BRITISH COLUMBIA
CENTRE *for* EXCELLENCE
in HIV/AIDS

PRIMARY CARE GUIDELINES FOR THE MANAGEMENT OF ADULTS LIVING WITH HIV/AIDS IN BRITISH COLUMBIA

ON BEHALF OF THE PRIMARY CARE GUIDELINES PANEL
BC CENTRE FOR EXCELLENCE IN HIV/AIDS

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DISCLAIMER

No financial or in-kind commercial support has been received for the development of these guidelines; no commercial organization has supported the development of these guidelines. The content of the guidelines has been developed by the authors and reflect best practices in HIV care in British Columbia. Both positive and negative trials are mentioned where possible. Generic names of medications are used in place of brand names where possible.

These Guidelines represent the view of the Primary Care Guidelines Writing Committee, in consultation with an external group of experts and are based on available scientific evidence current to July 31, 2021. These Guidelines may be superseded by subsequent Guidelines. Please check http://bccfe.ca/therapeutic-guidelines for the most recent Guidelines. Every health care professional is responsible for exercising their own professional skill and judgment and should consider these Guidelines in the context of the individual patient's circumstances, in consultation with that patient or their guardian(s), and when appropriate, external experts (e.g., specialty consultation).

These Guidelines are not medical advice nor are they intended to be the only approach to the management of a clinical problem. These Guidelines should not be relied on by any individual as a substitute for the advice or professional judgment of a health care professional.

WHAT'S NEW IN THE GUIDELINES

Updated: November 2022

Toxoplasma Serology
Table 3.3, Toxoplasma IgG serology, has been updated for agreement with the existing recommendations provided in the body of the Primary Care Guidelines. Toxoplasma IgG serology is indicated in all persons, regardless of CD4 cell count (Table 3.3). Previous versions stated toxoplasma IgG serology is indicated in persons with CD4 cell count <200 cells/mm3.

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CONFLICTS OF INTEREST

Dr. Silvia Guillemi: Dr. Guillemi has participated in advisory boards and received consulting fees from Gilead Sciences Canada, Inc. and ViiV Healthcare, Inc.

Dr. Marianne Harris: Dr. Harris has participated in advisory boards and received consulting fees from Gilead Sciences Canada, Inc., Merck Canada, Inc., and ViiV Healthcare, Inc.

Dr. Mark Hull: Dr. Hull has participated in advisory boards, participated in research, and received honoraria from Gilead Sciences Canada, Inc. and Merck Canada, Inc.

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1 INTRODUCTION

There has been a significant decrease in the morbidity and mortality of people living with HIV (PLWH) in the province of British Columbia since the introduction of potent antiretroviral treatment in 1996. According to the British Columbia Centre for Excellence in HIV/AIDS (BC-CfE) HIV Quarterly Monitoring Report for the fourth quarter of 2019, there were approximately 10,603 people in the province living with HIV.(1) Among them, around 7415 were receiving antiretroviral treatment in 2020.(2)

The *Primary Care Guidelines for the Management of HIV/AIDS in Adults in British Columbia*, along with other therapeutic guidelines, have been developed by the BC-CfE to provide support for care and treatment programs for PLWH. These guidelines also respond to the need to expand HIV treatment to meet the goals of 90-90-90 in British Columbia and respond to requests from primary care providers in the community for HIV-specific guidelines.

1.1 OBJECTIVES

1. To provide consensus-based guidelines for the management of primary care for PLWH.
2. To provide practical and easily accessible information and resources for primary care providers of PLWH in the province of British Columbia.

1.2 METHODS

1.2.1 Process Overview and Committee Composition

An expert committee composed of primary care and infectious disease physicians, a nurse practitioner, a pharmacist, and a person living with HIV prepared the original guidelines in 2011. Since the guidelines were first published, they have been consistently reviewed and revised to ensure that the information is up-to-date. In 2014/15, the original expert committee collectively undertook a review of the 2011 guidelines. The most recent review was finalized in 2021 by a review committee consisting of primary care, public health, and infectious disease physicians (refer to above). Where applicable, the committee updated epidemiology, baseline assessment, immunizations, and co-morbidities data and added new recommendations. The revisions were sent out to subject matter experts for review where necessary.

1.2.2 Consensus Development on the Basis of Evidence

The review committee met a total of eight times. Committee members developed sections, in consultation with external medical experts where appropriate, and presented their work at committee meetings, where all recommendations were discussed until consensus was reached. The final manuscript was reviewed by all committee members and then presented to and reviewed by members of the Committee for Drug Evaluation and Therapy (CDET) at the BC-CfE and reviewed by external reviewers (listed above).

Each recommendation in the guidelines has been assigned a level of evidence based on the GRADE criteria (refer to **Table 1.1**).(3) Note that this method of grading recommendations is different from previous versions of the BC-CfE Primary Care Guidelines.

Table 1.1: Grading recommendations assessment, development and evaluation (GRADE)

Code	Quality of Evidence	Definition
A	High	Further research is very unlikely to change our confidence in the estimate of effect. Several high-quality studies with consistent results In special cases: one large, high-quality multi-centre trial
B	Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. One high-quality study Several studies with some limitations
C	Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. One or more studies with severe limitations
D	Very Low	Any estimate of effect is very uncertain. Expert opinion No direct research evidence One or more studies with very severe limitations

Adapted from Guyatt, et al. 2008.(3)

References

1. BC Centre for Excellence in HIV/AIDS. HIV Quarterly Monitoring Report for British Columbia for the Fourth Quarter of 2019. 2019 [Available from: http://stophivaids.ca/qmr/2019-Q4/#/bc.]
2. BC Centre for Excellence in HIV/AIDS. B.C. HIV/AIDS Drug Treatment Program Monthly Report May 2020 [Available from: http://bccfe.ca/sites/default/files/uploads/publications/centredocs/cfe-status-report_may2020.pdf.]
3. Guyatt G, Oxman AD, Vist G, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength recommendations. BMJ. 2008;336(7650):924-6.

GLOSSARY OF ABBREVIATIONS

ACC/AHA	American College of Cardiology/American Heart Association
AFP	Serum alpha-fetoprotein
AIDS	Acquired immunodeficiency syndrome
ALT	Alanine aminotransferase
Anti-HBc (HBcAb)	Hepatitis B virus core antibody
Anti-HBs (HBsAb)	Hepatitis B virus surface antibody
apoB	Apolipoprotein B
ART	Antiretroviral therapy
ARV	Antiretroviral
ASO	AIDS service organization
AST	Aspartate aminotransferase
BCCDC	British Columbia Centre for Disease Control
BC-CfE	British Columbia Centre for Excellence in HIV/AIDS
BCG	Bacillus Calmette-Guérin, vaccine for TB disease
BC-PHMRL	BC Public Health Microbiology Reference Laboratory
BMD	Bone mineral density
BMI	Body mass index
CBC	Complete blood count
CDC	United States Centers for Disease Control
CDET	Committee for Drug Evaluation and Therapy
CHIWOS	Canadian HIV Women's Sexual & Reproductive Health Cohort Study
CKD	Chronic kidney disease
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
CSF	Cerebrospinal fluid
CT	Computed tomography
CVD	Cardiovascular disease
CxR	Chest radiography
CYP	Cytochrome P
D:A:D study	Data-collection on Adverse Effects of Anti-HIV Drugs (D:A:D) study
DM	Diabetes mellitus
DMPA	Depot medroxyprogesterone acetate
DXA	Dual energy X-ray absorptiometry
EBV	Epstein-Barr virus
ECG	Electrocardiogram

eGFR	Estimated glomerular filtration rate
EIA	Enzyme immunoassay
FBG	Fasting blood glucose
FRAX	Fracture risk assessment
FRS	Framingham Risk Score
G6PD	Glucose-6-phosphate dehydrogenase
GLP-1	Glucagon-like peptide-1
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HAV	Hepatitis A virus
HbA1C	Glycated hemoglobin
HBIg	Hepatitis B immunoglobulin
HBsAg	Hepatitis B virus surface antigen
HBV	Hepatitis B virus
HBV DNA	Hepatitis B virus deoxyribonucleic acid
HCV	Hepatitis C virus
HDL	High-density lipoprotein
HIVAN	HIV-associated nephropathy
HIV	Human immunodeficiency virus
HIV pVL	HIV plasma viral load (copies/mL)
HLA-B*5701	Human leukocyte antigen B*5701; genetic test to identify persons at a high risk for hypersensitivity reaction to the antiretroviral agent abacavir
HPV4	Quadrivalent human papillomavirus
HPV	Human papillomavirus
HRA	High-resolution anoscopy
HSR	Hypersensitivity reaction
hsCRP	High-sensitivity C-reactive protein
HTLV-I	Human T-lymphotropic virus type 1
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IGRA	Interferon gamma release assay, used to screen for tuberculosis infection
IM	Intramuscular
INH	Isoniazid (isonicotinic acid hydrazide)
INSTI	Integrase strand transfer inhibitor
IPD	Invasive pneumococcal disease
IR	Insulin resistance
IRIS	Immune reconstitution inflammatory syndrome
IU	International units
IUD	Intrauterine device
LABA	Long-acting beta-agonist

LAMA	Long-acting muscarinic antagonist
LDL	Low-density lipoprotein
LTBI	Latent tuberculosis (TB) infection
MAC	*Mycobacterium avium* complex
MCV	Mean corpuscular volume
MHT	Menopausal hormone therapy
MI	Myocardial infarction
MMR	Mumps, measles and rubella
MRI	Magnetic resonance imaging
MSM	Men who have sex with men
MSP	Medical services plan
NAAT	Nucleic acid amplification test
NACI	National Advisory Committee of Immunization (Canada)
NASH	Non-alcoholic steatohepatitis
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
NP	Nurse practitioner
OI	Opportunistic infection
Pap	Papanicolaou test
PCP	*Pneumocystis* pneumonia
PEP	Post-exposure prophylaxis
PCR	Polymerase chain reaction
PI	Protease inhibitor
PJP	*Pneumocystis jirovecii* pneumonia
PK	Pharmacokinetic
PLWH	People living with HIV
Pneu-C-13	Conjugate pneumococcal vaccine
Pneu-P-23	Polysaccharide pneumococcal vaccine
PPD	Purified protein derivative
PrEP	Pre-exposure prophylaxis
PTSD	Post-traumatic stress disorder
PWID	People who inject drugs
QTc	Corrected QT interval
RETAIN	Re-Engagement and Engagement in Treatment for Antiretroviral Interrupted and Naïve Populations Initiative
RNA	Ribonucleic acid
RPR	Rapid plasma reagin
SC	Subcutaneous
SGLT-2	Sodium-glucose cotransporter-2

STI	Sexually transmitted infection
STOP HIV/AIDS	Seek and Treat for Optimal Prevention HIV/AIDS Program
Td	Tetanus and diphtheria
TRT	Testosterone replacement therapy
TST	Tuberculin skin test
TB	Tuberculosis or Mycobacterium tuberculosis
TC	Total cholesterol
Tenofovir AF	Tenofovir alafenamide
Tenofovir DF	Tenofovir disoproxil fumarate
TG	Triglycerides
TMP-SMX	Trimethoprim-sulfamethoxazole
U=U	Undetectable = untransmittable
UACR	Urine albumin-to-creatinine ratio
VCH	Vancouver Coastal Health Authority
VZV	Varicella zoster virus
WHO	World Health Organization
WLWH	Women living with HIV
X-ray	Penetrating form of high-energy electromagnetic radiation

SUMMARY OF PRIMARY CARE RECOMMENDATIONS FOR THE MANAGEMENT OF HIV/AIDS

INITIAL ASSESSMENT OF PEOPLE LIVING WITH HIV (PLWH)

1. All PLWH should have timely access to a primary care clinician with knowledge in the management of HIV infection and should receive care in a culturally sensitive environment. Primary care clinicians without expertise in HIV care should consult with a physician with this expertise. (D)

2. All patients entering HIV care should have documented evidence of HIV antibody testing. If laboratory confirmation is not available, a repeat HIV antibody test should be performed. (D)

3. Clinicians should obtain a comprehensive present and past medical history, including HIV-related information, assessment of present medications, family history and psycho-social issues, and review of systems and conduct a complete physical examination upon the patient's entry into care. (D)

4. A baseline CD4 cell count (absolute and fraction) and quantitative HIV RNA (plasma viral load) should be done for all patients upon entry into care. (A)

5. All patients should be assessed for transmitted HIV drug resistance using genotypic drug resistance testing. Ideally, the drug resistance testing should be conducted on the first available sample of HIV plasma viral load. (B)

6. HLA-B*5701 testing is recommended once at baseline for all patients. HLA-B*5701-positive patients must not be given abacavir-containing regimens. (A)

7. Hematology (CBC with differential and platelet count) and comprehensive biochemistry (liver and renal function, lipid profile, fasting blood glucose and/or HbA1C) is recommended at baseline to support management of ART toxicities and to evaluate other potential co-morbidities. (D)

8. A chest X-ray should be performed at baseline in all PLWH. (D)

9. All patients should receive baseline screening for a variety of other infectious agents to assess the need for immunization, monitoring, and counselling (see **Section 4, Screening and Immunization for Selected Co-Morbid Infections**). (D)

10. PLWH should be advised of the risk of onward transmission, the effectiveness of HIV treatment in preventing transmission, other practices to prevent transmission, and the legal implications of HIV non-disclosure with their sexual partners. (D)

SCREENING AND IMMUNIZATION FOR SELECTED CO-MORBID INFECTIONS

Tuberculosis Screening

1. All PLWH should be screened at baseline for *Mycobacterium (M.) tuberculosis* (TB) infection. (A) Screening involves reviewing history of TB exposure and/or treatment history and previous tuberculin skin test (TST) and/or interferon gamma release assay (IGRA) results. (B) A chest X-ray should be undertaken if there is history of TB exposure or positive screening test. (B)

2. In BC, the TST using 5 tuberculin units (0.1 mL) of purified protein derivative (PPD) is the main test for diagnosing latent TB infection (LTBI), provided there are no contraindications. (B)

3. IGRAs are currently recommended as an adjunct test to TST and may be valuable in the following two situations: a) PLWH with CD4 cell count <200 cells/mm^3 who are TST-negative (if possible, the T-SPOT® assay is preferred); and b) PLWH with a history of contact with active TB and who are TST-negative. (C)

Toxoplasmosis Screening

1. All PLWH should be screened at baseline for Toxoplasma IgG antibodies to determine prior exposure to *Toxoplasma (T.) gondii.* (D)

