26).

Nurses and midwives need to be very mindful of the impact and effects of self-stigma or internalised stigma. Notably, internalised stigma acts as a barrier to medication adherence and clinic attendance and may have other detrimental effects on the HIV care continuum (27). It is therefore also important to measure stigma to enable us to enact measures to address it, to achieve quality of life and not only treatment goals (28).

Disclosure of HIV status within health care and the 'right to know'

Healthcare staff may claim they have a 'right to know' a patient's HIV status to 'protect themselves or others from infection'. There is no legal 'right' for a health professional to know a person's medical diagnosis. Further, it is well established that the consistent use of Standard Precautions is the best way to protect staff in healthcare settings from infection (29).

PLHIV are not legally obliged to disclose their HIV status to health professionals. Disclosure without consent can only be justified ethically and legally in certain circumstances: if there is an imminent risk to another person's health or safety or if it is directly needed for the treatment or care of that person, in accordance with local laws (30).

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Conversely, it is beneficial for treating professionals to have the full clinical picture to provide optimal treatment and avoid, for example, drug interactions or missed diagnoses of HIV-related conditions (30). Best practice involves creating a supportive environment in health services, where people can feel safe and confident in disclosing their HIV status.

For further information on this topic including clarification of legal aspects in the Australian setting on a state-by-state basis, see Cameron, 2014 (31).

Confidentiality

The principle of confidentiality is closely related to the concept of privacy and is both a legal and an ethical requirement (3). While laws about confidentiality and ethical obligations apply to people with all health conditions, confidentiality in HIV nursing and midwifery has acquired a greater significance, highlighting pre-existing weaknesses within the healthcare system.

Ethical management of information involves respecting privacy and confidentiality without compromising health or safety. Considerations for nursing and midwifery practice include implementing strategies to avoid inadvertent breaches of confidentiality – such as:

- ascertaining to whom the patient has or has not disclosed their HIV status and communicating and documenting this information.
- developing sound policy and systematic procedures requiring staff to check who is present with the patient when discussing discharge plans or medications to ensure HIV status is not disclosed.
- using numbers instead of names in clinic waiting rooms
- informing patients about limitations to confidentiality. For example, this could entail advising them of the legally mandated requirement for the nurse to inform child protection authorities if they disclose sexual contact with a minor (32).

Informed consent

Informed consent is a central ethical and legal principle in the provision of health care, including nursing and midwifery care. The requirement to obtain informed consent applies to all health interventions with certain well-defined exceptions (such as life-threatening situations) (2). The requirement for consent to be 'informed' is justified on the ethical grounds of:

- avoiding harm, unfairness, and exploitation, and
- protecting a person's autonomy or self-determination (2).

The requirements of informed consent include disclosure of all relevant information, comprehension (the person must understand the information being given and the implications of consent), competence (the person must be capable of making the decision), and consent must be freely given (voluntary) (2). Informed refusal can also be the outcome of the process.

For example, it is a legal requirement before undertaking HIV testing that a person provides informed consent (with rare exceptions such as where a legal order is made for compulsory testing or in emergencies) (33). This means that the person agrees to testing based on understanding the procedure, the reasons for testing and is capable of evaluating the personal implications of testing (34). In cases where routine HIV

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

testing is recommended (such as in pregnancy), informed consent should still be obtained. Breaches of the requirement to obtain informed consent can have serious consequences, including harm to patients and legal repercussions for the health worker (34).

Ethical nursing and midwifery care means treating each person as unique and assisting them to participate in informed decisions about their care (including refusing treatment or care) without disadvantage due to appearance, language, culture, religion, age, sexuality, economic status, disability, or health status. This approach ensures respect for the client's autonomy and upholds their right to informed consent.

Quality of life, advance care planning and end-of-life decision-making

Nurses can promote the rights of PLHIV by encouraging and supporting them to plan for their future care needs and treatment wishes, especially regarding end-of-life care and quality of life.

The meaning of 'quality of life' is personal and unique to everyone, encompassing physical, psychological, and social domains. It is now included as a goal in some national HIV targets (35, 36). HIV-related stigma and discrimination adversely affect quality of life (37, 38) along with other psychosocial determinants of quality of life (39).

Advance care planning addresses future healthcare needs and preferences. It records people's preferences about treatment and care decisions about care if they are no longer able to communicate these, in a clear statement to guide health professionals. Documents can include:

- Advance Care Directive
- Enduring power of attorney (medical treatment) or substitute decision-maker. (Terms can vary depending on the state or territory) (40).

While the lifespan of people with HIV on treatment is now close to that of HIV-negative people, end-of-life issues arise that require careful ethical deliberation and professional judgment. Nurses may care for patients who:

- question whether and when to stop antiretroviral therapy.
- face 'not for resuscitation' decisions.
- request assisted suicide.
- request voluntary assisted dying (VAD), where a person has medical assistance to end their life due to intolerable suffering.

These issues have both legal and ethical ramifications. Assisted suicide is illegal in Australia, and VAD is legal in all Australian states (but not territories), with strict criteria and controls. A strong grounding in ethics and ethical decision-making can assist nurses in navigating such issues with clients. Specialist advice and referral should be sought for PLHIV who raise these issues. See End of Life Directions for Aged Care for more information.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Emerging issues and their ethical implications – Pre Exposure Prophylaxis

Nurses are increasingly involved in biomedical HIV prevention including the provision of pre-exposure prophylaxis (PrEP). PrEP is the use of antiretroviral drugs taken by HIV-negative people to prevent HIV infection (see [PrEP for Prevention](#) and Biomedical prevention add link section of this resource).

As with any clinical innovation, the ethical implications of PrEP are important to consider. When first introduced, PrEP provoked controversy among bioethicists globally. Ethical debates around PrEP may concern *justice*. For example, Jay and Gostin (2012) argued that PrEP is very costly compared with alternatives, raising the ethical issue of distributive justice (40). They pointed out that the high cost and regular monitoring required could exclude people on low incomes, unstable housing, drug dependence or mental health problems, exacerbating health inequalities (40) unless PrEP is properly subsidised to ensure equity of access. In Australia, this is less of a concern due to PrEP's listing on the Pharmaceutical Benefits Scheme (PBS), but in many countries the cost is prohibitive, and availability is inequitable.

Bioethicists argue that, in resource allocation, any scheme should be equitable (41) yet, as Macklin pointed out, not all people with HIV in developing countries receive antiretroviral agents, let alone PrEP for those without HIV infection (41). The proportion of people globally on treatment now is much higher (approaching 76%) (43) than when this issue was raised. Still, Verguet *et al.* assert that PrEP is a high-cost intervention that will have maximum effect only in high-prevalence countries (where it may be less accessible) (44).

Other ethical principles of relevance to Prep *beneficence* – to promote benefits, and non-maleficence – avoid harm. There is a strong ethical claim supporting the use of PrEP to prevent HIV infection. However, this must be balanced with potential threats or harms. For example, ethical questions may be raised about PrEP's long-term safety, side effects and the development of resistance (44). In addition, with the advent of injectable long-acting treatment and PrEP, safeguards must be considered to prevent its coercive or involuntary use in marginalised populations, whilst ensuring equitable access to PrEP for those vulnerable groups who may benefit most from it (45).

There is a long history of medical mistrust amongst some groups – for instance, people with mental health problems who may have been subjected to court-ordered treatments, people who use substances, people who have been incarcerated, and other PLHIV in minority groups (46). Pregnant women with HIV can be subject to coercive practices including mandatory testing and forced treatment (47-49). Community engagement is critical to ensure PrEP can reach those most at risk (equity of access) whilst respecting their autonomy and human rights, and upholding the ethical principles of justice, respect, beneficence, and non-maleficence (46).

Nurses worldwide are central to the roll-out of treatments such as PrEP, in policy development around access, and research. PrEP programs will be optimally designed, implemented, and evaluated with the inclusion of nurses' and midwives' informed ethical perspectives, alongside those of other health professionals, PLHIV, and those most at risk. This discussion serves to emphasise the importance of examining the ethical implications of new technologies and participating in ethical inquiry, debate, and policy development in an informed and critical manner.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

HIV and ethics – Case example

A 32-year-old man was diagnosed with HIV infection 9 months ago, after presenting to a sexual health clinic for a routine sexual health screen. He attends the nursing clinic for HIV monitoring and has an undetectable viral load. You update his health history and note he is taking antiretroviral medication. You also take a sexual health history to determine if you need to offer another sexual health screen. During the sexual history interview, he tells you he has one regular female partner and casual male partners. When you ask about whether he has disclosed his HIV status to his partners, he informs you that he has disclosed his HIV status to his regular partner and is aware that as long as he has an undetectable viral load, there is no risk of sexual transmission of HIV to negative partners. See [U=U: ASHM Guidance for Health Professionals](#).

His female partner is HIV-negative; however, she is not aware he has sexual contact with men. He wants to disclose his sexuality to his female partner but is concerned about the effect it will have on his life and future.

- What effect would an HIV disclosure without consent have on the client's social supports and relationships?
- How would you maintain confidentiality about the client's sexual history if he and his partner are both attending the clinic at the same time?
- How might your personal moral beliefs influence the care you provide?
- What other ethical issues do you anticipate?

Conclusion

Ethics is at the heart of HIV nursing and midwifery, and both professions have been at the forefront of ethical practice since the start of the epidemic (50-52). Nurses and midwives must be educationally prepared and capable of contributing to and making sound moral decisions based on evidence and careful ethical deliberation. There is a continuing need for strong advocacy and ethical leadership in the HIV field, as well as research into ethical decision-making and skill development (53).