Hepatitis Screening

1. PLWH should be screened at baseline for hepatitis A virus (HAV) using total anti-HAV antibodies. (B)

2. PLWH should be screened at baseline for hepatitis B virus (HBV) using HBsAg (hepatitis B surface antigen), anti-HBs (hepatitis B surface antibody), and anti-HBc (hepatitis B core antibody). (B)

3. Individuals testing negative for HBsAg and anti-HBs but testing positive for anti-HBc (isolated positive core antibody) should have HBV DNA testing to rule out occult HBV infection, particularly if the CD4 count is <200 cells/mm^3. (D)

4. PLWH should be screened at baseline for hepatitis C virus (HCV) using a test for HCV antibodies. Positive HCV antibody test results should be confirmed by measuring HCV RNA PCR. Regular HCV antibody screening at least once annually is recommended for populations at risk for HCV transmission. (B)

Screening for Syphilis and Other Sexually Transmitted Infections (STIs)

1. All PLWH should be screened for syphilis at baseline with *Treponema pallidum*-specific enzyme immunoassay (EIA). (B) Syphilis screening should be repeated annually, or every 3-6 months in the presence of ongoing risk behaviours, or in the presence of symptoms. (D)

2. A lumbar puncture should always be performed for patients with a reactive syphilis serology who have neurologic or ocular symptoms or signs, irrespective of past syphilis treatment history. (D)

3. All PLWH should be screened at baseline for gonorrhea and chlamydia. (B) Screening should occur every 3-6 months in the presence of ongoing risk behaviours or in the presence of symptoms. (D)

Recommended Vaccines

Hepatitis A

1. All PLWH who are susceptible (anti-hepatitis A [HAV] negative) should be vaccinated against HAV, ideally when CD4 >200 cells/mm^3. (B)

2. The HAV vaccine should be administered intramuscularly at the standard dose, at 0, 1, and 6 months. (B)

Hepatitis B

1. All PLWH who are susceptible to hepatitis B virus (HBV) infection (HBsAg negative and anti-HBs less than 10 IU/mL) should be vaccinated against HBV, ideally when CD4 >200 cells/ mm^3. (B)

2. HBV vaccination should also be offered to PLWH who have positive hepatitis B total core antibody (anti-HBc) with negative HBsAg and anti-HBs results (titre less than 10 IU/mL) and undetectable HBV DNA. (D)

3. In the situations described above, HBV vaccine should be administered intramuscularly (IM) to PLWH 20 years of age and older at a higher dose (40 mcg).
   - Recombivax HB® (10 mcg/mL): give 4.0 mL IM at 0, 1, and 6 months (B)
   - Recombivax HB ® Adult Dialysis formulation (40 mcg/mL) give 1.0 mL IM at 0, 1, and 6 months (B)
   - Engerix®-B Adult (20 mcg/mL): give 2.0 mL IM at 0, 1, 2, and 6 months (B)

4. Post-serologic testing (using anti-HBs) within 1-6 months of completion of the vaccine series is recommended to monitor success of immune response to vaccine. (B)

Pneumococcal Disease

1. All PLWH should be vaccinated against pneumococcal disease using standard vaccine doses (A), regardless of CD4 cell counts and according to the following schedules:
   (i) Individuals who have not previously received any pneumococcal vaccine: One dose of conjugate pneumococcal vaccine (Pneu-C-13) is followed at least 8 weeks later by one dose of polysaccharide pneumococcal vaccine (Pneu-P-23). (B)
   (ii) Individuals who have received a pneumococcal polysaccharide vaccine (Pneu-P-23) previously: The Pneu-C-13 dose should be administered at least one year after any previous dose of Pneu-P-23. (C)
   (iii) If re-immunization with Pneu-P-23 is needed, it should be given at least 8 weeks after the Pneu-C-13 dose and at least 5 years after the initial Pneu-P-23 dose. (C)

Influenza

1. All PLWH should be vaccinated annually against influenza using standard doses of the inactivated vaccine, regardless of CD4 cell counts or HIV plasma viral load. (B)

Tetanus and Diphtheria

1. All PLWH should be offered a tetanus and diphtheria (Td) toxoid booster every 10 years, ideally when CD4 >200 cells/mm^3. (D)

Human Papillomavirus (HPV)

1. HPV-9 vaccine is recommended for all PLWH aged 9-27 years (A) and should be strongly considered in women and MSM aged 27 years and older. (B) A three-dose series is recommended in adults.

Additional Vaccines

Measles, Mumps, and Rubella (MMR)

1. All PLWH without evidence of immunity and with CD4 cell counts >200 cells/mm^3 should be considered for measles and/or mumps and/or rubella vaccination (given as a two-dose series of MMR vaccine). (B)

Varicella

1. All PLWH without evidence of immunity and with CD4 cell counts >200 cells/mm^3 may be considered for varicella vaccination (given as a two-dose series of varicella vaccine given >3 months apart). (D)

Herpes Zoster

1. The use of inactivated herpes zoster vaccine for prevention of shingles in PLWH over age 50 can now be considered. (D) Dosage and schedule: 0.5mL IM at 0 and 2-6 months. No requirement for repeat dosing currently exists. (D)

COVID-19

1. PLWH aged 18 years or older should be vaccinated for COVID-19 if they meet current Public Health criteria and if they have no contraindications (for up-to-date information refer to the BC-CfE therapeutic guidance, http://bccfe.ca/therapeutic-guidelines, or Immunize BC, https://immunizebc.ca/covid-19). (D)

Contraindicated Vaccines

1. The following live vaccines are contraindicated in PLWH: oral polio, live intranasal influenza vaccine, and BCG (Bacillus Calmette-Guérin). (B)

SPECIAL CONSIDERATIONS FOR CISGENDER WOMEN LIVING WITH HIV (WLWH)

Special Considerations Related to ART During Pregnancy and the Post-Partum Period

1. All pregnant PLWH should be treated with ART for their HIV infection, regardless of their immunologic or virologic status, to prevent infection of their fetus. (A)

2. Clinicians should review the latest recommendations regarding ART for individuals who are pregnant or of childbearing potential, since some drugs may be contraindicated or should be used with the guidance of specialized care providers. (D)

3. Preconception counselling is recommended for any PLWH contemplating pregnancy. (D) In BC, preconception counselling can be provided by referral the Oak Tree Clinic at BC Women's Hospital and

Health Centre (http://www.bcwomens.ca/health-professionals/refer-a-patient/oak-tree-clinic-hiv-care).

4. Pregnancy in PLWH is potentially high risk and complex; therefore, consultation with or referral to an obstetrician experienced in HIV is recommended. (D)

5. Breastfeeding is not recommended in Canada for PLWH, regardless of HIV viral load and use of ART. (D)

Reproductive Issues and Gynecologic Health in the Context of HIV

1. Contraception needs and pregnancy plans should be discussed with all individuals of childbearing potential (aged 15-50 years) upon initiation of HIV care and routinely thereafter, as pregnancy may affect the choice and timing of antiretrovirals. (D)

2. Selection of a contraceptive method should take into account the PLWH's desires about family planning and preferred contraceptive method, ART regimen, other medications, and co-morbid conditions. (D) Intrauterine devices (IUDs) can be considered as a safe and effective contraception option for PLWH. (B)

3. When prescribing ART, clinicians should take into account that some antiretrovirals (ARVs) have significant pharmacokinetic (PK) interactions with hormonal contraceptives; other effective contraception options should be considered to prevent unplanned pregnancy. (B) Switching to an ARV drug that does not have interactions with hormonal contraceptives may also be considered. (B)

Menopause

1. When systemic menopausal hormone therapy or non-hormonal medications are indicated for PLWH experiencing menopausal symptoms, potential drug interactions with ART should be considered. (B)

SPECIAL CONSIDERATIONS FOR TRANSGENDER INDIVIDUALS LIVING WITH HIV

1. Endocrine therapy for transgender individuals living with HIV should be provided in consultation with an endocrinologist or other clinician who has experience providing endocrine care to transgender individuals. (D)

2. Selection of an ART regimen for transgender individuals living with HIV should take into account the potential for drug-drug interactions between certain ARVs and hormonal agents used for gender-affirming therapy. (B)

3. Transmasculine individuals who have not had bilateral mastectomy (A) and transfeminine individuals between the ages of 40 and 74 who have taken estrogen-based hormone therapy for more than 5 years (C) should be screened according to the BC Cancer breast screening policy for cisgender (non-transgender) persons.

COMMON NON-INFECTIOUS CO-MORBIDITIES

Cardiovascular Disease

1. All PLWH should be screened for risk of cardiovascular disease at least annually, and modifiable cardiovascular risk factors should be addressed where possible. (D)

2. Blood pressure should be measured at least annually and at each visit (at least every 6 months) if abnormal. (D)

3. Assess lipids (total, HDL, and LDL cholesterol, and triglycerides) and/or apolipoprotein B at baseline and every 6-12 months once patient begins antiretroviral therapy. (B)

4. An electrocardiogram (ECG) should be considered at baseline and periodically (at intervals determined by the degree of risk) in patients taking protease inhibitors and/or rilpivirine with other PR- or QTc-prolonging drugs. (D)

Insulin Resistance (IR) and Diabetes Mellitus (DM)

1. Fasting blood glucose (FBG) and/or glycated hemoglobin (HbA1C) should be performed in all PLWH at baseline and at 6- to 12-month intervals during antiretroviral therapy. Abnormalities in fasting glucose and/or HbA1C should be evaluated and managed according to the Diabetes Canada guidelines (http://guidelines.diabetes.ca/). (A)

2. Initial management of blood glucose abnormalities in PLWH involves lifestyle changes (weight loss, diet, exercise). (A)

3. Oral anti-glycemic agents and injectable anti-glycemic agents should be used as required, keeping in mind drug interactions with some antiretrovirals. (A)

Bone

1. Clinicians should undertake preventive measures for bone loss in all PLWH, including weight-bearing exercises, maintaining ideal weight, reducing smoking and alcohol consumption, and optimizing vitamin D (1000-2000 IU/day) and calcium intake (in the form of diet and/or supplements if necessary). (D)

2. Screening for risk of fragility fractures using the Fracture Risk Assessment (FRAX) tool (https://www.sheffield.ac.uk/FRAX/tool.aspx?country=19) should start at the age of 40 years for cisgender women and 50 years for all PLWH. (D)

3. Clinicians should consider performing a baseline dual energy X-ray absorptiometry (DXA) scan to assess bone mineral density for: cisgender women living with HIV who are post-menopausal; all PLWH living with HIV aged 50 years and older; and PLWH of any age with a history of fragility fractures, >10% 10-year risk of major osteoporotic fracture by FRAX, and/or significant risk factors for osteoporosis (https://osteoporosis.ca/health-care-professionals/clinical-practice-guidelines/osteoporosis-guidelines/). (B) DXA scan should be repeated at intervals according to local provincial recommendations. (B)

4. If decreased bone density is diagnosed, secondary causes such as hypogonadism, alcoholism, glucocorticoid exposure, vitamin D deficiency, hyperparathyroidism, hyperthyroidism, renal phosphate wasting, and idiopathic hypercalciuria should be investigated and treated appropriately, including referral to a specialist if necessary. (D)

Renal Disease

1. It is recommended that laboratory assessment of renal function (i.e. serum creatinine, estimated glomerular filtration rate [eGFR], serum phosphate, urinalysis for protein and sediment, and spot urine for albumin to creatinine ratio [UACR]) should be performed in all PLWH at baseline and every 3-4 months after starting antiretrovirals, increasing to 6-month intervals when stable (depending on degree of risk). (D)

2. Blood pressure should be measured at least annually and at each visit (at least every 6 months) if abnormal. (D)

3. In case of renal dysfunction, clinicians should adjust doses of medications, including antiretrovirals that are cleared by the kidney. (B) An exception is tenofovir DF, which should be avoided in patients with or at high risk of renal disease and replaced with another agent in the presence of clinically significant renal dysfunction. (B)

Hypogonadism

1. Cisgender men living with HIV presenting with symptoms of hypogonadism should be assessed with a morning serum total testosterone level; an abnormal testosterone level should be confirmed with repeat testing. (B) An estimated bioavailable testosterone measurement may be helpful to assess certain individuals, including obese cisgender men with borderline low total testosterone levels. (B)

2. Testosterone replacement is indicated only for symptomatic cisgender men with total testosterone levels less than 10 mmol/L (B) and should be prescribed in consultation with a specialist. (D)

3. Endocrine therapy for transgender individuals living with HIV should be provided in consultation with an endocrinologist or other clinician who has experience providing endocrine care to transgender individuals. (D)

Neurocognitive Impairment

1. ART to suppress plasma viral load should be started early and administered continuously to prevent or minimize HIV-related neurocognitive impairment. (B)

2. In PLWH presenting with cognitive complaints that affect their daily functioning, an investigation should be done to rule out relevant underlying conditions. (B)

Lung Disease

1. Smoking cessation should be strongly encouraged in all PLWH because they are at a higher risk for chronic obstructive pulmonary disease (COPD) and lung cancer than smokers who do not have HIV. (A)

2. A chest X-ray should be performed at baseline in all PLWH. (D) Once infection has been treated or ruled out, patients with persistently abnormal chest X-ray findings should be investigated and referred to a respiratory specialist if necessary. (D)

3. PLWH of any age presenting with persistent respiratory complaints should be assessed via spirometry, especially those with additional risk factors such as smoking. (B)

4. COPD should be managed according to current Canadian Thoracic Society guideline (https://cts-sct.ca/guideline-library/). (A) Concomitant use of inhaled steroids with ritonavir or cobicistat should be avoided if possible. (B)

Liver Disease/Cirrhosis

1. Liver enzymes and liver function should be assessed in all PLWH at baseline and every 3-4 months after starting ART, increasing to 6-month intervals when stable. (D)

2. All PLWH who are co-infected with hepatitis C virus and have cirrhosis, all who are co-infected with hepatitis B virus (regardless of fibrosis stage), and all who have cirrhosis from another etiology should be screened for hepatocellular carcinoma every 6 months using ultrasound. (B)

3. All PLWH with cirrhosis should be referred for a baseline gastroscopy to screen for esophageal varices. (B)

Cancer

1. In PLWH, screening for breast, colorectal, and prostate cancer should follow current provincial recommendations for the general population. (A)

2. PLWH may be at an increased risk for lung cancer, HPV-related cancers (oropharyngeal, cervical, anal), lymphoma, and hepatocellular cancer as compared to the general population. Increased surveillance for these cancers is recommended. (D)

3. Annual cervical cancer screening should be offered to all PLWH with a cervix between ages 25-69. (C) If Pap smear results are abnormal, the individual should be referred for colposcopy and directed biopsy, as recommended by BC Cancer, with further treatment as indicated by results. (A)

4. After three or more consecutive normal cervical Pap results in individuals who are actively engaged in HIV care and have a CD4 count >500 cells/mm^3, less frequent screening can be considered on a case-by-case basis. (C)

5. Annual digital rectal examination is recommended as a screening test for anal cancer for all PLWH. (D) We do not currently recommend routine anal cytology (anal Paps) for anal cancer screening in PLWH. (D)

Mental Health

1. Mental health should be proactively assessed during clinic visits, and identified conditions should be managed using a stepped-care approach. (D)

2 BACKGROUND

2.1 INTRODUCTION

Today, HIV infection is a chronic manageable medical condition. Early diagnosis and initiation of potent antiretroviral therapy (ART) has dramatically improved the management of HIV infection and has led to substantial reductions in HIV-related morbidity and mortality.(1, 2) A study from 2013 estimated that a 20-year-old living with HIV and receiving ART in the U.S. or Canada could expect to live into their early 70s, a life expectancy approaching that of the general population.(3) In addition, there is now clear evidence that the widespread use of ART prevents HIV transmission at the individual (4-6) and population level.(7-9) In order for ART to be effective, individuals must be fully engaged in care, from the initial assessment following diagnosis, in order to receive timely initiation of ART and achieve long-term retention in care and virologic suppression. This concept, known as the HIV Cascade (or Continuum) of Care (10) has been adopted as the framework for assessing progress in HIV care and treatment in BC (Figure 2.1) and more generally as the 90-90-90 targets promoted by UNAIDS.(11) As of the end of 2018, an estimated 92% of people living with HIV (PLWH) in BC were diagnosed, 91% of those diagnosed were receiving ART, and of those on ART, 94% had a measured HIV viral load <200 copies/mL.(12) Providing appropriate and accessible primary care services is key to helping PLWH to remain fully engaged in HIV care and treatment.

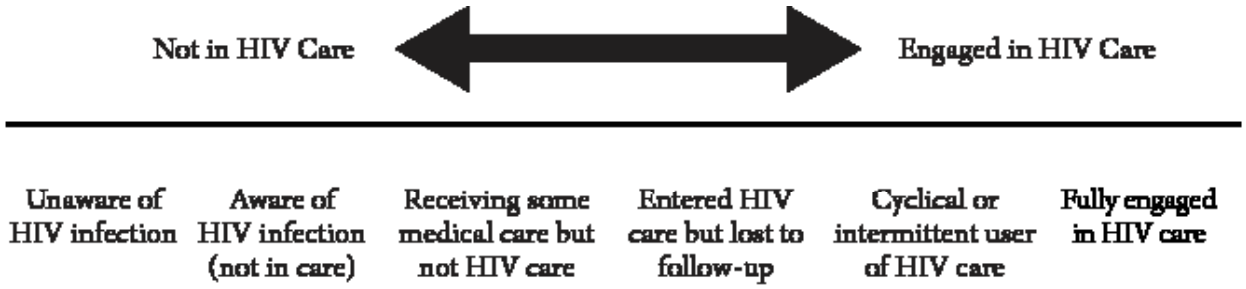

Figure 2.1: The HIV Cascade of Care.

2.2 MODES OF HIV TRANSMISSION

The key modes of HIV transmission – sexual contact, perinatal transmission, and exposure to infected blood (e.g. through sharing of injection drug paraphernalia or receipt of contaminated blood products) – were clarified early in the AIDS epidemic. In untreated PLWH, HIV is present in significant concentrations in blood, semen, vaginal and rectal fluids, breast milk, and other body fluids contaminated with blood. However, the likelihood of HIV transmission by different routes of exposure varies markedly, as shown in **Table 2.1** (adapted from Patel, et al. (13)).

Table 2.1: Risks of HIV transmission from a known PLWH without the use of ART in the source person

Method	Estimated Risk per 100 Events	Estimated Number of Exposures per Transmission Event
Sexual Exposures		
Receptive Penile-Vaginal Intercourse	0.06 – 0.11	1 in 1250
Insertive Anal Intercourse	0.4 – 0.28	1 in 900
Receptive Anal Intercourse	1.02 – 1.86	1 in 72
Needle Sharing with Injection Drug Use	0.4 – 0.9	1 in 160
Hollow Bore Needlestick Injury	0 – 0.46	1 in 435
Perinatal Exposure	18 – 25	1 in 5

Adapted from Patel, et al., 2014.(13) For further information see BC CfE HIV Post-Exposure Prophylaxis (PEP) Guidelines.

It has now been clearly demonstrated that even after repeated sexual exposures without using condoms, PLWH who are receiving ART and have maintained a plasma HIV viral load <200 copies/mL do not transmit HIV.(6) This has been shown for both heterosexual couples and men who have sex with men.(5)

Studies suggest that as many as 50% of HIV transmission events may occur from index persons who are in the acute and very early stages of illness.(14-17) Thus, early detection of HIV infection is a critical component of preventing further transmission.(18) Several factors contribute to the increased risk of transmission during acute infection, including:

- Absent or unrecognized symptoms of acute HIV infection;
- Very high levels of viremia during acute infection; and
- Likelihood that high-risk behaviours are ongoing during this period because the individual is unaware of their HIV status.

For specific guidance on the treatment of acute HIV infection, please refer to the BC Guidelines for the Management of Acute HIV Infection: (http://bccfe.ca/sites/default/files/uploads/Guidelines/Management-of-Acute-HIV-Infections-[16-MAY-2018].pdf)

2.3 NATURAL HISTORY OF HIV/AIDS

The mean time from HIV exposure to onset of acute seroconversion illness is generally 2-4 weeks, with a range of 5-29 days(19), and only an estimated 34% of PLWH will experience symptomatic seroconversion illness (see **Appendix 1, page 112**: Signs and symptoms associated with HIV Seroconversion Syndrome/ Acute Retroviral Syndrome and their frequency in symptomatic individuals).(20) During seroconversion without ART, there is an initial drop in CD4 cell counts and peak of viremia before CD4 cell counts increase (although to levels typically below pre-infection levels) and viral load decreases and stabilizes at a set point for several years (Figure 2.2). Without ART, there is considerable variability in the time of onset of further symptoms and late-stage disease. People whose CD4 cell counts stabilize above 500 cells/mm^3 may remain healthy for several years before CD4 cell counts begin to decline. In some cases, CD4 cell counts can

drop rapidly after infection in the absence of ART; however, the usual scenario is that without treatment, CD4 cell counts decline over approximately 5-8 years until symptoms begin to appear. A small proportion of PLWH (5-10%), called "long-term non-progressors," will maintain low viral load and stable CD4 cell counts for decades without specific treatment.(21)

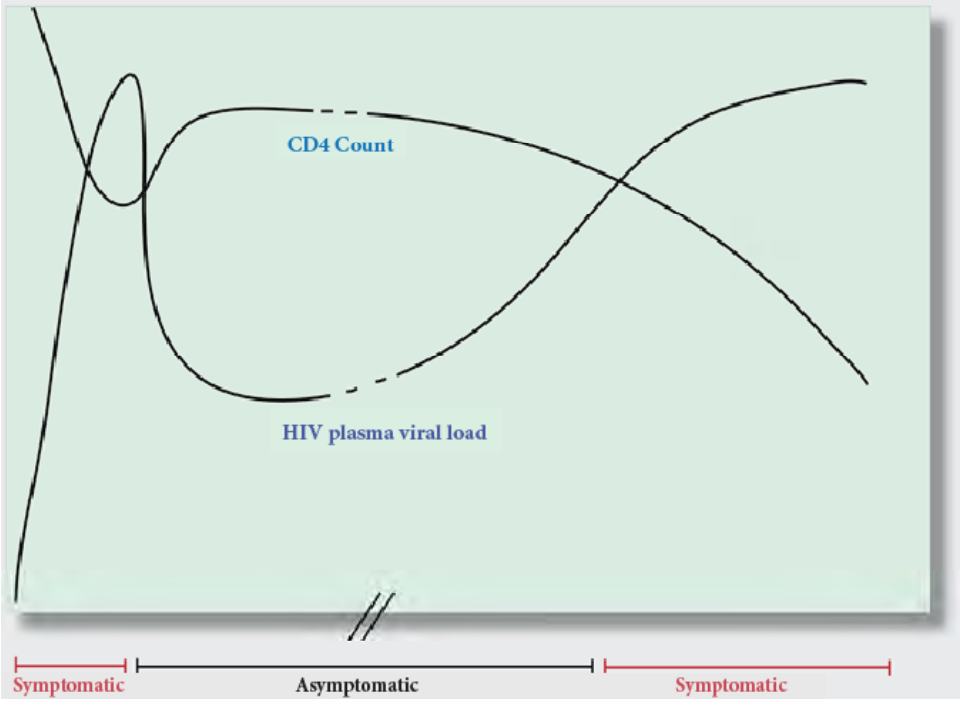

Figure 2.2: Natural history of HIV/AIDS

Adapted from Lewthwaite and Wilkins, 2005.(21)

Some PLWH may not exhibit any symptoms initially, while others may have minor symptoms and/or persistent generalized lymphadenopathy which often go unnoticed by the individual. During this initial stage, viral replication occurs in lymphoid tissue, and thrombocytopenia may occur. HIV may also begin to affect co-morbid conditions, such as hepatitis B and C, accelerating the progression of liver fibrosis. In the absence of ART, CD4 cell counts eventually decrease, rendering PLWH susceptible to a host of infections (caused by pathogens such as Mycobacterium tuberculosis, Streptococcus pneumonia and Varicella zoster virus) and HIV-related tumours. Acquired Immune Deficiency Syndrome (AIDS) (US CDC classification category C disease) is defined by the development of specified opportunistic infections and cancers (see **Appendix 2,** page 113). In addition, uncontrolled HIV replication and immune activation lead to a chronic inflammatory state, resulting in end-organ damage and co-morbid conditions.(22)

However, timely initiation of ART will effectively prevent disease progression. In previous eras, HIV treatment was often deferred until PLWH demonstrated some degree of disease progression; however, there is now clear evidence that treating PLWH immediately after diagnosis provides substantial clinical benefits and this should be emphasized at all clinical encounters.

2.4 HIV TESTING

According to the 2014 Testing Guidelines for the Diagnosis of HIV in British Columbia (https://www2.gov.bc.ca/assets/gov/health/about-bc-s-health-care-system/office-of-the-provincial-health-officer/hiv-testing-guidelines-bc.pdf), health care providers should know the HIV status of all patients under their care.

Specifically, providers should offer an HIV test:

- Routinely, every five years, to all patients aged 18-70 years;
- Routinely, every year, to all patients aged 18-70 years who belong to populations with a higher burden of HIV infection; and
- Once for patients older than 70 years of age, if HIV status is not known.

As well, health care providers in BC are recommended to offer an HIV test to all youth, adults and the elderly, whenever

- Ordering diagnostic bloodwork for a new or worsening medical condition
- Patients present with symptoms of HIV infection or advanced HIV disease
- Patients or their providers identify a risk for HIV acquisition
- Patients request an HIV test
- Patients are pregnant
- Testing for any sexually transmitted infection (STI); or
- Testing for hepatitis C, hepatitis B, or tuberculosis.

After an initial HIV test in all patients, providers should repeat an HIV test at a frequency of every 5 years, or earlier if another indication for HIV testing is identified. The optimum frequency of testing in BC's population is not yet determined, and the recommended frequency may change over time.

Some populations in BC experience a higher burden of HIV infection and morbidity. It is recommended that patients who are members of these populations should be offered HIV testing at least annually, or more frequently if another indication for HIV testing is identified. These populations include: gay, bisexual and other men who have sex with men; people who inject drugs; people who work in the sex trade; people who have immigrated from countries where HIV is endemic (largely countries from the Caribbean and sub-Saharan Africa); and Indigenous people. It is important to note that BC's Indigenous population is very diverse and there is a wide range of HIV prevalence between communities. As with other populations with a higher burden of HIV, recommendations on HIV testing frequency for Indigenous populations are subject to change.

It is also important to note that for HIV testing, obtaining informed consent is the same as for any other diagnostic test or treatment. As with other diagnostic tests, if the pretest probability of a positive result is high, more extensive discussion may be warranted.

For HIV testing, the window period refers to the interval between the time when a person is infected and when the test can first detect HIV infection. The median window period is approximately 18 days (interquartile range 16-24 days) for the fourth generation EIA (enzyme immunoassay; which detects both viral p24 antigen and host antibody) currently in use in BC.(23, 24) By 6 weeks after infection, 99% of

PLWH will develop detectable HIV antigen or antibody and have a positive fourth generation test result (See **Figure 2.3** for a timeline).

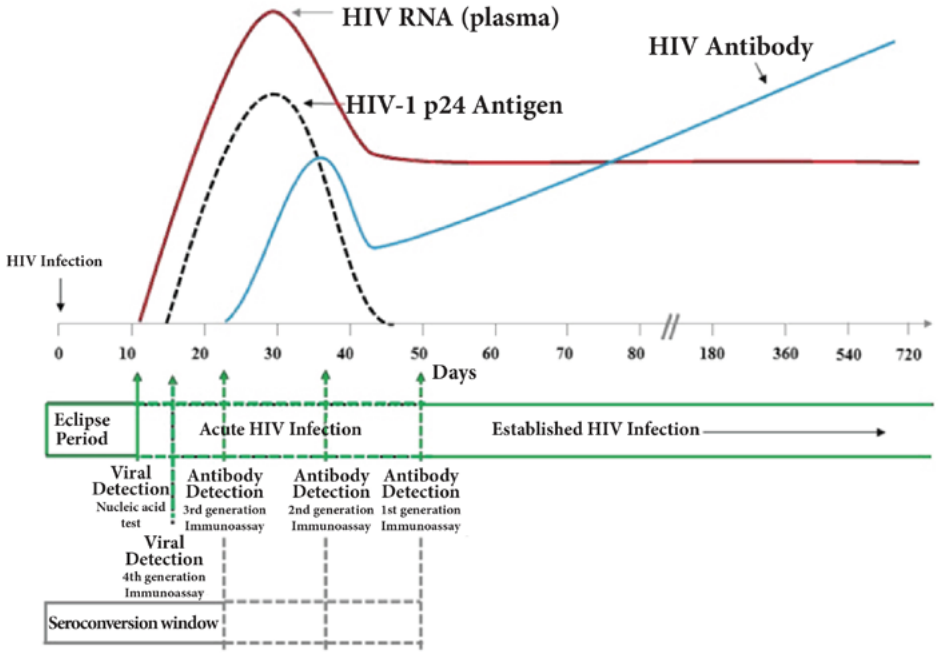

Figure 2.3: Sequence of appearance of laboratory markers for HIV-1 infection.