Some key issues with ethical implications have been discussed here, including stigma and discrimination, HIV disclosure, informed consent, confidentiality, and quality of life. The concepts and approaches discussed can apply to all ethical issues encountered within this challenging and inspiring specialty.

Within the collaborative, client-centred framework of the HIV sector, the nursing and midwifery professions contribute to the best outcomes for people with HIV. This is achieved through protecting and promoting human rights, individual and structural advocacy, and adhering to both professions' firm foundation in ethics.

Resources

ASHM has developed an online learning module to address systemic barriers to care, stigma, and discrimination to increase access to the health system by people at risk of or living with HIV, hepatitis B, or hepatitis C.

To access this free module, see [Removing barriers](#)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Nursing and HIV during the global COVID-19 pandemic and the emergence of Monkey pox (Mpox) infections.

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Last Reviewed: June 2024

Summary

This section discusses the intersection between HIV, COVID-19 and Monkeypox (Mpox) from a nursing perspective, highlighting important issues and strategies.

- Introduction
- Impact on Nursing and HIV Care throughout COVID-19
- Integrating infection prevention and control (IPC) measures
- Psychosocial Support and Patient Education
- Resources

Introduction

The COVID-19 pandemic has brought unprecedented challenges to health systems worldwide, affecting various aspects of health care, including HIV care. Amid this crisis, the emergence of infectious diseases such as Monkeypox (now referred to as Mpox) makes it more difficult to deliver health services, especially to vulnerable populations such as people living with HIV. Nurses play a central role in the complex intersection of HIV, Mpox and COVID-19, requiring a comprehensive understanding of nursing implications to ensure effective care.

Impact on Nursing and HIV Care throughout COVID-19

Nurses are on the front line of HIV management and provide comprehensive care that includes prevention, treatment, and support services (1). However, the COVID-19 pandemic has necessitated the use of telehealth and virtual platforms in the provision of HIV treatment. Nurses must adapt their practices to remote patient care while ensuring continuity of care and minimising the risk of contracting COVID-19 (2).

In addition, the coexistence of now referred to as Mpox) along with HIV presents unique challenges to nursing. Mpox, a zoonotic viral disease with clinical manifestations similar to smallpox, complicates diagnosis and treatment, especially in immunocompromised individuals such as HIV patients (3). People living with HIV are over-represented amongst those with Mpox (4), and those who are immunocompromised (with advanced HIV) are at increased risk of severe Mpox and death (5, 6).

Nurses must remain vigilant in recognising the signs and symptoms of Mpox, distinguishing it from other viral diseases and implementing appropriate infection control measures to prevent its spread in healthcare settings (7).

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Integrating infection prevention and control (IPC) measures

The COVID-19 pandemic has highlighted the importance of strict infection prevention and control (IPC) measures in healthcare settings (8). Nurses have an important role in implementing IPC protocols to reduce the risk of transmission of COVID-19 and prevent nosocomial infections among patients, including HIV infection and potential exposure to Mpox (9). This requires standard precautions such as hand hygiene, use of personal protective equipment, and environmental disinfection to protect patients and healthcare workers alike (10).

In addition, nurses must collaborate with interdisciplinary teams to develop customised IPC strategies that meet the unique needs of HIV and Mpox patients (11). This includes implementing a cohort protocol to minimise cross-contamination, optimising ventilation systems to reduce airborne transmission, and ensuring appropriate isolation facilities for suspected or confirmed cases (12). By prioritising IPC initiatives, nurses can improve patient safety and prevent the spread of infectious diseases in healthcare.

Psychosocial Support and Patient Education

In addition to clinical care, nurses play a key role in providing psychosocial support and patient education to individuals living with HIV and understanding the complexities of comorbidities (13). The COVID-19 pandemic has exacerbated existing social determinants of health that have increased stress, anxiety, and stigma among vulnerable populations (14). Nurses must use empathic communication techniques to respond to patients' emotional needs, promote emotional well-being, and mitigate the psychosocial impact of living with HIV amid a global health crisis (15).

In addition, patient education is important so that people can make informed decisions about their health and reduce the risk of disease transmission (16). Nurses must provide accurate and culturally sensitive information about HIV prevention, treatment, and strategies to control the spread of Mpox and COVID-19 (17). This includes promoting vaccination against COVID-19 and other preventable diseases including Mpox, promoting routine HIV testing and screening for opportunistic infections, and debunking myths and misconceptions about infectious diseases (18, 19). This will aid in preventing further marginalisation of an already vulnerable population, notably people living with HIV.

Conclusion

In summary, the COVID-19 pandemic has shaped the delivery of HIV care, requiring innovative approaches in the context of emerging infectious diseases such as Mpox. Nurses play a key role at the complex intersection of HIV, Mpox and COVID-19 by integrating infection prevention and control measures, providing psychosocial support and patient education. Using their expertise and collaboration with multidisciplinary teams, nurses can optimise treatment outcomes and mitigate the impact of infectious diseases on vulnerable populations.

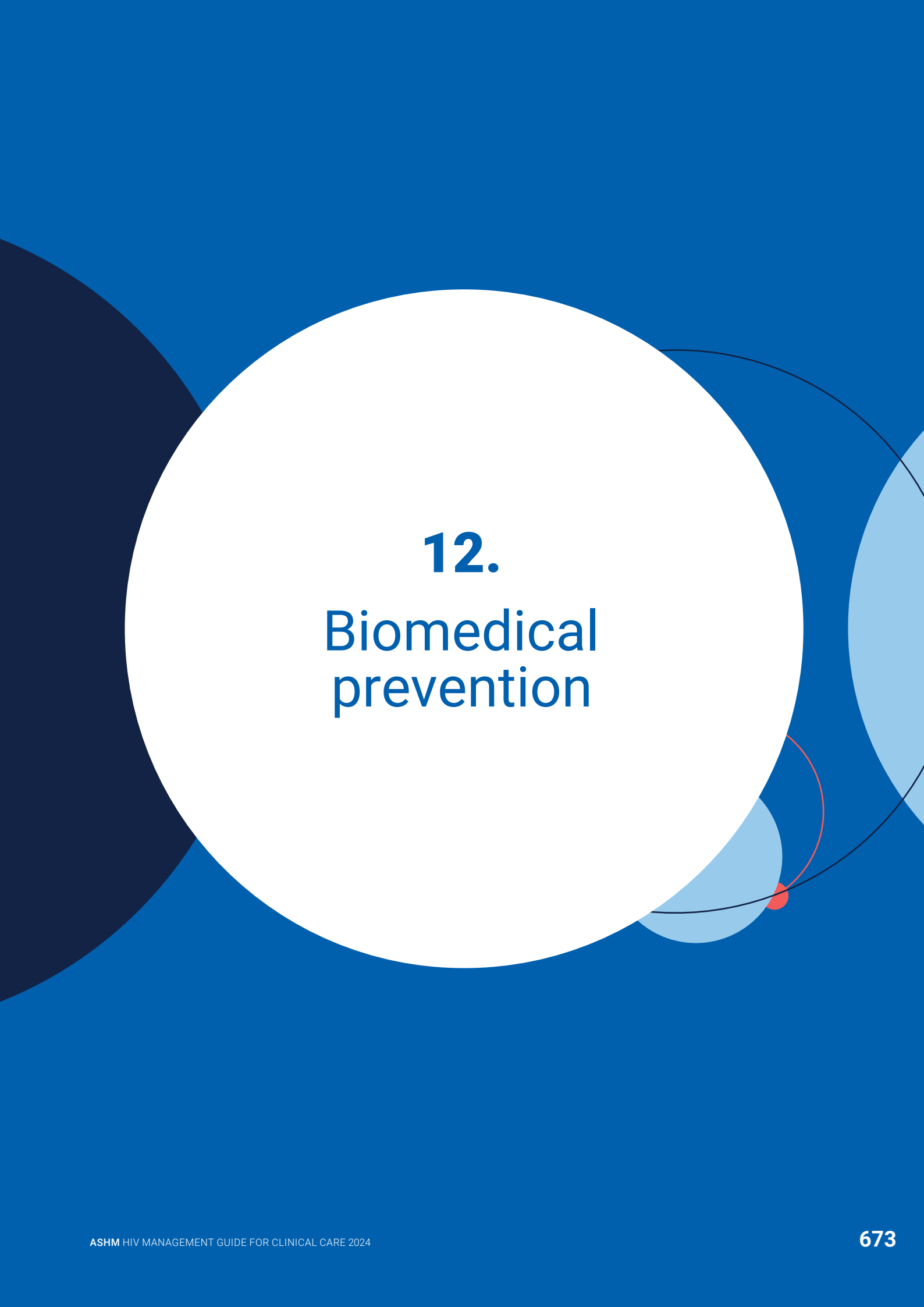
Resources

[Mpox control guideline \(NSW\)](#)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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12.