From CDC, 2014.(25)

All laboratories in BC currently utilize the fourth generation EIA antibody/antigen test(23) for all samples submitted for HIV serology. The sensitivity of the fourth generation EIA is approximately 99.9% and the specificity is approximately 99.7%. Any reactivity on the screening HIV EIA will automatically lead to a series of additional tests to help differentiate acute HIV infection from established HIV infection or a false positive HIV test (see **Figure 2.4**).

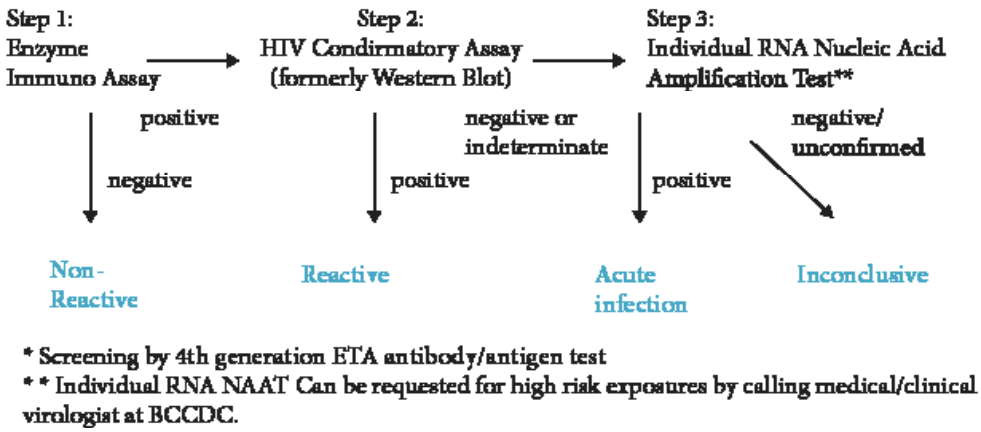

Figure 2.4: Current algorithm for EIA screening in BC.

Adapted from BC CDC, 2016.(23)

Once a diagnosis is made, follow-up medical care should be arranged as soon as reasonably possible. Patients should be provided with links and referrals to reliable information sources and local HIV support groups (see **Appendix 4,** page 116) if desired. The follow-up health care provider should work with the patient to determine what support systems are in place and whether further supports are needed. It is important to emphasize that, with appropriate treatment, HIV is a manageable chronic condition with a good prognosis and that the patient should expect the HIV medications to be simple to take with no or minimal side effects.

Regional public health teams may be helpful in linking newly diagnosed individuals to clinicians who are familiar with the management of HIV infection. A list of contact numbers can be found in **Appendix 4,** page 117.

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3 INITIAL ASSESSMENT OF PEOPLE LIVING WITH HIV (PLWH)

Recommendations:

1. All PLWH should have timely access to a primary care clinician with knowledge in the management of HIV infection and should receive care in a culturally sensitive environment. Primary care clinicians without expertise in HIV care should consult with a physician with this expertise. (D)

2. All patients entering HIV care should have documented evidence of HIV antibody testing. If laboratory confirmation is not available, a repeat HIV antibody test should be performed. (D)

3. Clinicians should obtain a comprehensive present and past medical history, including HIV-related information, assessment of present medications, family history and psycho-social issues, and review of systems and conduct a complete physical examination upon the patient's entry into care. (D)

4. A baseline CD4 cell count (absolute and fraction) and quantitative HIV RNA (plasma viral load) should be done for all patients upon entry into care. (A)

5. All patients should be assessed for transmitted HIV drug resistance using genotypic drug resistance testing. Ideally, the drug resistance testing should be conducted on the first available sample of HIV plasma viral load. (B)

6. HLA-B*5701 testing is recommended once at baseline for all patients. HLA-B*5701-positive patients must not be given abacavir-containing regimens. (A)

7. Hematology (CBC with differential and platelet count) and comprehensive biochemistry (liver and renal function, lipid profile, fasting blood glucose and/or HbA1C) is recommended at baseline to support management of ART toxicities and to evaluate other potential co-morbidities. (D)

8. A chest X-ray should be performed at baseline in all PLWH. (D)

9. All patients should receive baseline screening for a variety of other infectious agents to assess the need for immunization, monitoring, and counselling (see **Section 4, Screening and Immunization for Selected Co-Morbid Infections**). (D)

10. PLWH should be advised of the risk of onward transmission, the effectiveness of HIV treatment in preventing transmission, other practices to prevent transmission, and the legal implications of HIV non-disclosure with their sexual partners. (D)

Evidence:
Newly diagnosed individuals should be assessed by a primary care physician or nurse practitioner (NP) within a few days of receiving a positive HIV test result (ideally less than 2 weeks) so that the baseline laboratory workup can be ordered and the individual can receive appropriate counselling and rapid initiation of antiretroviral treatment (ART).(1-3) When a person is suspected to be in the very early stages of HIV infection or in acute infection, they should be assessed by an experienced HIV clinician within 1-2 days of diagnosis to initiate ART as soon as possible.(4, 5) Clinicians should provide evidence-based care that is linguistically and culturally appropriate to effectively engage and assist patients in their care. Low treatment adherence and poor engagement in care were found to predict almost 50% higher mortality in people with living with HIV (PLWH).(6) Clinicians with limited HIV experience should be encouraged to connect with an experienced mentor who will provide advice and consultation support when needed; alternatively, clinicians should access the provincial RACE line for a phone consult with a clinician with expertise in HIV (1-877-696-2131 http://www.raceconnect.ca). Furthermore, the BC-CfE provides an on-line training program, *HIV Treatment and Management*, which is specifically designed for primary care clinicians. For more information, visit: http://education.bccfe.ca.

Documentation of a positive HIV antibody test is necessary for a number of reasons. Patients may have tested non-nominally, anonymously, or outside of their local jurisdiction (i.e. in a different province or country), resulting in an absence of prior documentation. There is also the possibility of testing errors (specimen handling or mislabelling) when individuals are identified as HIV-positive for the first time. Patients may also be unclear about whether they have received an HIV antibody test in the past, or they may present with misinformation regarding previous test results.(7)

3.1 INITIAL ASSESSMENT

Clinicians should obtain a comprehensive present and past medical history, including HIV-related information, assessment of present medications, family history and psychosocial issues and review of systems. A complete physical examination should be performed upon the patient's entry into care or as soon afterwards as possible. In the setting of rapid ART initiation, clinicians may abbreviate the initial assessment and conduct a more targeted exam. A more comprehensive assessment should be done in follow-up.

Important elements of the initial assessment are included in **Table 3.1**.

Table 3.1: Initial assessment, medical history.

General History	• Review sources of past medical care; obtain medical records whenever possible • Past hospitalizations, past and current illnesses • Ongoing co-morbidities, i.e. liver disease, cardiovascular disease, diabetes mellitus, hypertension, kidney disease, osteopenia or osteoporosis, asthma or chronic obstructive pulmonary disease, etc. • History of sexually transmitted infections including: syphilis, chlamydia, gonorrhea, herpes simplex, trichomoniasis, chancroid, human papillomavirus (HPV) • Last cervical or anal Pap test, any abnormal Pap test result in the past • Tuberculosis history o Possible recent exposure to tuberculosis o History of positive purified protein derivative (PPD) testing, *Mycobacterium tuberculosis* (TB) disease, or treatment of latent TB infection • History of hepatitis A, B, and C; previous hepatitis C treatments • Current prescription and non-prescription medicines, including over-the-counter medications, nutritional supplements, complementary and alternative medicines, and hormones • Vaccination history, including hepatitis A and B series, pneumococcal vaccine (13 valent and 23 valent), flu shots, tetanus/diphtheria, HPV, varicella zoster, COVID-19 • Reproductive history, including pregnancies, births, termination of pregnancy; current contraceptive use and needs • Partner information for discussion of disclosure of HIV status • Allergies and intolerance; dates and type of reaction • Travel history/place of birth • Occupational history and hobbies
HIV-Related History	• HIV exposure history • Date and place of HIV diagnosis o Route of exposure, if known o Previous HIV status • Most recent viral load and CD4 cell count • History or symptoms of seroconversion illness • Nadir CD4 cell count and peak viral load • Drug-resistance testing (genotype) • Use of pre- or post- exposure prophylaxis • Previous HIV care • Current and previous antiretroviral regimens, date of initiation of ART, and HIV RNA levels while on ART • Previous ART adverse drug reactions • Opportunistic infections • Previous adverse reactions to drugs used for opportunistic infection prophylaxis • Providers who have been involved in the patient's HIV management • Patient's understanding of HIV disease and treatment

Mental Health History	• Mental health diagnoses, especially: o Depression o Anxiety o Post-traumatic stress disorder o Suicidal/violent behaviour o Severe and persistent mental illness • Psychotropic medications • Past psychiatric hospitalizations • Contact information for mental health providers, if applicable
Substance Use History	• Types of drugs; past and current use of: o Cannabis and cannabinoids (including vaping) o Stimulants, including methamphetamine, cocaine, crack cocaine o Opioids • Misuse or overuse of prescription drugs • Alcohol use, quantify weekly/monthly use • Tobacco including e-cigarettes; years of use and estimate of cumulative exposure • Frequency of substance use and usual route of administration • Risk behaviours—drug/needle sharing, exchanging sex for drugs, sexual risk-taking while under the influence of drugs or alcohol • History of treatment and barriers to treatment
Sexual History	• Current sexual activity • Sexual practices—vaginal, anal, oral • Gender identity • Past and current partners • Risk behaviour assessment, including use of latex or polyurethane barriers, number of partners
Psycho-social Assessment	• Housing status • Employment and insurance status • Educational level • Family and partner contacts • Diet and exercise • Stability of personal relationships o Domestic violence screening • Immigration status

Review of Systems	• Constitutional—weight loss, malaise, fevers, night sweats, changes in appetite, changes in sleep, adenopathy • Eyes—change in vision, including blurry vision, double vision, flashes of light, or loss of vision • Ears, nose, throat—dysphagia, odynophagia, hearing loss, discharge, dental pain, periodontal disease, oral herpes simplex, oral thrush, oral hairy leukoplakia • Pulmonary—cough, dyspnea at rest or on exertion, hemoptysis, sputum • Cardiac—chest pain, palpitations • Abdominal—nausea, vomiting, diarrhea, constipation, blood per rectum, hemorrhoids • Genitourinary: o Vaginal or penile discharge, vaginal pain, dysuria, genital/rectal warts, classic and atypical herpes simplex virus o Obstetrics/gynecology - menstrual status, bleeding, infections, last Pap test and result • Extremities—muscle wasting, muscle weakness, muscle pain, joint swelling • Neurologic—cognitive changes; tingling, burning, pain, or numbness in the extremities; weakness

In the course of taking a medical history, health care providers should also assess the individual's understanding of HIV disease (including risk for HIV transmission), explore their understanding of and readiness to initiate ART, note potential barriers to treatment adherence, and identify their psychosocial needs. The baseline evaluation should also include a discussion of risk reduction and disclosure to sexual and/or needle-sharing partners, especially with individuals who are not receiving HIV treatment and are still at high risk of HIV transmission (see **Section 3.4**).

3.2 PHYSICAL EXAMINATION

Clinicians should perform a comprehensive physical examination at baseline and when appropriate, with particular attention to systems potentially affected by HIV (see Table 3.2). Since weight fluctuations are common in PLWH, clinicians should measure weight at each visit (see US CDC's body mass index [BMI] calculator: http://www.cdc.gov/healthyweight/assessing/bmi/adult_bmi/english_bmi_calculator/bmi_calculator.html), as well as vital signs, with particular attention to blood pressure.(8)

Table 3.2: HIV-related physical examination.

Vital signs	• With special attention to blood pressure, weight, and height
Pain Assessment	• Assess at each visit
General	• Body habitus, obesity, wasting, lipodystrophy, frailty, and ambulatory ability

Ophthalmologic	• Perform or refer for a funduscopic examination when CD4 cell count <50 cells/mm^3 • Pallor, hemorrhages, or icterus • Vision changes
Head, Ears, Nose, Throat	• Sinus infection, odynophagia, dysphagia, hearing loss, parotid enlargement
Oral	• Oral candidiasis (thrush), hairy leukoplakia (examine lateral borders of tongue), Kaposi's sarcoma, gingival disease, aphthous ulcers
Dermatologic	• Rash, pruritus, psoriasis, molluscum contagiosum, seborrheic dermatitis, Kaposi's sarcoma, onychomycosis, diffuse folliculitis with pruritus, melanoma, medication-related rash, cutaneous fungal infections, purpura, petechiae, herpes simplex and zoster infections
Lymph Nodes	• Generalized or localized lymphadenopathy
Endocrinologic	• Abnormal subcutaneous fat redistribution • Thyroid gland assessment
Pulmonary	• Lung fields for wheezes, rhonchi, rales, or dullness
Cardiac Examination	• Heart rhythm, heart murmur, bruits or rub, peripheral edema, peripheral pulses
Abdominal	• Hepatosplenomegaly, multiple lipomata in the subcutaneous fat, increased visceral fat, abdominal masses or tumours, tenderness
Genital	• Genitourinary - vaginal or penile discharge, vaginal pain, ulcerative genital disease, venereal warts • Obstetrics/gynecology - careful pelvic examination • Cervical Pap test in persons with a cervix as per BC Cancer guidelines (http://www.bccancer.bc.ca/screening/Documents/Cervix-Program-Overview.pdf)
Rectal	• Visible anal lesions or evidence of skin abnormality around the anus, ulcers, warts, fissures, haemorrhoids, tumours • Digital rectal exam
Musculoskeletal	• Extremities, muscle wasting • Joint inflammatory changes
Neuropsychiatric	• Reflex, sensory, motor, and gait abnormalities • Signs of multifocal motor and sensory nerve abnormalities, especially peripheral neuropathy • Cranial nerves • Cognitive status examination, attention, memory, speech problems • Mental health: depression, mania, anxiety, signs of personality disorder

3.3 BASELINE LABORATORY EVALUATION

Two main surrogate markers are used to monitor the disease progression in PLWH: CD4 cell count to assess immune function and plasma HIV RNA (viral load) to assess level of HIV viremia.

The absolute CD4 cell count is a significant clinical indicator of immunocompetence in PLWH.(9) It is a calculated value based on the total white blood cell (WBC) count and the percentages of total and CD4 T-lymphocytes.(10) This absolute number may fluctuate in individuals or may be influenced by factors that affect the total WBC count and lymphocyte percentages, such as the use of bone marrow-suppressive medications or the presence of acute infections. Splenectomy or co-infection with human T-lymphotropic virus type 1 (HTLV-I) may cause misleadingly elevated CD4 cell counts. These markers are used to stage HIV disease initially and are subsequently used as predictors of disease progression and survival.(11) CD4 cell counts are also used to determine the risk of opportunistic infections (OIs), the need for prophylaxis for OIs or other AIDS-defining illnesses, and when to stop prophylaxis.(12, 13) HIV plasma viral load (HIV pVL) is the most important indicator of infectivity and response to ART and should be measured in all PLWH at initial assessment, at initiation of therapy and on a regular basis thereafter.(12) A patient's baseline viral load level and the magnitude of viral load decline after initiation of ART provide prognostic information about the probability of disease progression.(14) Commercially available HIV-1 RNA assays do not detect HIV-2 viral load (for more information regarding HIV-2 refer to the HIV-2 infection chapter in the United States Department of Health and Human Services (DHHS) guidelines; https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/AdultandAdolescentGL.pdf).(15)

All patients should be assessed for transmitted HIV drug resistance using genotypic drug resistance testing, regardless of the estimated duration of HIV infection. Ideally, drug resistance testing should be conducted on the first available sample of HIV plasma viral load. A resistance test should be done in individuals who reengage in care and are not currently receiving ART, recognizing that the absence of resistance mutations due to lack of selective pressure may not accurately reflect drug activity.(15) Standard genotypic drug resistance testing in ART-naïve persons involves testing for mutations in the reverse transcriptase and protease genes. Although reports of transmission of virus resistant to integrase strand transfer inhibitors (INSTIs) are rare, clinicians are increasingly prescribing this class of antiretrovirals and there is potential for the transmission of INSTI-resistant virus.(16-19) In BC, when HIV resistance testing is requested for a patient whose plasma viral load exceeds 250 copies/mL for the first time since diagnosis, the sample automatically undergoes testing for resistance to the INSTI class.(11) In BC, resistance testing can be requested in archived viral load samples. For more information regarding drug resistance testing, refer to the Laboratory Program tab on the BC-CfE website (http://bccfe.ca/research/laboratory-program/laboratory-test-order-forms).

HLA-B*5701 is not a specific HIV test, but rather a genetic test. Screening for HLA-B*5701 identifies persons at a high risk for hypersensitivity reaction (HSR) to the antiretroviral agent abacavir. Screening should be performed prior to starting any patient on an abacavir-containing regimen (including fixed-dose combinations, e.g. Kivexa, Triumeq®). HSRs, including fatalities, have been documented in individuals re-challenged with abacavir after a suspected HSR. In addition, screening for HLA-B*5701 should be performed, if not done previously, for patients who are re-initiating abacavir following a gap in therapy, even if they had previously tolerated the drug, because there is a potential for HSR in this setting.(20, 21)

Hematological panel (CBC with differential and platelet count) should be done at baseline since anemia, leukopenia and thrombocytopenia are common in people with untreated HIV infection. A comprehensive chemistry panel (including creatinine, eGFR, serum phosphorus, urinalysis, urine albumin to creatine

ratio (UACR), albumin, total bilirubin, aspartate transaminase, and alanine transaminase) is important to assess baseline renal and hepatic function and pre-existing conditions. Screening for diabetes mellitus with fasting glucose and/or hemoglobin A1C is recommended due to the increased incidence of diabetes in this population. A lipid profile should be done upon initial assessment when possible, since many ART drugs, HIV infection itself, and other host factors can increase cholesterol and triglyceride levels.

A chest radiography should be done at baseline to rule out underlying lung disease and for use as a baseline comparison in future evaluations of any respiratory illness, particularly in persons from high TB prevalence populations (**see Table 3.3**).

All individuals should receive baseline screening for a variety of other infectious agents, including other sexually transmitted infections and hepatitis A, B, and C virus, to assess the need for treatment, immunization, monitoring, and counselling (see **Section 4**). Rates of sexually transmitted infections have increased significantly in men who have sex with men, and screening at baseline for gonorrhea and chlamydia in urine and other sites of contact (oral and anal) are recommended. Furthermore, all PLWH should receive a syphilis test at baseline.

For laboratory monitoring of patients receiving ART please refer to Chapter 3 in the BC-CfE Therapeutic Guidelines for Antiretroviral (ARV) Treatment of Adult HIV Infection.(12)

Table 3.3: Baseline laboratory assessment

	Test	Baseline
HIV Infection Status	HIV diagnostic test: 4th generation HIV Ag/Ab	
Immunologic Assessment	CD4 absolute cell count and percentage	✓
HIV Plasma Viral Load (HIV pVL)	Quantitative RNA testing	✓
Drug Resistance Testing	HIV genotypic drug resistance	✓ (At the time of first HIV pVL)
HLA-B*5701		At baseline or before initiating or restarting therapy with abacavir, if not previously done
Hematologic Assessment	Complete blood count (CBC) with differential and platelet count	✓
Renal Function	Creatinine, estimated glomerular filtration rate (eGFR), phosphate, urinalysis, spot urine for albumin to creatinine ratio (UACR)	✓
Liver Tests	alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, albumin	✓

	Test	Baseline
Fasting Lipid Profile**	Total cholesterol (TC), high density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), triglycerides (TG), and/or apolipoprotein B	✓
Blood Glucose§	Fasting glucose and/or HbA1C	✓
Hepatitis B Serology	HepBsAb, HepBsAg, HepBcAb†	✓
Hepatitis C Serology	HCV antibody, and HCV RNA&	✓
Hepatitis A Serology	HAV total antibody	✓
STI assessment	Syphilis serology, chlamydia, and gonorrhea‡	✓
TB screening	TST and IGRA in selected populations£	✓
Cryptococcus	Cryptococcal antigen in serum	In persons with CD4 cell count <100 cells/mm^3
Toxoplasma	Toxoplasma IgG serology	In all persons regardless of CD4 cell count
Pregnancy test	For people of childbearing potential	✓
Pap test	Cytology: cervical Pap test	In persons with a cervix

** The Canadian Cardiovascular Society recognizes HIV as a significant risk factor for premature cardiovascular disease and as an indication for screening for cardiovascular risk factors, including lipids. In addition, some ARV agents may contribute to dyslipidemia. Apolipoprotein B (apoB) levels should be monitored, particularly in patients with high triglyceride levels.(22)

§ Diabetes mellitus (DM) is more prevalent in PLWH than in the general population, particularly in the setting of hepatitis C co-infection. DM risk may be exacerbated by certain antiretroviral medications. Diabetes Canada recommends monitoring fasting blood glucose and/or glycated hemoglobin (HbA1C).(23)

† Anti-HBs: Hepatitis B surface antibody, HBsAg: Hepatitis B surface antigen, Anti-HBc: Hepatitis B core antibody

& HCV: Hepatitis C virus. HCV RNA screening is indicated in persons who have been successfully treated for HCV or who spontaneously cleared prior infection. HCV antibody-negative individuals with elevated ALT may need HCV RNA testing.

‡ STI testing is recommended for all sexually active PLWH. Testing for chlamydia and gonorrhea consists of nucleic acid amplification test (NAAT) from throat/urine/rectum based on sexual activity and exposure. Repeat testing q3-6 months is recommended in populations with ongoing potential for infection.

£ TST: Tuberculin skin test. IGRA: Interferon Gamma Release Assay. Use of TST/IGRA depends on availability and local standard of care. IGRA should, however, be administered before TST if both are to be used, given the potential for a false positive IGRA after PPD.

3.4 COUNSELLING PLWH REGARDING HIV TRANSMISSION RISK

Recommendation:

1. PLWH should be advised of the risk of onward transmission, practices to prevent transmission, especially the effectiveness of HIV treatment in preventing transmission, and the legal implications of HIV non-disclosure with their sexual partners.

Evidence:
Safer sex and substance use practices to prevent onward transmission of HIV should be discussed with PLWH, and are especially important while the plasma HIV viral load is high (e.g. prior to starting ART and during the first few weeks of therapy or when there is treatment interruption). Condom use with each sexual act and safe injection practices are recommended. Practical information for PLWH is available from CATIE (www.catie.ca):

- CATIE Safer Sex Guide: Safer Sex Guide | CATIE - Canada's source for HIV and hepatitis C information
- CATIE Safer Injection: Safer injection | CATIE - Canada's source for HIV and hepatitis C information

For HIV-uninfected contacts, HIV post-exposure prophylaxis (PEP) is available in BC, and is effective for prevention of HIV acquisition if started within 72 hours after an unprotected exposure event, but is not appropriate for repeated use as a long-term solution (HIV Post-Exposure Prophylaxis | BC Centre for Excellence in HIV/AIDS (bccfe.ca)). HIV pre-exposure prophylaxis (PrEP) is available in BC for individuals at ongoing high risk of acquiring HIV (HIV Pre-Exposure Prophylaxis (PrEP) | BC Centre for Excellence in (bccfe.ca)).

It has now been clearly demonstrated that even after repeated sexual exposures without using condoms, PLWH who are adherent to ART and have HIV plasma viral load <200 copies/mL do not transmit HIV via sexual contact. This principle of "undetectable = untransmittable" or "U=U" has been shown for both heterosexual couples and men who have sex with men.(24-28) However, the Supreme Court of Canada (2012) ruled that there is an obligation to disclose HIV-positive status in relation to vaginal or anal sex unless both of the following conditions are met: a condom is used and the PLWH has "low" viral load (<1500 copies/mL). Under these circumstances, the Supreme Court of Canada holds that there is no realistic possibility of transmission. If PLWH were to engage in sexual activity that is considered to have a "realistic possibility of HIV transmission" without first disclosing their HIV status, they can be subject to criminal prosecution (most often aggravated sexual assault).(29, 30) PLWH should be advised of the legal implications of HIV non-disclosure. Further information for PLWH is available from:

- CATIE: HIV treatment and an undetectable viral load to prevent HIV transmission | CATIE - Canada's source for HIV and hepatitis C information
- Canadian HIV/AIDS Legal Network: https://www.hivlegalnetwork.ca/site/the-criminalization-of-hiv-non-disclosure-in-canada-report/?lang=en

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4 SCREENING AND IMMUNIZATION FOR SELECTED CO-MORBID INFECTIONS

4.1 SCREENING FOR CO-MORBID INFECTIONS

Tuberculosis Screening

Recommendations:

1. All PLWH should be screened at baseline for *Mycobacterium (M.) tuberculosis* (TB) infection. (A) Screening involves reviewing history of TB exposure and/or treatment history and previous tuberculin skin test (TST) and/or interferon gamma release assay (IGRA) results. (B) A chest X-ray should be undertaken if there is history of TB exposure or positive screening test. (B)

2. In BC, the TST using 5 tuberculin units (0.1 mL) of purified protein derivative (PPD) is the main test for diagnosing latent TB infection (LTBI), provided there are no contraindications. (B)

3. IGRAs are currently recommended as an adjunct test to TST and may be valuable in the following two situations: a) PLWH with CD4 cell count <200 cells/mm^3 who are TST-negative (if possible, the T-SPOT® assay is preferred); and b) PLWH with a history of contact with active TB and who are TST-negative. (C)

Evidence:
Among people living with HIV (PLWH) who are not receiving antiretroviral treatment (ART), the annual risk of reactivating latent tuberculosis (TB) infection (LTBI) may be as high as 10 per 100 person-years, making HIV the most powerful known factor in promoting reactivation of TB.(1) Although it is considered an AIDS-defining illness, TB can occur at any stage in the course of HIV infection as determined by the CD4 cell count.(2) The risk of acquiring TB increases with advancing immunosuppression and decreases dramatically in individuals receiving effective ART.(3, 4) Thus, the identification of LTBI and the early initiation of ART are key measures to prevent the development of active TB disease, and are of high priority in the care of PLWH.(5)

The tuberculin skin test (TST), consisting of the intradermal injection of a small amount of purified protein derived from *M. tuberculosis* bacteria, is the standard screening test for TB. In a person who has cell-mediated immunity to these tuberculin antigens, a cell-mediated, delayed hypersensitivity reaction will occur within 48-72 hours. The reaction will cause localized swelling and will manifest as induration of the skin at the injection site. Induration of ≥5 mm is considered significant in PLWH.(1) TST remains the standard method of diagnosing LTBI(1) in Canada, although it is recognized that TST has certain limitations. The sensitivity of the TST decreases in parallel with an individual's CD4 cell count. The TST has particularly low sensitivity in people with CD4 <200 cells/mm^3. False positive TST results are possible in those who have received Bacille Calmette-Guerin (BCG) vaccination.(6)

Interferon gamma release assay (IGRA) is an *in vitro* immunologic test that was developed more than a decade ago to diagnose TB infection, among other conditions. Currently, there are two IGRA tests available in BC – QuantiFERON®-Gold-in-Tube (QFT-GIT) and T-SPOT®.TB (T-SPOT®) assays. Overall superiority of either IGRA test has yet to be clearly demonstrated,(7) despite some studies suggesting IGRA may be less affected by low CD4 count (especially T-SPOT®) or prior BCG vaccination.(8-10) Therefore, IGRA is currently recommended as an adjunct test to TST and may be valuable in the following two situations:(10, 11) a) PLWH with CD4 count <200 cells/mm^3 who are TST-negative (if possible, T-SPOT® is preferred); and b) PLWH with a history of contact with active TB and who are TST-negative.

If an IGRA is desired, this may be arranged through referral to the provincial TB services program at the BC Centre for Disease Control (BCCDC). A publicly funded IGRA test can only be ordered by BCCDC TB Services physicians, by Federal Corrections, and select physician specialists. Furthermore, only certain laboratory sites around the province are designated collection sites for an IGRA. Please refer to the BCCDC IGRA guidelines (TB_manual_IGRA_guidelines.pdf (bccdc.ca)) for information on how to refer a patient/client for testing and for links to most current testing sites.

A TST should be performed unless there is documentation of one of the following: (a) history of a previous positive TST; (b) history of a positive IGRA; (c) documented prior or current active TB; or (d) a previous severe reaction to TST. Individuals with advanced HIV disease who initially had negative TST results (and negative IGRA, if done) are also recommended for repeat TST testing if their CD4 cell counts increase to >200 cells/mm^3, indicating immunocompetence sufficient to mount a response to the test. TST is contraindicated in the following patients: those with a history of severe blistering TST reactions in the past; those with extensive burns or eczema present over TST testing sites; those with documented active TB or a well-documented history of adequate treatment for TB infection or disease in the past; and those who have received measles immunization within the past 4 weeks, as this has been shown to increase the likelihood of false-negative TST results.(1)

A review of previous chest X-rays, TST results (and IGRA, if done), and history of TB disease or exposure is part of TB screening for PLWH.(12) However, PLWH appear to be more likely to have active TB in the absence of typical clinical or radiologic features, such as cough or chest X-ray abnormalities.(13)

Patients with positive TST or IGRA should be treated for LTBI. A systematic review including eleven clinical trials concluded that treatment of LTBI significantly reduces the risk of active TB in PLWH with a positive TST.(14) TB screening may be updated if there is evidence of new exposure to TB. However, PLWH who are in close contact with anyone with infectious TB should receive LTBI treatment, regardless of their TB screening test results (https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-opportunistic-infection/whats-new-guidelines).