Biomedical prevention

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Biomedical prevention of HIV infection

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Last reviewed: June 2024

Background

The HIV epidemic in Australia

Australia has a concentrated human immunodeficiency virus (HIV) epidemic. In 2018, sexual contact between men accounted for approximately 70% of new HIV diagnoses; heterosexual exposure contributed 23%, and only 3% were attributable to injecting drug use alone. (1) During 2014-2018, the annual number of HIV diagnoses declined by 23% overall (1), but a more substantial decline (by 30%) was recorded among men who have sex with men (MSM), while no decline was seen in Aboriginal and Torres Strait Islander people (hereafter referred to as Indigenous), heterosexual people or those born overseas. At a closer examination, the decline in cases of HIV infection among MSM was not uniform: in the last 10 years, notifications declined by 21% in Australian-born MSM but almost doubled (from 28% to 52%) among overseas-born MSM. (1) Among heterosexuals, the notification rate in females remained stable during 2013-2017 (between 0.7 and 0.9 per 100,000) and was lower than in males (0.9 vs 7.1 per 100,000 in 2017). Among Indigenous people, the rate of HIV notifications increased by 41% between 2013 and 2016 and was mainly attributed to heterosexual sex and injecting drug use. Among female sex workers, HIV incidence remained stable at or below 0.13 per 100 person-years during 2013–2017 and was 0.13 per 100 person-years in 2017. (1) Similarly, for people who inject drugs (PWID), HIV prevalence has remained low in the past 10 years (at 2.1% in 2017, and 0.7% if MSM were excluded). However, among Indigenous men in these programs, HIV prevalence increased almost five times between 2011 and 2017 (from 0.9% to 4.2% (1)).

Overall, recent declines in HIV incidence and notifications concurred with several key initiatives at the heart of HIV biomedical prevention, specifically:

- Improved uptake in HIV testing and treatment with simpler HIV treatment regimens. Consequently, 74% of people with HIV infection in 2017 reached viral load suppression, thereby achieving zero risk of onward HIV transmission. (1)
- Widespread access to HIV pre-exposure prophylaxis. By the end of 2018, 18,530 people, of whom 99% were male, were receiving Pharmaceutical Benefits Scheme (PBS)-subsidised PrEP in Australia. (2) Largely related to PrEP implementation, a 25% decline in new HIV diagnoses was observed among MSM in New South Wales in the 12 months following the commencement of the EPIC-NSW study. (3)

The divergence in rates of HIV infection between the non-indigenous and indigenous Australians possibly relates to a number of factors, including a higher proportion of undiagnosed cases of HIV infection, sexual and drug-injecting practices and, importantly, a slower adoption of biomedical prevention strategies such as treatment as prevention and PrEP in the Indigenous population. (4) Hence, intensive HIV prevention and treatment efforts, including the use of PrEP, are required to reverse this alarming trend. (5)

In other population groups, harm reduction strategies for PWID and HIV infection, and sexually transmissible infection (STI) prevention strategies for sex workers, have been highly successful in keeping the prevalence and incidence of HIV infection at extremely low levels in Australia and among the lowest in the world.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Current health promotion and HIV prevention strategies support PWID and sex workers to maintain these achievements, while access to PrEP may expand HIV prevention options. (6)

There are no available recent data about HIV testing uptake and access to biomedical HIV prevention for temporary residents who are ineligible to access Medicare (short-term visitors, international students, skilled workers and some temporary residents awaiting decisions regarding their permanent residency as partners of citizens or permanent residents, asylum seekers and refugees).

HIV prevention strategies

MSM represent the predominant part of the Australian population at most risk of HIV infection. The most effective way to prevent the sexual transmission of HIV and other STIs is to prevent exposure. Condom use and other behavioural methods of risk reduction, such as HIV serosorting, strategic positioning, negotiated safe practices with sexual partners and clean injecting equipment, have been used by MSM throughout the HIV epidemic to reduce the risk of HIV infection. The consistent use of condoms is the mainstay of any personal, or population level, sexual risk reduction strategy. However, the overall effectiveness of condoms in preventing HIV infection during anal sex was estimated to be suboptimal at 70%(7), mainly due to frequent condom failure (e.g. breakage, slippage, leakage, and delayed and intermittent application during sex).(8) While condom use should continue to be promoted for prevention of HIV infection and STIs, this strategy alone it is unlikely to reduce the incidence of new HIV infection.

In the last decade, there have been substantial advances in the therapeutic and preventative use of antiretroviral therapy (ART), which has assumed a cornerstone role in the current strategy for HIV prevention. Table 1 summarises various preventative uses of ART and its efficacy.

Table 1. Antiretroviral therapy as prevention

Prevention strategy	Acronym	Description	Efficacy
Postexposure prophylaxis	PEP OPEP (occupational PEP) NPEP (non-occupational PEP)	28 days of ART taken as soon after, and within 72 hours of, an occupational or non-occupational (sexual or injecting drug use) actual or potential HIV exposure event	OPEP: 81% risk reduction(9) NPEP: no empirical data, strongly supported by non-human primate and prevention of mother-to-child HIV transmission studies(10) (11)
Prevention of mother-to-child HIV transmission	PMTCT	Universal antenatal HIV screening, maternal ART, caesarean section#, short-course postnatal ART for the newborn and avoidance of breast feeding	< 1% risk of vertical transmission (from a 13-40% risk without intervention)(12)
Treatment as prevention	TasP	ART to men or women with HIV infection in serodiscordant relationships	≥ 96%(13)
Pre-exposure prophylaxis *	PrEP	Daily ART (usually coformulated tenofovir disoproxil fumarate and emtricitabine – Truvada) in HIV negative men and women	Men who have sex with men: 44-92% (14) Heterosexual men and women: 75- 90% (15) IDU: 49 – 74%(16)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

ART: antiretroviral therapy; HIV: human immunodeficiency virus; IDU: injection drug user

Additional benefit of caesarean section in women on antiretroviral therapy with an undetectable viral load is not established

*Maximum efficiency is dependent on high levels of adherence and detectable drug in plasma. The range represents the overall efficacy and, in those participants with detectable drug, best efficacy. The study in IDUs used tenofovir disoproxil fumarate alone.

The following information focuses on the latest developments in HIV prevention and how clinicians, mainly general practitioners and nurses, can contribute to the assessment and care of HIV-negative men and women using antiretroviral drugs for HIV prevention. Four preventative methods will be reviewed, specifically treatment as prevention (TasP), non-occupational post-exposure prophylaxis (NPEP), pre-exposure prophylaxis (PrEP) and topical microbicides containing antiretroviral drugs.

Treatment as prevention

More recent Australian clinical guidance on U=U is available.

Read the guidance: <https://unifiedhiv.wpenginepowered.com/prep-guidelines/introduction/>

Terminology

Treatment as prevention (TasP) refers to the use of antiretroviral drugs to decrease the risk of HIV transmission. When taken consistently, antiretroviral drugs can reduce the HIV viral load in an HIV-infected individual's blood, semen, vaginal fluid and rectal fluid to a level at which blood tests cannot detect the virus (17). Such viral load is considered 'undetectable' and equivalent to viral suppression.

The concept of TasP and evidence of its public health and individual benefits

The relationship between HIV viral load and HIV transmission probability was first reported in 2000 by Quinn and colleagues based on their observations from the Rakai cohort in Uganda. (18) That study concluded that the risk of HIV transmission was negligible with serum HIV-1 RNA levels of less than 1500 copies/mL. The critical importance of HIV viral load in sexual HIV transmission was observed by other studies as well. (19) Several subsequent studies enabled further investigation of this by reporting methods for measuring the concentration of HIV in semen using quantitative culture (20), the development of a PCR technique for more accurate measurement of viral load (21) and the reduction in HIV viral load in both semen (22, 23) and female genital secretions during ART. (24)

The concept of TasP is based on the logic that ART that suppresses HIV replication should also reduce HIV transmission. In 2000, the National Institute of Allergy and Infectious Diseases/National Institutes of Health (NIAID/NIH)-sponsored HIV Prevention Trials Network (HPTN) initiated research to evaluate this concept. In 2011, the HPTN 052 trial reported that, among HIV-serodiscordant couples, ART given to the HIV-positive partner with a CD4+ T cell count <550 cells/mL decreased HIV transmission to HIV-negative partners by 96% when compared with those who started ART at CD4+ T cell counts <350 cells/mL. (25)

In 2014, the PARTNER study, in which more than 1,000 heterosexual and homosexual couples were enrolled across 14 European countries and reported 58,000 episodes of sex without a condom, observed zero transmissions where plasma HIV RNA in the HIV-positive partner was undetectable. (26) The Opposites Attract observational cohort study, conducted in Australia, Brazil and Thailand found no phylogenetically linked HIV transmissions in 343 MSM couples when the HIV-positive partner had undetectable plasma HIV RNA. (27)

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Results of these three studies confirmed the undisputed effectiveness of early ART initiation as a public health HIV prevention intervention, but its value for implementation in clinical practice was sealed by the results from the Strategic Timing of AntiRetroviral Treatment (START) trial conducted by the International Network for Strategic Initiatives in Global HIV Trials (INSIGHT). (28) At the time, the key unanswered question for TasP was whether initiation of ART early in the course of HIV infection, when risk of AIDS is low to negligible, would provide HIV-positive people with clinical benefits that outweighed the risks. For TasP to be beneficial for HIV-positive people, early ART would have to reduce their risk of developing serious non-AIDS events as well as AIDS.

Two randomised trials addressing the question of when to start ART were completed prior to START: the Haiti trial (29) and HPTN 052 (25). Both trials investigated whether HIV infection could be left untreated as long as the CD4+ T cell count remained > 200/μL. Consequently, in 2007, a global consensus was reached to commence ART at CD4+ T cell counts of < 350/μL. The specific question for the START study, when it started in 2009, was whether initiation of ART at CD4+ T cell counts of >500/μL (immediate ART) was superior to deferral of ART until the CD4+ T cell count fell to 350/μL. In addition, a broader question was whether ART could be implemented as a public health strategy (that is TasP). (30) The results of this study confirmed that immediate initiation of ART was superior to deferral of ART with regard to both AIDS-related and serious non-AIDS-related events, and no increased rate of adverse effects associated with this strategy was observed. There was no evidence that the beneficial effect of immediate ART differed by age, sex, race, region of the world, CD4+ T cell count, HIV viral load, or risk factors for serious non-AIDS events. (28) Overall, the results of this trial aligned the ART benefits to the HIV-positive individual with benefits to public health.

TasP implementation

Based on this high-quality evidence, ART is now recommended for all HIV-infected individuals upon diagnosis and irrespective of CD4+ T cell count, for both individual health and public health benefits. If used consistently as TasP, ART can eliminate mother-to-child (31), heterosexual (13) and male homosexual (32, 33) transmission of HIV infection. And, despite the lack of data for persons who inject drugs, a similar benefit can be assumed regarding prevention of HIV transmission via injecting drug use.

Undetectable is untransmittable

In recent years, support for TasP has been growing. It culminated in a consensus statement issued on 21st July 2016 that Undetectable is equal Untransmittable. (34) Undetectable = Untransmittable (or U=U) is the health promotion campaign to promote understanding of the updated clinical findings that demonstrate if someone is on ART and has a sustained undetectable HIV viral load, there is effectively no risk of sexually transmitting the virus to an HIV-negative partner. (35) Internationally and in Australia, there is a widespread support for U=U. By 5th May 2019, the U=U consensus statement had been endorsed by 910 organizations from nearly 100 countries worldwide. (36)

In July 2018, ASHM developed the evidence-based Guide for Clinicians and other Healthcare Providers to facilitate the discussion of Undetectable = Untransmittable (35).

Clinicians are likely to be the first resort for a person with newly-diagnosed HIV infection looking for information about HIV. Effectively, the U=U guide helps clinicians to promote knowledge about HIV transmission, facilitate discussions about HIV testing and viral load agreements, and to break down some of the stigma surrounding HIV, which remains a key reason for delaying testing or treatment. The guide addresses a number of important issues related to ART which are listed in Table 2.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Table 2. Issues to consider and discuss with patients on ART

- Evidence about U=U
- Implications of undetectable HIV viral load
- Patients who do not have a sustained undetectable HIV viral load
- PEP and PrEP for partners of HIV-positive persons;
- Disclosure in the context of U=U;
- Combination prevention for HIV and STI;
- Psychosocial support;
- Legal advice for individuals and legal obligations for clinicians
- References to additional resources for patients.

Post-exposure prophylaxis

More recent Australian clinical guidelines on PEP are available.

Read the guidelines: <https://unifiedhiv.wpenginepowered.com/pep-guidelines/introduction/>

Terminology

Post-exposure prophylaxis (PEP) was one of the first strategies to employ antiretroviral drugs for the prevention of HIV infection. It involves a 28-day course of antiretroviral drugs initiated within 72 hours of a potential high-risk exposure to HIV. (37)

The concept of PEP and evidence of its efficacy

Animal models showed that within 3-5 days after initial exposure, HIV replicates in the skin and mucosa before spreading through lymphatic vessels and developing into a systemic infection (38). This delay in systemic spread leaves a “window of opportunity” for post-exposure prophylaxis (PEP) using antiretroviral drugs designed to block replication of HIV.

The efficacy of PEP in preventing retroviral infection was first demonstrated in non-human primate models in the early 1990s. (39, 40) The use of occupational PEP has been recommended since zidovudine was first found to be associated with a significantly lower likelihood (by 81%) of HIV infection following percutaneous exposure among healthcare workers in a case-control study conducted in 1997. (41) For ethical reasons, PEP efficacy has never been evaluated in controlled studies in humans, but RCTs of PEP efficacy have been conducted in primate models, especially simian immunodeficiency virus (SIV) infection of macaques. (42) The use of PEP is also supported by results of the trials demonstrating the efficacy of antiretroviral drugs in preventing mother-to-child HIV transmission. (43) Over time, PEP indications have expanded to cover non-occupational exposure, including accidental exposure, consensual sex, and sexual assault.

Studies showed that HIV seroconversions are rare in MSM who complete the prescribed course of PEP. (44-46); however, adherence to the 28-day schedule is important (47,48)

Non-occupational PEP has been in wide-spread use in Australia since 1999 and is recommended by the Australian Government’s Department of Health and Ageing. (49) The Australian National PEP guidelines (50) recommend 28 days of ART with two or three drugs (at prescriber’s discretion) for an HIV transmission risk event of $\geq$ 1:15,000. Australian MSM and, to a lesser extent, people who inject drugs, are the principal target groups.

In recent years, there have been increases in PEP use among MSM, particularly in Australia (51), UK (52), and the USA (53), which could be attributed to improved knowledge and awareness of PEP, PrEP implementation

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

and increased access to antiretroviral drugs for HIV prophylaxis. However, unlike TasP and PrEP, PEP has not achieved the same the levels of uptake and public health impact because of its inherent limitations: people who were exposed to HIV have to recognise the potential risk, and request and start PEP within 72 hours of exposure. (50)

PEP implementation

Any doctor or nurse working in HIV and sexual health, family planning, an emergency department or in general practice require a minimum of PEP literacy (see Table 3). Nurses in particular have diverse roles in the assessment and provision of PEP (see Table 4).

Table 3. Minimum post-exposure prophylaxis (PEP) literacy

- What constitutes a risk event – how to assess risk
- How to access help (PEP hotlines, emergency departments, sexual health clinics, HIV care providers)
- The importance of timing – PEP should be started as soon as possible after a risk event
- The duration of therapy
- Adherence education and support
- The need for a high level of adherence to the regimen
- Choosing the optimum dosing time based on the patient's routine work and leisure patterns, including discussion about the dosing window – a rigid fixed time to dose sets patients up to miss a dose and fail
- Strategies to assist adherence – teaching cueing (the act of associating pill taking with a habitual behaviour), visual and electronic reminders, pill boxes, preparing for the unexpected: for example, keeping a supply at work, in the car, in a bag, at a friend's house.
- What to do if a dose is missed
- Likely regimen related side-effects
- What to do and how to access help if side-effects occur
- The nurse can provide the first port of call and access to help by encouraging re-presentation and providing telephone access and support

Table 4: Nursing roles in non-occupational PEP

- Management of state-wide services
- PEP assessment, initiation and care in emergency departments and sexual health and HIV care settings
- PEP hotlines
- PEP research
- Participating in development of state and national guidelines
- Providing education and support.

Most potential exposures to HIV occur outside business hours or over a weekend. In 2017, 51% of HIV risk events prompting assessment for PEP at St Vincent's Hospital, Sydney occurred on a Saturday or Sunday. Of the 170 (49%) that occurred during a week day, 10% were between the hours of 08:30 and 17:00; the usual operating hours of clinics that provide PEP. Thus, emergency departments assess the majority of presentation for PEP and nurses who work in emergency departments are a particular group who need to be PEP literate.

In addition to a minimum PEP skill set, nurses provided with adequate training, support and resources are also capable of independently assessing and managing patients requiring antiretroviral drugs as PEP.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

The National PEP Guidelines provide comprehensive information about risk assessment. In brief:

- An HIV risk event needs to have occurred
- The person with whom the event occurred needs to be HIV positive or from a population likely to have HIV infection
- The patient needs to present for assessment within 72 hours of the event

Table 5 presents a simple flow-chart that can be used as a PEP risk assessment tool.

Table 5. Risk assessment for non-occupational PEP

Consider PEP if conditions 1, 2 and 3 are met
1 High-risk exposure • Condomless receptive intercourse (anal or vaginal) • Condomless insertive intercourse (anal or vaginal) • Use of contaminated injecting equipment Notes: Condomless means no condom used or condom slippage or breakage Condomless receptive oral intercourse with ejaculation MAY BE CONSIDERED as a high-risk exposure providing the source is known to be HIV positive with a detectable HIV viral load and there is oral mucosal disease or an open lesion in the mouth or throat. Significant exposure of non-intact skin with blood, sperm or vaginal fluids MAY ALSO BE CONSIDERED as a high-risk exposure providing the source is known to be HIV positive with a detectable HIV viral load.
2 Source is known to have HIV infection OR Source is likely to be at increased risk of HIV infection § Men who have sex with men § Heterosexual person who injects drugs § A person from a high HIV prevalence country (HIV prevalence > 1.0%) § A sex worker OUTSIDE of Australia Notes: PEP is NOT RECOMMENDED following insertive or receptive anal, vaginal or oral sex, sharing of needles or other injecting equipment, and mucous membrane and non-intact skin exposure when the source's viral load is KNOWN to be undetectable – this is provided the source is known to be compliant with medication, attends regular follow-up and has no intercurrent STI. Information about high HIV prevalence countries is available at: http://aidsinfo.unaids.org/
3 The person presents within 72 hours of exposure
1 + 2 + 3 = PEP

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

For a comprehensive guide to risk assessment, see the Australian National PEP guidelines available at: <https://pep.guidelines.org.au/>

PEP does not always prevent HIV acquisition. The time to first PEP dose, incomplete PEP adherence, continued HIV risk behaviour and primary antiretroviral drug resistance have each been linked to PEP failure.(54) (55)

Time to first dose

PEP appears to be most effective when administered as soon as possible after exposure. In macaques, tenofovir initiated within 24 hours of a SIV challenge provided 100% protection from infection vs 50% and 25% when initiated at 48 and 72 hours, respectively.(56) In seven human cases of seroconversion following PEP, the median time from exposure to first dose of PEP medication was 45.5 hours (range 14-72.4 hours) and three of the seroconversions to HIV in this series initiated NPEP after 48 hours post exposure, although this difference was not statistically significant.(57) Health practitioners should be aware of the critical nature of time with regards to PEP, educate accordingly, facilitate rapid referral if required and, in emergency departments, allocate a high triage priority to patients who present for PEP.