Positive TST results should be followed by treatment for LTBI, once active TB disease is ruled out, through referral to provincial TB Services offered by the BCCDC.

Toxoplasmosis Screening

Recommendation:

1. All PLWH should be screened at baseline for Toxoplasma IgG antibodies to determine prior exposure to *Toxoplasma (T.) gondii*. (D)

Evidence:

Seroprevalence of *T. gondii* in North American adults is approximately 10-20%. Toxoplasma encephalitis (TE) is the most frequent clinical manifestation of central nervous system (CNS) disease in PLWH.(15) The serologic test for *Toxoplasma* cannot be used to diagnose or reliably exclude toxoplasmosis in PLWH. (12) Positive serology identifies individuals at a greater risk of disease. Peripheral blood serology is positive for Toxoplasma IgG (but negative for IgM) in the vast majority of patients with AIDS-related TE. However, in one study from San Francisco, 16% of those presenting with AIDS-related TE had negative serum serology for IgG by immunofluorescence.(15) Among *T. gondii*-infected (i.e. *Toxoplasma* IgG antibody positive) adult PLWH not receiving prophylaxis and with CD4 cell counts <100 cells/mm^3, the probability of developing clinical toxoplasmosis is approximately 38%.(12)

Hepatitis Screening

Recommendations:

1. PLWH should be screened at baseline for hepatitis A virus (HAV) using total anti-HAV antibodies. (B)

2. PLWH should be screened at baseline for hepatitis B virus (HBV) using HBsAg (hepatitis B surface antigen), anti-HBs (hepatitis B surface antibody), and anti-HBc (hepatitis B core antibody). (B)

3. Individuals testing negative for HBsAg and anti-HBs but testing positive for anti-HBc (isolated positive core antibody) should have HBV DNA testing to rule out occult HBV infection, particularly if the CD4 count is <200 cells/mm^3. (D)

4. PLWH should be screened at baseline for hepatitis C virus (HCV) using a test for HCV antibodies. Positive HCV antibody test results should be confirmed by measuring HCV RNA PCR. Regular HCV antibody screening at least once annually is recommended for populations at risk for HCV transmission. (B)

Evidence:

Hepatitis A virus (HAV) is most frequently transmitted by the fecal-oral route, through direct contact with infected people, or indirectly by ingesting contaminated water or food. Transmission through sexual activities that involve direct or indirect oral-anal contact can also occur.(16) In Canada, the number of cases of HAV has steadily declined since 2003.(17) The main risk factors for HAV infection include: sexual behaviours involving anal contact, particularly among men who have sex with men (MSM); travel or residence in endemic countries; and illicit drug use.(17-19) Because these risk factors and populations are highly prevalent among PLWH, all PLWH without previous evidence of vaccination or diagnosis of HAV should be vaccinated.

HIV and hepatitis B virus (HBV) share routes of transmission, including percutaneous (principally among people who inject drugs [PWID]), sexual (anal, vaginal, and oral) and vertical transmission.(16) The reported prevalence of HIV-HBV co-infection is between 6-10%, with higher rates observed in PWID, MSM, and individuals from endemic areas.(20) HIV-HBV co-infection is associated with an eight-fold increase in risk of mortality compared to HBV mono-infection.(21) Therefore, traditional HBV markers, such as HBsAg (surface antigen), anti-HBs (surface antibodies), and anti-HBc (core antibodies), will assist in distinguishing individuals who are chronically infected from those who have developed a natural or acquired immune response or those susceptible to HBV infection (thus, in need of receiving immunization).

Assessment for liver disease from chronic HBV infection and screening for hepatocellular carcinoma should follow standard Canadian guidelines.(22) However, all PLWH with chronic HBV infection should be offered ART including tenofovir disoproxil fumarate (DF) or tenofovir alafenamide (AF) in combination with emtricitabine in order to control HBV viral replication.

In Canada, the prevalence of HIV-hepatitis C (HCV) co-infection ranges from 20% to almost 90% in certain subgroups.(23) HCV is highly prevalent among PWID; a review of international studies suggests that between 50-95% of PWID are infected with HCV.(24) Canadian studies report HCV rates as high as 82% among PWID.(25, 26) If left untreated, HCV infection becomes chronic in up to 85% of co-infected individuals, potentially leading to progressive fibrosis and ultimately cirrhosis and death.(24) A meta-analysis of seventeen studies concluded that the rate of progression to hepatic fibrosis among individuals co-infected with HIV-HCV appears constant across all stages of fibrosis, and that chronic HCV outcomes are worse among co-infected individuals. Over the period studied, ART did not appear to fully reverse the adverse effect of HIV infection on HCV disease prognosis.(27) The probability of survival is also reduced among HIV-HCV co-infected individuals compared to those who are HIV mono-infected.(28)

Anti-HCV antibody is the standard screening test; however, approximately 6% of HIV-HCV co-infected patients do not develop HCV antibodies.(29) HCV RNA testing should be considered if the index of suspicion for HCV infection is high, for instance in individuals presenting with ongoing risk factors (e.g. sharing needles) or those with unexplained abnormally elevated liver enzymes. Patients with confirmed HIV-HCV co-infection should have their HCV infection managed according to current HCV guidelines.(30)

Screening for Syphilis and other Sexually Transmitted Infections (STIs)

Recommendations:

1. All PLWH should be screened for syphilis at baseline with *Treponema pallidum*-specific enzyme immunoassay (EIA). (B) Syphilis screening should be repeated annually, or every 3-6 months in the presence of ongoing risk behaviours, or in the presence of symptoms. (D)

2. A lumbar puncture should always be performed for patients with a reactive syphilis serology who have neurologic or ocular symptoms or signs, irrespective of past syphilis treatment history. (D)

3. All PLWH should be screened at baseline for gonorrhea and chlamydia. (B) Screening should occur every 3-6 months in the presence of ongoing risk behaviours or in the presence of symptoms. (D)

Evidence:

In North America, sexual transmission is the predominant route for acquiring HIV. This has prompted the recommendation to screen all PLWH for asymptomatic sexually transmitted infections (STIs). A cohort study reported a baseline STI prevalence of 14% among PLWH (n=212, 95% confidence interval [CI] 9%-19%) and the incidence of new infections was 20.8 cases per 100 person-years (95% CI 14.8-28.4).(31)

The prevalence of STIs in British Columbia is increasing. The provincial prevalence of infectious syphilis, as elsewhere in North America, has increased over the past fifteen years. With the exception of a short period of decline in 2009-2010, infectious syphilis rates have increased steadily to 14.1 per 100,000 population as of 2017.(32) Similarly, the overall provincial trend for genital gonorrhea has increased steadily since 1998, with a case load in 2017 of 58.2 per 100,000 population. In 2017, the prevalence of genital chlamydia was 322 per 100,000 population, continuing an overall increase since 1998. MSM continue to be the most affected, representing 83.4% of new syphilis cases in the same period. In 2017, amongst 554 MSM whose HIV status was known (96.7% of cases), 42.6% were living with HIV at the time of their syphilis diagnosis.

Traditionally, syphilis screening has been done with a non-treponemal test (e.g. rapid plasma reagin [RPR]) followed by a treponemal test (e.g. fluorescent treponemal antibody absorption). In July 2014, the BC Public Health Microbiology Reference Laboratory (BC-PHMRL) switched the preliminary screening test for syphilis from the RPR antibody test to an enzyme immunoassay (EIA), a *Treponema pallidum*-specific antibody test. Given that *Treponema pallidum* antibodies persist for the life of an individual, the EIA test will detect a greater number of old syphilis cases. Confirmatory tests including the RPR do not need to be ordered by clinicians as they are automatically done by the BC-PHMRL.(33)

A lumbar puncture should always be performed for patients with a reactive syphilis serology who have neurologic or ocular symptoms or signs, irrespective of past syphilis treatment history. In asymptomatic patients, a lumbar puncture may be considered for those patients with an RPR titre of > 1:32 or a CD4 of < 350 cell/mm^3, which are laboratory criteria that improve the ability to identify asymptomatic neurosyphilis.(34) However, studies defining the clinical outcomes associated with a broader versus more narrow utilization of lumbar puncture in asymptomatic PLWH with syphilis have not been conducted.

For gonorrhea and chlamydia, a Nucleic Acid Amplification Test (NAAT) should be conducted at baseline in all PLWH using first-catch urine specimen and site-specific testing as indicated (oropharyngeal and rectal swabs) for MSM and others with potential sexual exposure at these sites. The validated multisite APTIMA swab is recommended for use (as opposed to the urethral/cervical swab). In PLWH who have a cervix, a cervical swab could be taken. Although not validated, vaginal swabs can be used for screening in transfeminine individuals who are post-operative (i.e. after gender-affirming surgery). In cases of possible sexual assault, pharyngeal, anal, and/or vaginal swabs should be taken.(35)

Prevalent and incident asymptomatic STIs are common among MSM living with HIV, and thus increasing the frequency of screening to every 3-6 months is warranted for those with ongoing risk for infection (i.e. ongoing sexual activity with casual or multiple partners).

4.2 IMMUNIZATIONS AND HIV

Prevention of intercurrent illness is a crucial aspect of HIV care.(29, 36) The use of vaccines provides an opportunity to prevent infectious diseases in PLWH, who are more susceptible to these diseases.(17) Immunosuppression can reduce the effectiveness of vaccines and increase the risks associated with live vaccines.(17, 19, 37) CD4 cell counts are an important measure that can be used to help optimize the timing of immunizations and predict patient response to vaccines – in general, if a PLWH has a CD4 cell count ≥200 cells/mm^3 they will have a better response to vaccination.

General principles that primary care providers can follow for PLWH are shown below (adapted from the BCCDC Immunization Guide and the Canadian Immunization Guide)(17):

- Immunize at the time when maximum immune response can be anticipated (i.e. early in the course of HIV disease or following CD4 recovery with antiretroviral therapy).
- It is safer, and likely more effective, to immunize when CD4 cell counts are >200 cells/mm^3.
- Use caution in the use of live vaccines based on CD4 cell counts.
- Use of the measles, mumps, and rubella (MMR) and varicella vaccines in those with CD4 <200 cells/mm^3 is not recommended.
- There is no contraindication to the use of inactivated or component vaccines at any CD4 level.

4.2.1 RECOMMENDED VACCINES

Hepatitis A

Recommendations:

1. All PLWH who are susceptible (anti-hepatitis A [HAV] negative) should be vaccinated against HAV, ideally when CD4 >200 cells/mm^3. (B)

2. The HAV vaccine should be administered intramuscularly at the standard dose, at 0, 1, and 6 months. (B)

Evidence:
Serologic response rates of all HAV vaccines are between 95-100% amongst HIV-negative individuals.(17) Seroconversion rates are lower among PLWH for many vaccines and HAV seroconversion is no exception, with rates ranging from 48-64% (depending on the timing of measurement of serological response).(38, 39) A meta-analysis reported an overall response rate of 64% for PLWH.(40) A three-dose regimen (at 0, 1, 6 months) has been shown to have better results than a two-dose regimen (at 0 and 6 months) among

PLWH, with one comparative study reporting seroconversion rates of 78% and 61%, respectively.(41) The standard HAV vaccination doses are 1.0 mL intramuscularly (IM).(37)

Hepatitis B

Recommendations:

1. All PLWH who are susceptible to hepatitis B virus (HBV) infection (HBsAg negative and anti-HBs less than 10 IU/mL) should be vaccinated against HBV, ideally when CD4 >200 cells/ mm^3. (B)

2. HBV vaccination should also be offered to PLWH who have positive hepatitis B total core antibody (anti-HBc) with negative HBsAg and anti-HBs results (titre less than 10 IU/mL) and undetectable HBV DNA. (D)

3. In the situations described above, HBV vaccine should be administered intramuscularly (IM) to PLWH 20 years of age and older at a higher dose (40 mcg).
   - Recombivax HB® (10 mcg/mL): give 4.0 mL IM at 0, 1, and 6 months (B)
   - Recombivax HB ® Adult Dialysis formulation (40 mcg/mL) give 1.0 mL IM at 0, 1, and 6 months (B)
   - Engerix®-B Adult (20 mcg/mL): give 2.0 mL IM at 0, 1, 2, and 6 months (B)

4. Post-serologic testing (using anti-HBs) within 1-6 months of completion of the vaccine series is recommended to monitor success of immune response to vaccine. (B)

Evidence:
The overall seroconversion rate (defined as Anti-HBs >10 mIU/mL) to standard HBV vaccine dosing (10 mcg of Recombivax HB® or 20 mcg of Engerix®-B IM [deltoid]) following a 0, 1, and 6 month dosing regimen appears to be on the order of 26-65%.(17, 42-44) The etiology of poor seroconversion rates in PLWH is multi-factorial and not completely elucidated. Contributing factors may include age, sex, race, CD4 cell count (both nadir and at time of vaccination), HIV viral load, treatment with antiretrovirals, smoking and alcohol abuse. The benefit of using higher doses of HBV vaccine in immunocompromised individuals is now well-established, both in HIV and in other immunodeficiency states.(42, 45, 46) In particular, higher HBV seroconversion rates are reported in PLWH on antiretroviral therapy (ART) with low HIV plasma viral load and high CD4 cell counts. The low seroconversion rate is an indication to conduct post-vaccination testing (HBsAg and anti-HBs) on one occasion, between 1 and 6 months after the completion of the initial vaccination series.(47)

PLWH with isolated antibody to hepatitis B core antigen (HBsAg negative and surface antibody titre <10 IU/mL and no detectable HBV DNA) may also benefit from HBV vaccination.(48)

Once an anti-HBs antibody titre of >10 IU/mL has been documented, no further testing or vaccination is required, even if a later measurement is found to be <10 IU/mL.