Incomplete adherence

Intolerable side-effects of antiretroviral drugs result in many people failing to complete the prescribed course of PEP. In a meta-analysis of PEP adherence, completion rates were 57% overall and 67% in MSM.(58) Toxicity-driven discontinuation was commoner with three-drug regimens than with two-drug regimens (2% vs 9% respectively).(17) The World Health Organization (WHO) recommends that three antiretroviral drugs be universally used.(18).

Given that between one half and one third of people do not complete the prescribed course of PEP, principally because of side-effects, the choice of safe, tolerable drugs for use in PEP is paramount and health practitioners have an important role in supporting people on PEP who experience side-effects (see Table 3). In Australia, Truvada (emtricitabine and tenofovir disoproxil fumarate) with the integrase inhibitor raltegravir is widely used as a three-drug NPEP. In MSM, it has been shown to be well tolerated with high rates of on-drug adherence, treatment completion and, where a protease inhibitor is the third drug, a low risk of potentially dangerous drug reactions.(59) More recently, Truvada with the non-nucleoside reverse transcriptase inhibitor (NNRTI) rilpivirine and Truvada with the integrase inhibitor dolutegravir have both been evaluated as three-drug PEP in MSM; both have also demonstrated low toxicity, high adherence, high completion rates and the added convenience of once-daily dosing.(60) (61)

Continued risk of HIV acquisition and use of PEP

PEP use is a good indicator of future HIV risk and acquisition. Australian MSM who have ever used PEP are around three times more likely to eventually acquire HIV infection when compared to men who had never used PEP.(62) This heightened risk is less about drug failure and more about inability to modify risk behaviour or, indeed, a negative past experience while on PEP. The importance of carefully evaluating and choosing the best agents to use as PEP has been discussed. By employing a variety of behavioural interventions, sexual risk (as measured by condomless anal sex) in MSM can be reduced, at least in the short term, by about third.(63) So referral to appropriate services of MSM interested in addressing risk behaviour remains important in the new era of PEP. PEP initiation after a risk event is usually a stressful time and clients often reflect on their risk behaviours, thus presenting an opportunity for brief intervention and referral. While behavioural interventions in MSM interested in change are effective, referral of MSM uninterested or ambivalent about change in

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

behaviour is not. Lecturing and scare tactics are equally unproductive. In 2017, 79 (22%) of 358 people had > 1 episode of PEP through the Sydney St Vincent's PEP service. Re-presentation for PEP is a new opportunity to keep an HIV-negative person HIV negative and to explore and address the context of the risk. Health practitioners have an important role in providing a positive, non-judgmental and enabling environment. 'I'm really glad you've presented for assessment', 'I'm really pleased you've started (re-started) PEP' are positive and affirming ways to start a client PEP encounter. An HIV-negative MSM who has difficulty consistently using condoms and is deterred from using PEP because of health-care provider attitude or censure may become an HIV-positive MSM.

NPEP has been the predominant use of antiretroviral drugs to prevent HIV infection in HIV-negative Australian MSM and others at high risk of infection; however, pre-exposure prophylaxis (PrEP) (see below) has the potential to change this situation. PEP will still, however, have a place as:

- A gateway to PrEP
- An adjunct to PrEP in the context of poor adherence and a high-risk HIV event
- An option for MSM who are not at high or imminent risk of HIV acquisition but who still have intermittent risk events and have not started PrEP
- A risk reduction strategy for MSM who choose not to use PrEP

Pre-exposure prophylaxis

Terminology

WHO defines pre-exposure prophylaxis (PrEP) as the use of oral tenofovir disoproxil fumarate (TDF) or co-formulated TDF/emtricitabine (TDF/FTC) or co-formulated TDF/lamivudine (TDF/3TC) by HIV-negative people to prevent HIV acquisition (FTC and 3TC are considered interchangeable). In 2019, the US Food and Drug Administration approved emtricitabine + tenofovir alafenamide (FTC/TAF or F/TAF, Descovy®) as another drug that can be used for PrEP.

PrEP can be taken on a daily basis (daily PrEP) or around the time of exposure as event-driven PrEP, also known as event-based PrEP (EB-PrEP) and on-demand PrEP.

The concept of PrEP and evidence of its efficacy

The concept of using antiretroviral drugs prior to, or around the time of, risk events and is similar to that for prevention of mother-to-child transmission of HIV infection (11), PEP (50) and the use chemoprophylaxis for the prevention of other infectious diseases (e.g., malaria (64).

TDF/FTC was originally selected for PrEP because of its pharmacologic and pharmacokinetic properties. According to prescribing information (65) it has potency against wild-type HIV, but low potential of selecting for TDF-resistant mutants, low likelihood of metabolic/mitochondrial toxicity, and a pharmacologic profile supporting daily use. Adverse reactions, particularly new onset or worsening of renal disease, are extremely rare. Evidence for the effectiveness of both daily and intermittent TDF/FTC PrEP regimens was first obtained from animal studies, including macaque models infected with SIV or simian-human immunodeficiency virus (SHIV). (66, 67)

International Pre-Exposure Prophylaxis initiative (iPrEx) was the first randomised clinical trial of PrEP efficacy, which enrolled 2,499 participants in six countries and reported that PrEP reduced HIV incidence

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

by 44% (95%CI:15–63) and that detectable drug in the blood was strongly correlated with the prophylactic effect of up to 99% protection. (68) Since then, eighteen randomised clinical trials, open-label extension trials and demonstration studies investigated the efficacy of PrEP and reported that when used with optimal medication adherence, daily PrEP is a highly effective HIV prevention strategy for MSM, heterosexual men and women, transgender people, and people who inject drugs at-risk of HIV acquisition. (69) As is the case with ART, adherence is the key determinant of PrEP efficacy. (69) In addition, EB-PrEP was investigated in a limited number of studies, which showed high effectiveness and acceptability of this PREP schedule in MSM, including those who engaged in risk events infrequently. (70–72) The relative reduction in incidence of new HIV infection due to EB-PrEP was 86% (95% CI: 40% – 98%) in a double-blind randomised controlled trial (IPERGAY) conducted in France and Canada (70) and 97% (95% CI 81%–100%) in its open label extension. (71)

Very few cases of antiretroviral drug resistance were observed in people taking daily DTF/FTC for PrEP, and all of them were associated with very poor adherence to PrEP. (73) No effects on reproductive health outcomes were reported. Key safety issues associated with daily PrEP among participants in RCTs included: a start-up syndrome (nausea, vomiting and dizziness) experienced by 1–18% of trial participants, Grade 2–3 creatinine elevations in 0.2% of participants and 0.4% to 1.5% loss of bone mineral density, which was not associated with fracture risk and returned towards baseline after stopping PrEP. (73)

For a full review of PrEP safety and efficacy please see the CDC Preexposure Prophylaxis for the Prevention of HIV Infection in the United States – 2021 Update: A Clinical Practice Guideline <https://stacks.cdc.gov/view/cdc/112360>

Co-formulated tenofovir and emtricitabine for use as PrEP by people at risk of HIV infection is now recommended as standard of care in clinical guidelines in the US, Europe and Australia (74), as well as globally through WHO guidelines. (75) Based on recent evidence (70–72), EB-PrEP has recently been recommended by the WHO as an option for MSM and by the updated PrEP guidelines in Australia. (76)

PrEP implementation

PrEP access

Expanded PrEP implementation in Australia started with two population-based implementation trials, EPIC-NSW in New South Wales (77, 78) and PrEPX in Victoria. (79, 80) Now, PrEP is a key pillar of the National HIV Strategy.

Antiretroviral drugs used as PrEP in Australia are now registered with the Therapeutic Goods Administration (TGA) for that indication (81) and they are subsidised by the Australian Pharmaceutical Benefits Scheme (PBS). (82) Generic co-formulated TDF/FTC for use as PrEP can also be legally imported into Australia for personal use and is currently cheaper than the cost of a PBS prescription (\$39.50/30 days for non-concession card holders). Various websites offer access to PrEP via self-importation and some offer free access, for those unable to afford PrEP, via a coupon system e.g. PAN (PrEPaccessNOW) at: <http://pan.org.au/assistance-scheme/> As with any on-line purchase, caution should be exercised. Reputable sites verified and recommended by AIDS organisations or established Australian PrEP providers should only be used for on-line purchase.