Vaccine non-responders following the first series should receive a complete second series of three doses. If they fail to respond to a second series, they should be recorded as susceptible and receive hepatitis B immune globulin (HBIg) following a high risk hepatitis B exposure.(49)

Pneumococcal Disease

Recommendations:

1. All PLWH should be vaccinated against pneumococcal disease using standard vaccine doses (A), regardless of CD4 cell counts and according to the following schedules:
    i. Individuals who have not previously received any pneumococcal vaccine: One dose of conjugate pneumococcal vaccine (Pneu-C-13) is followed at least 8 weeks later by one dose of polysaccharide pneumococcal vaccine (Pneu-P-23). (B)
    ii. Individuals who have received a pneumococcal polysaccharide vaccine (Pneu-P-23) previously: The Pneu-C-13 dose should be administered at least one year after any previous dose of Pneu-P-23. (C)
    iii. If re-immunization with Pneu-P-23 is needed, it should be given at least 8 weeks after the Pneu-C-13 dose and at least 5 years after the initial Pneu-P-23 dose. (C)

Evidence:

PLWH are at a higher risk of developing invasive pneumococcal disease than HIV-negative individuals. (50-54) *Streptococcus pneumoniae* is the most common agent causing pneumonia in PLWH, and may also lead to invasive (bacteremia, meningitis) disease.(55, 56) Low CD4 cell count is associated with a significant increased risk for invasive pneumococcal disease (IPD), but pneumonia can occur at any CD4 level. Other risk factors influencing the development of bacterial pneumonia include cigarette smoking, low socioeconomic status, alcohol abuse, injection drug use, co-morbidities (including asthma and underlying lung disease [e.g. COPD]), malnutrition, uncontrolled viral replication, and lack of ART.(57-59)

Two forms of pneumococcal vaccine are currently available in BC: conjugated vaccine (Pneu-C-13 - Prevnar vaccine) and polysaccharide vaccine (Pneu-P-23 – Pneumovax®). These vaccines have been shown in the general pediatric and adult populations to reduce the risk of IPD. The efficacy of any form of the pneumococcal vaccine is unclear for PLWH with CD4 cell counts <200 cells/mm^3. A study of PLWH on ART showed a failure to induce serotype-specific antibodies when administering Pneu-P-23 to PLWH with CD4 cell counts <100 cells/mm^3.(60) However, another study demonstrated that, although Pneu-P-23 failed to prevent the occurrence of IPD, it decreased the severity and mortality of illness related to IPD. (61) Research on the efficacy of the pneumococcal conjugate 7-valent vaccine (Pneu-C-7) in PLWH has demonstrated improved health outcomes,(62, 63) yet also showed the emergence of non-vaccine type pneumococci, which may highlight the need for greater breadth of *Streptococcus pneumoniae* serotype coverage in regard to conjugated vaccines.(64, 65) Research is ongoing to develop an optimal vaccine regimen against IPD in PLWH.

While one study comparing Pneu-C-7 to Pneu-P-23 found that the conjugated vaccine elicited better serologic response,(66) other studies have looked into possible synergistic effect of a dual vaccination regimen that incorporates both the conjugate and the polysaccharide vaccines, with the conjugate vaccine used first as an immune primer.(67-71) In addition, the sequence of vaccination is important, as initial receipt of Pneu-P-23 followed by conjugate vaccine results in lower antibody levels than initial vaccination with the conjugate vaccine.(72) PLWH who receive the polysaccharide vaccine first should have delayed administration of the conjugate vaccine at least 12 months later. The National Advisory Committee on Immunization (NACI) concluded that there is good evidence to recommend the use of Pneu-C-13 for PLWH, given the efficacy and immunogenicity of Pneu-C-7.(73) The Pneu-C-13 vaccination dose is 0.5 mL IM and the Pneu-P-23 vaccination dose is 0.5 mL (subcutaneously [SC] or IM), although SC administration is associated with more discomfort at the injection site.(37)

Influenza

Recommendation:

1. All PLWH should be vaccinated annually against influenza using standard doses of the inactivated vaccine, regardless of CD4 cell counts or HIV plasma viral load. (B)

Evidence:

Caused by influenza A and B viruses, influenza occurs in Canada every year, generally during late fall and the winter months. Influenza A viruses are the most common cause of annual influenza epidemics.(17) The annual incidence of influenza varies widely, depending on the virulence of circulating strains and the susceptibility of the population, which is affected by antigenic changes in the virus, vaccine match, and vaccine coverage.(17) PLWH form part of the group at the greatest risk of serious infections, complications, hospitalizations, and/or death from influenza.(17, 74) In PLWH, influenza vaccine reduces the incidence of respiratory illnesses from 49% to 29% and of laboratory-confirmed influenza from 21% to 0%.(75)

As is the case with other vaccines, influenza vaccine efficacy is impaired in PLWH. One study estimated that vaccine efficacy decreased from 65% in PLWH with CD4 cell counts >100 cells/mm^3 to 11% in those with lower CD4 cell counts.(76) However, the benefits of the influenza vaccine in preventing severe illness and hospital/intensive care unit admissions prompted the US Centers for Disease Control (CDC) to recommend the use of the vaccine in PLWH, regardless of CD4 cell counts or HIV plasma viral load.(77) A single annual IM dose of 0.5 mL is currently recommended.(17, 37) There is no indication for pre- or post-immunization serology testing.(17) Inactivated influenza vaccine is recommended and live attenuated intranasal vaccine should not be used in this population.(19, 29, 37, 78)

Influenza vaccines publicly funded in British Columbia vary year to year. For details of which vaccines are being used in any given season, refer to the BCCDC's Immunization Manual (http://www.bccdc.ca/dis-cond/comm-manual/CDManualChap2.htm).(79)

Tetanus and Diphtheria

Recommendation:

1. All PLWH should be offered a tetanus and diphtheria (Td) toxoid booster every 10 years, ideally when CD4 >200 cells/mm^3. (D)

Evidence:
The recommendation above is based on the assumption that the diphtheria vaccine is being offered to an adult who has completed a primary series of childhood vaccinations. Routine immunization against diphtheria in infancy and childhood is a common practice throughout the world and has contributed to a significant decline in morbidity and mortality from this disease.(80) Serosurveys of healthy adult populations in Canada indicate that approximately 20% of those surveyed (higher in some age groups) do not have protective levels of antibody to diphtheria. Thus, the potential for re-emergence of this disease exists.(81)

The immunity conferred by diphtheria vaccine is antitoxic, not antibacterial. Vaccination thus protects against the systemic effects of diphtheria toxin but not directly against local infection.(81) After the primary vaccination series in immunocompetent individuals, over 99% develop antibody levels that are considered protective against disease.(80) The antitoxin is believed to persist at protective levels for 10 years or more. Titres decline slowly with time but are boosted by additional vaccine doses.(80)

Tetanus is rare in Canada. However, serosurveys suggest that a substantial proportion of Canadians have non-protective tetanus antitoxin levels. Factors associated with lack of immunity to tetanus include increasing age, birth outside Canada, and absence of immunization records.(81) The antibody response to tetanus boosters given to adults living with HIV or other humoral immune deficiencies is suboptimal.(80)

Human Papillomavirus (HPV)

Recommendation:

1. HPV-9 vaccine is recommended for all PLWH aged 9-27 years (A) and should be strongly considered in women and MSM aged 27 years and older. (B) A three-dose series is recommended in adults.

Evidence:
Human papillomavirus (HPV) is a sexually transmitted pathogen that causes ano-genital disease in all sexes. The link between HPV and cervical cancer is well established: HPV DNA is detected in 96.6% of cervical cancer tissue and the vast majority of cervical cancers can be attributed to HPV infection.(82-84) Based on both epidemiologic and phylogenetic data, the high-risk HPV types for cervical cancer, in order of frequency, are: 16, 18, 33, 45, 31, 58, 52, and 35; probably high risk are: 51, 56, 39, and 59.(85) Overall, 70% of cervical cancer cases are caused by the two most common HPV types – 16 and 18 (high risk) – and 90% of genital warts are caused by HPV 6 and 11 (low risk).(86) The same HPV genotypes that cause

cancer of the cervix also cause most cases of anal cancer,(87) a significant proportion of vulvar and vaginal cancer, and penile cancer.

HIV-mediated immune suppression appears to facilitate HPV persistence and its oncogenic potential. In part, this appears to be due to direct enhancement of HPV integration in the presence of HIV.(82)

In an international study, 77% of women living with HIV (WLWH) had HPV detected at least once (incident infection). HPV 16 was the most frequent genotype, with mixed infection seen in 26%.(83) Persistent infection was seen in 41.5% of women. The Canadian Women's HIV study group found high-risk HPV genotypes, as detected by genital tract sampling in WLWH, with 62.1% of women being HPV-positive at least once for one or more of the twenty-seven HPV types tested. An improved response to treatment for cervical dysplasia was observed for women on ART.(84, 88)

Men who have sex with men (MSM) are at an increased risk for oropharyngeal and anal cancers associated with HPV, of which 90% are caused by vaccine-preventable HPV strains 16 and 18. External genital warts can also be challenging to treat in MSM living with HIV and are mostly due to vaccine-preventable HPV. The quadrivalent human papillomavirus (HPV4) vaccine has been shown to decrease risk of developing anal cancer precursors (75%) and external genital warts (90%).(89)

Canada's National Advisory Committee of Immunization (NACI) recommends HPV-9 vaccine (containing strains types 6, 11, 16, 18, 31, 33, 45, 52, 58), for all individuals between 9 and 26 years of age.(90) In addition use of HPV vaccine can be administered in women after age 27 and should be strongly considered for MSM age 27 and older. Administration of the vaccine up to age 45 is on-label in Canada.(91)

Table 4.1: Recommended vaccines for adults living with HIV

Vaccine	Recommendation
Hepatitis A Vaccine* (Inactivated virus vaccine)	**Formulations:** Vaqta®, Havrix®, Avaxim® **Schedule:** 0, 1, 6 months (different from standard schedule of 0, and 6-12 months) for susceptible individuals. **Dosage:** Standard adult dose (formulation dependent) **Route of administration:** Intramuscular (IM)
Hepatitis B Vaccine* (Monovalent recombinant DNA vaccine)	**Formulations:** Recombivax HB® (10 mcg/1.0 mL) or Engerix®-B (20 mcg/1.0mL) **Schedule:** 0, 1, 6 months for Recombivax HB® and 0, 1, 2, 6 months for Engerix®-B for susceptible individuals. **Dosage:** 40 mcg, 4 mL of Recombivax HB® or 2 mL of Engerix®-B **Route of administration:** IM

Vaccine	Recommendation
Pneumococcal Vaccine* **Pneu-P-23** (23-valent pneumococcal polysaccharide vaccine), and **Pneu-C-13** (13-valent conjugate pneumococcal vaccine)	**Formulations: Pneu-P-23** - Pneumovax® 23. Pneu-C-13 - Prevnar13® **Schedule:** A) No prior **Pneu-P-23**: One dose of Pneu-C-13 followed 8 weeks later by **Pneu-P-23**. Then, a single **Pneu-P-23** booster 5 years later; B) Previous **Pneu-P-23**: One dose of Pneu-C-13 at least one year after any prior **Pneu-P-23**. A single **Pneu-P-23** booster at least 5 years after the initial **Pneu-P-23** dose, and at least 8 weeks after Pneu-C-13. **Dosage:** 0.5 mL. **Route of administration:** polysaccharide vaccine may be given subcutaneous (SC) or IM; conjugate vaccine must be given IM
Influenza Vaccine*(Inactivated virus vaccine)	**Formulations:** change annually; see BC Immunization Manual (http://www.bccdc.ca/dis-cond/comm-manual/CDManual-Chap2.htm) **Schedule:** Single yearly injection **Dosage:** 0.5 mL **Route of administration:** IM
Td (Tetanus, diphtheria)* - adsorbed	**Formulations:** Td® **Schedule:** Routine boosters every 10 years **Dosage:** 0.5 mL **Route of administration:** IM
HPV-9 Vaccine**	**Formulation:** Gardasil ® 9 **Schedule:** 0, 2 and 6 months **Dosage:** 0.5mL **Route of administration:** IM

* All publicly funded in BC

** Publicly funded up to age 26

4.2.2 ADDITIONAL VACCINES

Note: This guideline does not provide an exhaustive list of vaccines available to PLWH, including travel vaccines or additional vaccines that may be appropriate in specific circumstances.
Please see NACI guidelines for further information regarding additional vaccines for PLWH: https://www.canada.ca/en/public-health/services/publications/healthy-living/canadian-immunization-guide-part-3-vaccination-specific-populations/page-8-immunization-immunocompromised-persons.html#a29

Measles, Mumps and Rubella (MMR)

Recommendation:

1. All PLWH without evidence of immunity and with CD4 cell counts >200 cells/mm^3 should be considered for measles and/or mumps and/or rubella vaccination (given as a two-dose series of MMR vaccine). (B)

Evidence:
In general, live-virus vaccines should not be used among PLWH. In severely immunocompromised populations, measles can present critically and in a prolonged fashion, with a high risk for severe complications.(92-95) Measles, Mumps, Rubella (MMR) vaccination in PLWH with CD4 cell counts >200 cells/mm^3 appears to be safe with no serious adverse events reported.(96-98) Thus, all PLWH without severe immunosuppression (i.e. with CD4 cell count >200 cells/mm^3) and no evidence of immunity to measles, mumps, or rubella should be considered for the MMR vaccine.(29, 99) Evidence of immunity includes being born before 1970 or having previously received two doses of measles- or mumps-containing vaccine. All PLWH born before 1957 or who have previously received one dose of rubella-containing vaccine, have serologic proof of immunity, or have had prior lab confirmed rubella disease, are considered to have immunity against rubella. Thus, serological testing may be indicated to confirm the diagnosis of measles, mumps, or rubella or to determine immune status. Serologic testing is not recommended before or after receiving measles-, mumps- or rubella-containing vaccine. If serology is inadvertently done subsequent to appropriate MMR immunization and does not demonstrate immunity, re-immunization is not necessary.(100)

Varicella

Recommendation:

1. All PLWH without evidence of immunity and with CD4 cell counts >200 cells/mm^3 may be considered for varicella vaccination (given as a two-dose series of varicella vaccine given >3 months apart). (D)

Evidence:
At the time of publication of these guidelines, there were no published data on varicella vaccination among susceptible PLWH. However, based on expert opinion, varicella vaccine may be safe to offer to susceptible individuals with CD4 counts >200 cells/mm^3. Live attenuated varicella vaccine remains contraindicated in PLWH with CD4 counts <200 cells/mm^3. The varicella vaccine is administered as two doses >3 months apart.