Access to PrEP is crucial to realising its benefits. General practitioners and nurses should be aware of people not currently benefiting from PrEP who might do so (younger men and people born overseas without access to Medicare – see Background to this chapter) and assess their barriers to, and options for, access.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

PrEP uptake trends

By the end of December 2018, approximately 18,530 individuals were accessing Medicare-subsidised PrEP in Australia, approximately half of them were in NSW and 99.1% of all users were males. (83) However, at a time of increasing PrEP uptake, increases in condomless anal intercourse were recorded in gay communities in Sydney and Melbourne as well as increasing diagnoses of STIs, such as anal gonorrhoea and chlamydia and new syphilis diagnoses. (84) The latter can be partly attributed to increased STI testing in MSM using PrEP, though this trend was significant regardless of the frequency of testing. (80)

PrEP prescribing

According to the national PrEP guidelines, all general practitioners and other medical specialists can prescribe PrEP using a PBS streamlined authority arrangement. No specialist training is required to prescribe PrEP. Resources and training guidance are available for clinicians who are new to prescribing PrEP. (76)

The newly updated ASHM 2019 PrEP guidelines (76) recommend daily PrEP for all people at risk of HIV infection. In addition, they also recommend that on-demand PrEP should be offered as an alternative option to cis-gender MSM.

According to the current 8th National HIV strategy, which aims for fast PrEP uptake and broad coverage among people who are at medium or high risk of being infected with HIV (85), and the updated national PrEP guidelines (76), general practitioners and nurses will play an increasing role in the provision of PrEP. They will play a key role in assessing people for clinical and behavioural eligibility for PrEP; provide PrEP prescriptions and regular follow-up and support services. The goals of PrEP services are described in Table 6.

Table 6. Goals of PrEP services (from the national PrEP guidelines (76))

For many general practitioners and nurses new to PrEP, prescribing may be unfamiliar but is described in detail in the updated ASHM 2019 PrEP guidelines. (76) PrEP training and resources are also available on the ASHM website to assist clinicians.

Assessment of suitability for PrEP

When assessing people for PrEP eligibility and suitability, it is important for general practitioners and nurses to understand a shift in the national PrEP prescribing guidance, from targeted to broader access to PrEP. (76) Targeted PrEP prescribing (focused on high risk MSM) was the key feature of Australian PrEP implementation guidelines up to now, due to the limited PrEP availability prior to the PBS listing of PrEP. The goal of the current 8th National HIV strategy is fast PrEP uptake and broad coverage of people who are at medium or high risk of being infected with HIV. (85) Therefore, clinicians are now recommended to assess whether PrEP suits the needs of their patients, and that can be done by using assessment criteria listed in Table 7. The guidelines also include recommendations on how to discuss behavioural risk reduction strategies.

Table 7. PrEP suitability criteria for different population groups (from the National PrEP guidelines (76))

Note: for more detail on how to apply these criteria in practice, please see Chapters 4 and 14 of the guidelines.

Nurses' roles in PrEP

PrEP use in Australia as part of an individual and population HIV risk reduction strategy is now wide-spread. Nurses have an important role to play (Table 8).

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Table 8. The nurse's role in pre-exposure prophylaxis

• Providing a nurse-led PrEP service • Ensuring that those at risk know about PrEP and current pathways to access in Australia • Referring onwards to providers who can facilitate PrEP access • Adherence education and support ◦ The need for a high level of adherence to the regimen and dosing schedule ◦ Choosing the optimum dosing time based on the client's routine work and leisure patterns, including discussion around the dosing window – a rigid, fixed time to dose sets clients up to miss a dose and fail ◦ Strategies to assist adherence – teaching cueing (the act of associating pill taking with a habitual behaviour), visual and electronic reminders, pill boxes, preparing for the unexpected: keeping a supply at work, in the car, in a bag, at a friend's house, borrowing from a friend ◦ What to do if a dose(s) is/are missed ◦ For vulnerable groups, intensive support, case management, directly administered or observed therapy (DOT), partial-DOT, financial incentives. • Education about maintaining healthy bones • How to access help if unexpected side-effects occur ◦ The nurse can provide the first port of call and access to help by encouraging re-presentation and providing telephone access and support

Adherence to the PrEP dosing schedule is also crucial to realising its benefits. People who most need PrEP may well be those who most struggle to maintain high levels of adherence. They are often MSM, and others, who have problems with alcohol or drug use or significant mental health problems. Rather than exclude these vulnerable groups from PrEP access because of concerns about poor engagement and adherence, ways should be found to support the adherence required. In the IDU Bangkok PrEP study, participants received Truvada by directly observed therapy (DOT) 86% (SD 25%) of the time and were compensated for travel and the time required by the study procedures.⁽⁸⁶⁾

Key components of medication adherence counselling are presented in Table 9.

Table 9. Key components of medication adherence counselling (from the national PrEP guidelines (76)).

Nurses can and ought to have a pivotal role in exploring and providing innovative methods of PrEP medication adherence support in marginalised, vulnerable populations, which could include DOT, other forms of highly supported therapy and the provision of financial incentives.

Models of PrEP services

The prescription and provision of PrEP is straightforward for many medical practitioners. However, those who are less experienced in serving populations at high risk of acquiring HIV infection and STIs (e.g. MSM, transgender and gender-diverse people, indigenous Australians, women involved in sex work, people whose partners are at high risk for HIV/STI, and people who inject drugs) may wish to consider establishing relationships with experienced and accredited HIV s100 prescribers, HIV clinics and sexual health centres, that can provide information and support if required and may be able to do so via Telehealth. Initiatives such as telementoring ⁽⁸⁷⁾ and innovative Information and Communication Technology (ICT) solutions offered by eHealth NSW ⁽⁸⁸⁾ are good examples of how communication technologies can support new PrEP prescribers in remote areas where traditional sexual health services may be limited.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

When embarking on PrEP prescribing, consider the capacity of your practice to accommodate new patients and maintain their follow-up every 3 months. Several approaches may be helpful in dealing with these changes to practice:

- Careful planning of clinic appointments to allow sufficient space for PrEP initiation and regular follow-up visits
- Where resources allow, automating most steps in the patient pathway, to reduce the patient registration-to-PrEP prescription time
- Having clinical nurse specialists, or trained nurses with clinician supervision in charge of PrEP-related services where possible
- Developing systems and procedures for recording and monitoring PrEP use
- Developing a customised communications plan for PrEP demand creation

Conclusions

Biomedical strategies based on the use of antiretroviral drugs are currently front and centre stage of HIV prevention. General practitioners and nurses have a key role in service provision, education, support and innovative research as TasP, PEP and PrEP assume a more prominent role in HIV prevention.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Microbicides for the prevention of HIV infection

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Last reviewed: August 2019

Background

Microbicides are chemical entities that can be formulated in gels, films, tablets, capsules or intravaginal rings (IVR) for application to the vagina or rectum to prevent the transmission of HIV and other sexually transmissible infections (1, 2). While male condoms are known to protect against HIV acquisition (3), oftentimes negotiating their use is difficult for women. Male or female condoms are also unsuitable for women who want to conceive children (2). To address this need, microbicide research and development began in the 1990s with the aim to develop female-controlled strategies, which could be used discreetly by women, to protect themselves against HIV transmission from their male partners (2). The concept of rectal microbicides soon followed aimed to protect male, female and transgender people from unprotected rectal anal intercourse (RAI) (4).

The aim of a microbicide is to inactivate or block HIV replication during the early stages of the virus life-cycle to prevent establishment of infection at the mucosa. Microbicides are designed for use either around coitus (event driven e.g. using a gel before and/or after sex) or independent of coitus such as daily dosing (e.g. gel) or sustained release formulations (e.g. IVR) (2). An advantage of microbicides is the delivery of high concentrations of the active pharmaceutical agent at the site of HIV exposure thereby avoiding significant systemic exposure and potential side effects (2).

While several microbicide candidates have been evaluated in efficacy trials, there are currently no licensed microbicides approved for HIV prevention. There is now a priority for the development and advancement of sustained release microbicides, as well as systemically delivered antiretrovirals (ARV) as pre-exposure prophylaxis (PrEP), that is less reliant on adherence by the user (5). However, it is recognised within the microbicide field that a diversity of delivery technologies (topical and systemic) is needed to meet the needs and preferences of women from different cultural contexts and throughout their reproductive life-time (6).

Rectal microbicides have been primarily aimed at protecting men who have sex with men (MSM) from HIV acquisition by RAI although they can be used in transgender (7) and heterosexual women engaging in RAI. In the United States, 36% of women 25-44 years of age have reported ever having RAI in their lifetime (8).

Terminology

The first-generation microbicides, comprising non-ionic detergents or acids, accurately reflects the terminology (i.e. microbicide) of an agent that directly inactivates microorganisms, including HIV. However, this nomenclature is also extended to topically applied agents containing ARVs (i.e. ARV-based microbicides) that specifically block HIV replication (e.g. the nucleotide reverse transcriptase inhibitor, tenofovir) rather than directly inactivating the virus (2). A more accurate description to encompass nonspecific and HIV specific microbicides is "Topical Pre-exposure Prophylaxis" (Topical PrEP). Nevertheless, the term microbicides persists and will be used in this section regardless of the mechanism of action of the active pharmaceutical ingredient formulated for vaginal or rectal delivery via a gel, tablets, capsule, film or ring.

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Burden of HIV infection in women globally and in Australia

Despite major advances in HIV treatment and prevention, HIV infection remains a significant global health threat including in women. In 2017, around 7000 adolescent girls and young women became infected with HIV every week (9). Most of this burden is in sub-Saharan Africa where around 3 out of 4 new HIV infections occur in 15-19 year old girls, and 15-24 year old young women are twice as likely to be infected with HIV compared to their male counterparts (9). In contrast, the burden of HIV infection in Australia is concentrated in the male population with 10% of the estimated 26,000 individuals with HIV infection in 2017 among women 15 years or older (9). Among Indigenous Australians, a higher proportion of diagnoses occur among women (10).

Microbicides demonstrating efficacy in clinical trials

IVRs comprising a silicone matrix that releases the ARV drug dapivirine, over one month is the only microbicide evaluated in a phase III clinical trial demonstrating efficacy (27 and 31%) in preventing HIV transmission in women as determined in The Ring Study and ASPIRE studies (11, 12). The dapivirine ring is currently being evaluated in parallel open-label studies (DREAM and HOPE) led by the International Partnership for Microbicides (IPM) and the US National Institutes of Health-funded Microbicides Trials Network (MTN) and is under regulatory review.

Oral PrEP in MSM

The microbicide field has been overtaken by oral PrEP comprising of ARVs (i.e. tenofovir and emtricitabine [Truvada]) normally used for HIV treatment (see Biomedical Prevention Section). Several clinical trials (iPrEX, Partners PrEP, TDF2, PROUD) have demonstrated the efficacy of oral daily PrEP in MSM and high-risk heterosexual men and women including serodiscordant couples (13-15). The ANRS IPERGAY study, that evaluated event driven oral PrEP with Truvada, also demonstrated efficacy in preventing HIV in MSM (16). Effectiveness of oral PrEP in a real world setting, as observed in an open-label trial in MSM, was greater than efficacy observed in clinical trials (17). When taken every day, oral PrEP has the potential to reduce HIV transmission by more than 99 percent (18). Daily use of Truvada for HIV PrEP was recommended for HIV negative individuals who are at high risk of acquiring HIV by the WHO in 2015 and is recommended in the United States, Europe and Australia (19).

Oral PrEP in women

While the TDF2 (15) and Partners PrEP (14) studies indicate that oral PrEP can work in women, other trials in high-risk women (FEM-PrEP and VOICE) showed no efficacy (20, 21). This lack of efficacy was largely attributed to poor adherence (22). However, other factors such HIV subtype exposure, mode of transmission, and the percent of stable serodiscordant couples argue that more accurate estimates of oral PrEP for women at high risk in southern Africa are needed (23). Oral PrEP is less forgiving to lapses in dosing in women compared to men. Heterosexual women and transgender men engaging in vaginal sex must take PrEP every day for effective protection against HIV (19). The difference in oral PrEP protection in men versus women may be explained by pharmacodynamic differences where 100-fold lower-levels of the active form of tenofovir is present in genital tissues of women versus rectal tissue (24).

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Long-acting injectables and implants

There are exciting advances in the development of long-acting injectable and implants to deliver sustained levels of ARV drugs (25, 26). However, like oral PrEP these modalities deliver the drug systemically, which may discourage their use. Major advantages of these delivery strategies are that dosing is discrete and independent of coitus, which should maximise adherence and efficacy. The HIV prevention clinical pipeline includes long-acting cabotegravir (an integrase inhibitor) as well as daily oral PrEP with Descovy, comprising emtricitabine and tenofovir alafenamide (a tenofovir prodrug that specifically accumulates in cells to minimise systemic side effects), and antibody-mediated prevention with broadly neutralizing antibodies (bNabs). Please refer to AVAC website for more details (https://www.archive.avac.org/sites/default/files/infographics/Percolating_PipelineJan2018.pdf).

Multipurpose prevention technologies (MPTs)

Multipurpose prevention technologies (MPTs) are designed to target HIV prevention as well as an additional indication such as preventing unintended pregnancies or transmission of other sexually transmissible infections (STIs) such as herpes simplex virus (HSV) infection. Delivery strategies under development include sustained release IVRs (27). While a ring with additional indications, such as preventing pregnancy, may increase uptake by reducing stigma normally associated with the use of specific HIV prevention modalities, MPTs manufacture is likely to be expensive and obtaining regulatory approval will be challenging due to the presence of two or more active pharmaceutical ingredients (27). Please refer to the AVAC website for more information in MPTs (<https://www.avac.org/prevention-option/multipurpose-prevention-technologies>).

Classes of microbicides and mode of action

Nonspecific microbicides

Surfactants and detergents

Microbicides were originally intended to have broad-spectrum activity against all STIs and contain non-drug compounds for over the counter use without a prescription (2). The first generation microbicides were non-specific agents comprising surfactants and detergents that directly inactivate viral and bacterial STIs (28). The nonionic surfactant, nonoxynol-9 (an over the counter spermicide) and the detergent, sodium dodecyl sulphate (sodium lauryl sulphate or SAVVY), dissolve the lipid envelope and denature membrane proteins of sexually-transmitted pathogens, respectively. These agents have a low therapeutic window and frequent use of nonoxynol-9 causes vaginal inflammation and disruption of the vagina epithelium, as observed in vitro and in a mouse model (29, 30). Consistent with these findings, a Phase II/III clinical trial in sex workers demonstrated that vaginal application of nonoxynol-9 several times a day increased risk of HIV acquisition compared to women using placebo gel (31). Trials to evaluate the efficacy of SAVVY in preventing HIV transmission were ceased due to futility (32, 33). These agents are no longer considered safe or viable options for microbicides.

Acid buffering agents

A second class of nonspecific first generation microbicides is acid buffering agents. The acid buffering agents BufferGel[®] and ACIDFORM are designed to maintain the low antimicrobial pH of the vagina (pH 3.5 – 4.5) in the presence of semen (which transiently increases the vaginal pH to neutral) thus preventing the window of opportunity for acid labile pathogens such as HIV and other sexually-transmitted pathogens to infect the

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

mucosa (34, 35). BufferGel® was found to be safe in a phase IIb clinical trial; however it failed to prevent HIV transmission in women (36). In contrast to BufferGel®, which solely relies on protons for lowering the pH, ACIDFORM (now called Amphora®) contains a combination of acids, including lactic acid, which is produced by protective vaginal *Lactobacillus* spp. Lactic acid at concentrations found in the cervicovaginal fluid from women (37, 38) has orders of magnitude greater HIV virucidal activity compared to protons alone (39). Lactic acid is also active against *Chlamydia trachomatis* and *Neisseria gonorrhoeae* in vitro (40). ACIDFORM is currently being progressed as a non-hormonal contraceptive, for the prevention of urogenital chlamydia and gonorrhoea in women, and as an antimicrobial MPT vaginal gel to prevent recurrent bacterial vaginosis (41) (<https://www.sciencedirect.com/science/article/abs/pii/S0010782405004816>).

Moderately specific microbicides

Linear Polyanions

Members of the moderately specific microbicide class are mainly macromolecular linear anionic polymers such as cellulose sulfate (UsherCell), carrageenan (Carraguard), PRO 2000 and cellulose acetate phthalate (CAP) (28). Linear polyanions generally have broad-spectrum activity against several viral and bacterial pathogens including HIV, HSV, human papillomavirus, *Neisseria gonorrhoeae* and *Chlamydia trachomatis* (28). Linear polyanions block host cell viral entry via electrostatic interactions with the viral envelope proteins and/or host cell receptors (42, 43). Linear polyanions usually lack potency against HIV compared to ARVs and more potent inhibitors of HIV that uses the CXCR4 chemokine receptor compared to CCR5 (44), with the latter HIV strains accounting for most cases of HIV transmission via the mucosa (45).

The performance of linear polyanion-based microbicides has been disappointing in HIV efficacy trials. Carraguard failed to prevent the sexual transmission of HIV in women, while cellulose sulfate showed a trend towards increased HIV acquisition (46, 47). Despite PRO 2000 demonstrating 30% efficacy in a phase IIb trial (36), it failed to prevent HIV transmission in a follow up phase III study (48). The lack of in vivo efficacy demonstrated by linear polyanions against HIV transmission can be ascribed to several factors. These include attenuation of their anti-HIV activity by semen (49) as well as bioavailability in the female genital tract before and after coitus (50), which is compounded by their low potency relative to specific ARVs.

Dendrimers

The dendrimer (dendri- = tree, -mer = branching), SPL7013, is a distinct synthetic macromolecular class, which in contrast to linear polyanions, comprises a defined chemical structure and similar potency against CCR5 and CXCR4-using HIV isolates (51, 52). 3% SPL7013 Gel (VivaGel®) has progressed through extensive phase I safety, acceptability and vaginal retention studies (53-60). However, its further development as a vaginal microbicide to prevent HIV infection was put on hold due to a catalytic shift in the microbicide field prompted by the clinical failure of the early microbicide classes (61), although other classes of dendrimers have been pursued in the development of vagina and rectal microbicides (reviewed by das Neves et al 2016) (62). There has been a move away from coitally-dependent gels to sustained release formulations due to issues with poor adherence driving lack of efficacy in women, even with a more potent ARV-based microbicide (63).

Antiretroviral-based microbicides

1% Tenofovir Gel

Given the lack of efficacy observed with nonspecific and moderately specific microbicides, the microbicide field pivoted towards the development of potent ARVs, used to treat HIV infection, for microbicide development (2).

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

These antivirals were mainly inhibitors of the HIV reverse transcriptase, that block an early stage of the virus life-cycle (2). The ARV-based microbicide gel comprising 1% tenofovir, a nucleotide analogue reverse transcriptase inhibitor, was developed. Tenofovir was selected due to the long intracellular half-life of the active form (tenofovir diphosphate), its high genetic barrier for development of drug resistance, tolerability, and the relatively low prevalence, at the time, of circulating tenofovir-resistant HIV harbouring the K65R mutation (2, 64).

While 1% tenofovir gel demonstrated efficacy in the phase IIB CAPRISA 004 trial in preventing the sexual transmission of HIV in women compared to a placebo gel (65), these findings were not confirmed in the follow up phase III FACTS 001 study (63). These results can be explained in part due to lack of adherence, confirmed by monitoring of tenofovir levels. The poor adherence is likely due to the impractical BAT24 dosing regimen (applying gel twice not more than 12 hours before and after coitus) and the difficulty of integrating this regimen into the daily lives of younger women (65, 66). The VOICE study, that included arms assessing daily non-coitally dependent intravaginal dosing of 1% tenofovir gel, also failed to show efficacy due to lack of adherence (20). 1% TFV gel for intravaginal use is no longer being pursued as a microbicide for women.

Tenofovir based IVRs and films are under various stages of preclinical/clinical development in addition to other ARV-based microbicides and delivery modalities. In addition, despite the disappointing phase III clinical data for 1% tenofovir gel in women (63), rectal microbicide gels containing 1% tenofovir are still being pursued (4). Please refer to the following website for a more information on the ARV-based prevention preclinical and clinical pipeline (<https://www.avac.org/infographic/arv-based-prevention-pipeline>).

Intravaginal rings

Given the disappointing clinical trial outcomes with 1% tenofovir gel, the field shifted its attention away from gels towards sustained release modalities such as IVRs (67). IVRs releasing the nonnucleoside RT inhibitor, dapivirine, were evaluated in parallel in phase III studies (The ASPIRE and the RING studies) (12) (68). Both studies demonstrated modest yet significant dapivirine ring efficacy (27% and 31%) in preventing HIV infection in women compared to IVR without drug (12, 68). These were landmark studies in the microbicide field representing the first phase III clinical trials showing significant HIV protective effect of a topical microbicide in women. Dapvirine rings are currently being evaluated in the DREAM and HOPE open label studies and moving towards licensure.

Antibody-based microbicides

HIV-specific monoclonal antibodies (mAb) are also being advanced for HIV prevention and treatment, recently reviewed by Anderson and colleagues (69). These broadly neutralizing monoclonal antibodies (bNAbs) are derived from HIV positive individuals and target various epitopes on the HIV envelope (69). They can be divided into three generations based on potency and neutralisation breadth (69). In addition to direct HIV-1 neutralizing activity, many of these antibodies are reported to block HIV infection through several additional Fc-mediated antiviral effector functions such as antibody-dependent cell-mediated cytotoxicity (ADCC) (69).

Numerous studies have evaluated either intravenous administration of various HIV mAbs or topical administration of HIV mAbs in protecting against simian-HIV (SHIV) mucosal challenge (vaginal or rectal) in monkeys (69-71) (72) (73) (63, 74). Collectively these studies demonstrated the viability of both parenteral and mucosal delivery of mAbs to prevent vaginal and rectal transmission of SHIV and underpin current clinical studies evaluating bNAbs for HIV prevention in humans (69). Efficacy of the vaginally administered mAb VRC01 against HIV-1 transmission has also been demonstrated in the humanised mouse model (75).

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Currently, there is a major focus on delivering bNAbs systemically (passive immunization) for preventing the sexual transmission of HIV-1 with several clinical trials planned or ongoing (avac.org) (69). In contrast, there is relatively less attention on the development of mAbs for use as a topical microbicide. The cost of production of clinical grade human monoclonal antibodies is likely a major hurdle (69). To address cost and scale of production of mAbs, transgenic technologies have been pursued with mAb production in plants being the most prominent in the context of HIV prevention strategies. Two groups, one in the USA and the other in Europe have progressed mAbs produced in plants to phase I clinical trials (69, 76) that include successful delivery via an IVR (77). A phase I study of a topical microbicide gel comprising human anti-HIV-1 mAbs has also been completed and found to be safe over a 12 day period of daily dosing (78).

Another strategy representing an inexpensive source of antibodies for vaginal or rectal microbicides is generating mAbs targeting the HIV envelope in cows (79). While there are currently no clinical trials of bovine mAbs there is an interest in this technology as demonstrated by a published study from a leader in the bNAb field based in the United States (80) and pioneering studies performed in Australia (79, 81, 82).

Rectal Microbicides and Douches

Tenofovir gel

While shown to be safe in clinical trials performed in women (65, 83), the vaginal tenofovir gel formulation is hyperosmolar and disrupts epithelial integrity (84, 85) raising concerns of safety for use in the rectal compartment, which is relatively more fragile than the vagina, comprising a single layer of columnar epithelium. Accordingly, a 1% tenofovir gel formulation with 73% lower osmolality was developed for dual compartment use (86).

The reduced glycerine content 1% tenofovir gel modified for rectal use was safe when used daily or before and after receptive anal intercourse in MSM and transgender women from Thailand, South America, mainland United States and Peru as demonstrated in the MTN-017 phase II study (87). Based on convergence interviews, 83% of participants had ≥80% adherence to the daily gel and 93% had ≥80% adherence to twice-weekly use of the gel before and after RAI (87). Adherence to RAI-associated rectal gel use was as high as adherence observed in the same study for daily oral PrEP (88). These studies demonstrate that rectal microbicides have promise for use in MSM and transgender women and await testing in efficacy trials.

Douches

To promote adherence, microbicide strategies should ideally be compatible with normal sexual behaviours. The use of cleansing enemas prior to RAI is an example of a typical behaviour in MSM. A study demonstrated that the use of a hypo-osmolar douche containing tenofovir achieved rapid and therapeutically relevant concentrations of the active form of this ARV in mouse colorectal tissue. This promising strategy awaits confirmation in non-human primates and humans (89).

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

Biological factors that attenuate topical microbicide efficacy

1% Tenofovir gel was shown to achieve an overall efficacy of 39% in the CAPRISA 004 study compared to women receiving placebo gel and 54% efficacy in women who had >80% adherence to gel use (65). Since only 54% efficacy in preventing HIV acquisition was achieved in highly adherent women, this suggests that other factors, apart from lack of adherence, are contributing to the poor efficacy of 1% tenofovir gel. It has become apparent that biological factors including the presence of genital inflammation (90) due to dysbiotic or suboptimal vaginal microbiota, as exemplified by bacterial vaginosis, as well as the presence of symptomatic and asymptomatic STIs contribute to attenuating the anti-HIV efficacy of 1% tenofovir gel.

In a post hoc prospective analysis of data from the CAPRISA 004 study, 1% tenofovir gel was 57% protective against HIV in women without genital inflammation, as determined by concentrations of nine pro-inflammatory cytokines in cervicovaginal lavages, and only 3% protective if genital inflammation was present (90). The role of dysbiotic or suboptimal vaginal microbiota associated with genital inflammation and driving increased HIV risk was demonstrated in a prospective study in adolescent girls and young women in sub-Saharan Africa (91). Individuals who were colonised with a highly diverse vaginal microbiota had just over a 4 fold increased risk of acquiring HIV infection from their male partners compared to women colonised with a beneficial *Lactobacillus* species (*L. crispatus*) (91). These women also had significantly increased levels of pro-inflammatory cytokines and chemokines in genital secretions and an increase in activated CD4+ T cells in the cervix providing a plausible mechanism for increased HIV risk (91) that could attenuate the efficacy of topical PrEP.

In addition, compared to women with a *Lactobacillus*-dominated vaginal microbiota, women with bacterial vaginosis have disrupted cervicovaginal epithelial barrier integrity that can promote penetration of HIV through the epithelial barrier to infect subepithelial HIV target cells. In addition, women with bacterial vaginosis have adverse changes in the protective properties of cervical mucous which acts as a physical barrier to prevent HIV entering the cervix (92, 93).

A dysbiotic vaginal microbiota has also been shown to modulate the efficacy of 1% tenofovir gel in the CAPRISA 004 study by metabolising tenofovir (94). This study showed that tenofovir-reduced HIV incidence by 61% in women with *Lactobacillus*-dominated microbiota and only by 18% in women colonised with a highly diverse vaginal microbiota (i.e. non-*Lactobacillus* bacteria dominated) (94). Mucosal tenofovir levels were lower in women with non-*Lactobacillus* bacteria and these bacteria were responsible for metabolising tenofovir (94). Studies are ongoing to determine if other ARVs used for topical PrEP (e.g. dapivirine) are also metabolised in a dysbiotic microbiota. In contrast, the efficacy of oral daily PrEP (either tenofovir monotherapy or Truvada) was not significantly different among African women with healthy vs abnormal vaginal microbiota as defined by Nugent Score (95). However, not all adolescent girls and young women in South Africa with a diverse vaginal microbiota are positive by the Nugent method (91). Further studies will be needed to determine whether the vaginal microbiota can impact on the efficacy of oral PrEP.

Collectively these studies have prompted an interest in strategies to reduce genital inflammation, including modifying a dysbiotic vaginal microbiota by the use of antibiotics, pre/probiotics or postbiotics to augment HIV prevention efforts (22) (96) (40).

CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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CONTENTS	1. EPIDEMIOLOGY & NATURAL HISTORY	2. VIROLOGY & IMMUNOLOGY	3. DIAGNOSTIC & MONITORING TESTS	4. PRIMARY HIV INFECTION
5. HIV-INFECTIOUS DISEASE & CANCER	6. OTHER HIV-ASSOCIATED DISEASE	7. CO-INFECTIONS	8. ARV DRUGS & OTHER THERAPIES	9. CO-MORBIDITIES
10. SPECIAL PATIENT POPULATIONS	11. NURSES & MIDWIVES	12. BIOMEDICAL PREVENTION		

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