A varicella susceptible person is defined as someone who does not have a history of varicella or herpes zoster after 12 months of age and who does not have a history of age-appropriate varicella immunization. A self-reported history of varicella is adequate for those born before 2004; for those born in 2004 and later, history of a diagnosis by a health care provider is required for reliability. Children who have a history of

either physician-diagnosed herpes zoster or lab-confirmed varicella after their first dose of vaccine do not require a second dose. If disease history is uncertain, provide a second dose.(101)

Herpes Zoster

Recommendation:

1. The use of inactivated herpes zoster vaccine for prevention of shingles in PLWH over age 50 can now be considered. (D) Dosage and schedule: 0.5mL IM at 0 and 2-6 months. No requirement for repeat dosing currently exists. (D)

Evidence:
Herpes zoster, commonly known as shingles, is a cutaneous manifestation of the reactivation of the varicella zoster virus (VZV), which causes chickenpox. Manifestations increase after age 50 in the general population and include complications such as post-herpetic neuralgia. The use of Shingrix® (a non-live recombinant herpes zoster vaccine) in healthy HIV-negative adults aged 50 and older for prevention of shingles is currently recommended by NACI in Canada.(102) Efficacy of the recombinant vaccine was evaluated in a large phase III clinical trial which enrolled >30,000 participants.(103, 104) The efficacy for the prevention of herpes zoster was 96.6% (95% CI 89.6-99.3) in persons aged 50-59 years and 97.4% (95% CI 90.1–99.7) in persons aged 60-69 years. Efficacy for prevention of postherpetic neuralgia was 91.2% (95% CI 75.9-97.7) in adults aged ≥50 years and 88.8% (95% CI 68.7-97.1) in those aged ≥70 years.

Immune compromised individuals were not included in the original studies, and at present NACI recommends vaccination in the setting of immune compromise on a case-by-case basis. Nonetheless since this is an inactivated vaccine, no additional precautions in the context of controlled HIV infection are anticipated, and use for PLWH is recommended by expert opinion by the US Centers for Disease Control Guidelines for the treatment and prevention of opportunistic infections.(105)

At present, this vaccine is not covered by Provincial Pharmacare, and private coverage or out of pocket payment would be required.

COVID-19

Recommendation:

1. PLWH aged 18 years or older should be vaccinated for COVID-19 if they meet current Public Health criteria and if they have no contraindications (for up-to-date information refer to the BC-CfE therapeutic guidance, http://bccfe.ca/therapeutic-guidelines, or Immunize BC, https://immunizebc.ca/covid-19). (D)

Evidence:
PLWH aged 18 years or older should be vaccinated for COVID-19 if they have no contraindications (see below). These vaccines are not expected to be associated with more serious or different adverse events

among PLWH or other immunocompromised individuals. While the evidence is mixed, PLWH may be at increased risk of serious illness due to COVID-19, and in the absence of contraindications should receive any of the COVID-19 vaccines currently approved in Canada as appropriate for their age group, regardless of CD4 count (i.e.: Pfizer-BioNTech, Moderna, AstraZeneca, and Janssen vaccines).

PLWH who have CD4 counts <200 cells/mm^3 or are not virologically suppressed should be counselled regarding the unknown efficacy and safety of the vaccines given that such subjects were not included in the vaccine licensing studies. For more information, visit the BC-CfE Committee for Drug Evaluation and Therapy (CDET) statement on the use of COVID-19 mRNA vaccines in PLWH: http://bccfe.ca/therapeutic-guidelines/healthcare-providers/therapeutic-guidelines/bc-centre-excellence-hivaids-cdet-committee-statement.

4.2.3 CONTRAINDICATED VACCINES

Recommendation:

1. The following live vaccines are contraindicated in PLWH: oral polio, live intranasal influenza vaccine, and BCG (Bacillus Calmette-Guérin). (B)

Evidence:
For PLWH, additional live vaccines (often used in the context of foreign travel) are either contraindicated or should be used with caution in circumstances where the benefits of a live vaccination are likely to outweigh the risks. Primary care providers may wish to consult with a physician with expertise in HIV or immunization about offering such vaccines to PLWH.(106)

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5 SPECIAL CONSIDERATIONS FOR CISGENDER WOMEN* LIVING WITH HIV (WLWH)

Note: Guidelines and resources specific to pregnancy and post-partum care, and infant care can be found on the Oak Tree Clinic/BC Women's Hospital and Health Centre website: http://www.bcwomens.ca/health-professionals/professional-resources/hiv-aids-resources.

5.1 INTRODUCTION

In Canada in 2018, 29% of newly diagnosed HIV cases were in women,(1) and among the estimated 63,110 people living with HIV (PLWH) in Canada in 2016, 23 % were women.(2) The majority of women living with HIV (WLWH) acquired the disease via heterosexual contact (64%). This holds true for women born in Canada or other non-endemic countries, as well as immigrants from HIV-endemic countries. Injection drug use is the second most common means of transmission for women (28%).(3) In BC, the proportion of women affected by HIV is smaller than for the country as a whole: 8% of British Columbians newly diagnosed with HIV in 2017 were women.(4) Similar to national trends, heterosexual contact is the most common route of HIV transmission for women in BC, followed by injection drug use.

Frequently, women are caretakers for children/partners/parents and extended family members/friends, and they may not give sufficient priority to their own medical/psychosocial care and well-being. Furthermore, women frequently face unequal power and socioeconomic relationships with their partners. These social factors may increase women's isolation and depression and compromise their adherence to medical care and their antiretroviral therapy (ART). Continued gender inequities with regard to the social determinants of health, particularly poverty and unstable housing, are significant factors disproportionately impacting women and their ability to participate in HIV care. Women who are Indigenous or from other racialized groups and sex workers are especially vulnerable due to multiple intersecting barriers. WLWH in Canada have very high rates of trauma and post-traumatic stress.(5) Many women are affected by multiple forms of trauma, including adverse childhood events, intergenerational trauma, historical trauma, institutional trauma, and stigma. Refugee women have commonly experienced severe trauma related to armed conflict in their country of origin and sexual assault. Based on data from the Canadian HIV Women's Sexual & Reproductive Health Cohort Study (CHIWOS) study, which included more than 1440 WLWH from three Canadian provinces, more than 79% of WLWH reported experiencing violence in adulthood – four times higher than the prevalence among the general population of women in Canada.(6, 7)

Since trauma is recognized as a root cause of multiple health challenges and is an important social determinant of health, in order to be successful in the care of WLWH, clinicians should address at each HIV visit the social determinants of health, including the person's current personal safety and food and

* In this chapter, the term *women* refers to any persons whose gender identity or expression (i.e. woman) coincides with their sex assigned at birth (i.e. female), also referred to as *cisgender women*. For a discussion of terms used to describe persons whose gender identity or expression do not coincide with their sex assigned at birth, see the footnote on **page 75**.

housing security, using a trauma informed care model (https://www.traumainformedcare.chcs.org/what-is-trauma-informed-care/).(8)

A useful Canadian resource for women-centred HIV care is available at: https://whai.ca/resource/caring-for-women-living-with-hiv-women-centred-hiv-care-toolkit/.

It should be noted that not all individuals with a cervix or with pregnancy potential self-identify as women, and not all individuals who self-identify as women have a cervix or have childbearing potential. For this reason, all recommendations are written using gender inclusive language.

It is important for clinicians to provide trauma-informed care and communicate clearly and respectfully with PLWH, to ensure that they receive care that is appropriate to their needs and life circumstances without judgment, assumptions, or unwanted disclosure with respect to their life, gender, and sexuality. This includes respecting the gender identity and expression of individuals (e.g. using their preferred pronoun and name in conversations and in emails and letters from the clinic addressed to the patient), and creating a safe, non-judgmental space for the person to discuss issues related to their sexual, reproductive, and general health. Cultivating this cultural safety for all, including transgender and non-binary individuals, is also an important part of trauma-informed care.

5.2 SPECIAL CONSIDERATIONS RELATED TO ART DURING PREGNANCY AND THE POST-PARTUM PERIOD

Recommendations:

1. All pregnant PLWH should be treated with ART for their HIV infection, regardless of their immunologic or virologic status, to prevent infection of their fetus. (A)

2. Clinicians should review the latest recommendations regarding ART for individuals who are pregnant or of childbearing potential, since some drugs may be contraindicated or should be used with the guidance of specialized care providers. (D)

3. Preconception counselling is recommended for any PLWH contemplating pregnancy. (D) In BC, preconception counselling can be provided by referral the Oak Tree Clinic at BC Women's Hospital and Health Centre (http://www.bcwomens.ca/health-professionals/refer-a-patient/oak-tree-clinic-hiv-care).

4. Pregnancy in PLWH is potentially high risk and complex; therefore, consultation with or referral to an obstetrician experienced in HIV is recommended. (D)

5. Breastfeeding is not recommended in Canada for PLWH, regardless of HIV viral load and use of ART. (D)

Evidence:
The indications for and goals of ART are the same for all PLWH. Pregnancy plans and wishes should be discussed with all PLWH in reproductive age potential, in each HIV visit. If pregnancy is desired, preconception counselling should be offered, including education around the importance of attaining maximal and sustained viral suppression before attempting conception and maintaining it throughout pregnancy and delivery, for the health of the pregnant person, to prevent sexual HIV transmission to partners without HIV, and to minimize the risk of HIV transmission to the infant. ART regimen selection preconception and during pregnancy should be made in accordance with current BC Guidelines for the Care of HIV Positive Pregnant Women (http://www.bcwomens.ca/health-professionals/professional-resources/hiv-aids-resources), and in consultation with providers who have expertise in this area.

When providing care for individuals planning pregnancy and any individuals of childbearing potential who are not using effective and consistent contraception, providers should carefully review all medications (antiretrovirals [ARVs] and concomitant medications) and avoid drugs with potential reproductive toxicity. The time of greatest developmental risk to the fetus is the first trimester, often before pregnancy is even recognized.

Like many other chronic conditions (e.g. diabetes), HIV can affect the medical management of pregnancy. Nausea and vomiting during early pregnancy can affect ART adherence. Therefore, pregnancy in PLWH is considered high risk and complex. Consultation with an obstetrician specialising in the management of HIV is recommended. In BC, preconception counselling, ARV regimen guidance, and specialized obstetrical services can be obtained from the Oak Tree Clinic in Vancouver: http://www.bcwomens.ca/our-services/specialized-services/oak-tree-clinic or 604-875-2212; a referral form is available on their website (http://www.bcwomens.ca/health-professionals/refer-a-patient/oak-tree-clinic-hiv-care).

Following delivery, clinical, immunologic, and virologic follow-up should continue as recommended for non-pregnant adults and adolescents. ART should be continued post-partum for the optimal health of the individual. Several studies have demonstrated that adherence to ART may worsen in the post-partum period.(9, 10) Clinicians caring for postpartum individuals should specifically address ART adherence, including an evaluation of specific facilitators and barriers to adherence.

Because use of ART during lactation reduces but does not eliminate the risk of transmission of HIV in breast milk, PLWH in BC should be counselled to avoid breastfeeding, where safe alternatives can be provided.(11) In BC, free formula is provided for all babies born to mothers living with HIV for one year, coordinated by the Oak Tree Clinic. PLWH should avoid pre-mastication of food fed to their infants because the practice has been associated with transmission of HIV from parent to child.(12)

5.3 REPRODUCTIVE ISSUES AND GYNECOLOGIC HEALTH IN THE CONTEXT OF HIV

Recommendations:

1. Contraception needs and pregnancy plans should be discussed with all individuals of childbearing potential (aged 15-50 years) upon initiation of HIV care and routinely thereafter, as pregnancy may affect the choice and timing of antiretrovirals. (D)

2. Selection of a contraceptive method should take into account the PLWH's desires about family planning and preferred contraceptive method, ART regimen, other medications, and co-morbid conditions. (D) Intrauterine devices (IUDs) can be considered as a safe and effective contraception option for PLWH. (B)

3. When prescribing ART, clinicians should take into account that some ARVs have significant pharmacokinetic (PK) interactions with hormonal contraceptives; other effective contraception options should be considered to prevent unplanned pregnancy. (B) Switching to an ARV drug that does not have interactions with hormonal contraceptives may also be considered. (B)

Evidence:

The incidence and prevalence of gynecological problems are high among WLWH throughout the course of their HIV disease.(13) At the initial patient assessment, a comprehensive gynecologic history should be obtained. Most WLWH with gonorrhea and chlamydia infections will be asymptomatic. For recommendations regarding screening for sexually transmitted infections (STIs), see **Section 4.1**, page 41.

Approximately 80% of newly diagnosed WLWH in Canada are of childbearing age.(1) Since perinatal HIV transmission can be prevented by the appropriate timely use of ART, PLWH of childbearing potential can expect to have HIV-negative children. Therefore, pregnancy intentions, as well as desire for contraception, should be discussed with individuals of childbearing potential at each health care visit. The goal of these discussions is to ensure that PLWH make informed decisions about pregnancy, contraception, and reproductive health and to prevent unintended pregnancies.(14) HIV status of the sexual partner should be discussed, although it should be noted that with effective ART resulting in a suppressed viral load, it has now been demonstrated there is no risk of HIV acquisition for HIV-negative sexual partners.(15)

Providers should be aware of common interactions between ART and medications taken for contraception, which may lower contraceptive efficacy and may result in unintended pregnancy. Ritonavir and cobicistat (used to boost levels of protease inhibitors [PIs] and the integrase inhibitor elvitegravir), and some non-nucleoside reverse transcriptase inhibitors (NNRTIs, specifically efavirenz, etravirine, and nevirapine) have significant drug interactions with combined oral contraceptives and newer combined hormonal contraceptive methods (e.g. transdermal patch, vaginal ring). Drug interactions can lead to a decrease or an increase in blood levels of ethinyl estradiol and/or norethindrone or norgestimate, which in turn can potentially decrease contraceptive efficacy or increase estrogen- or progestin-related adverse effects, including thrombo-embolic risk. There are limited data on drug interactions between ARV agents

and progestin-only contraceptive methods; however, studies have found no significant changes in ARV drug concentrations of nelfinavir, nevirapine, or efavirenz when used with depot medroxyprogesterone acetate (DMPA), and there is no evidence of reduced DMPA effectiveness.(16, 17) Conditions which confer additional risk with combined hormonal methods, such as diabetes mellitus, hyperlipidemia, and chronic liver disease, are more common in PLWH. In general, those who are taking boosted PIs, elvitegravir/cobicistat, efavirenz, etravirine, or nevirapine should use an alternative or additional method of contraception (e.g. barrier methods).

For recommendations on the use of hormonal contraceptives, see the World Health Organization's (WHO) 2019 guidance statement (https://extranet.who.int/iris/restricted/handle/10665/326653).(18) For up-to-date information on drug-drug interactions between ARVs and hormonal contraceptives, see the Toronto General Hospital's Immunodeficiency Clinic's guide (https://hivclinic.ca/wp-content/uploads/2019/09/Hormonal-therapy_contraceptives-HRT_Eng.pdf).

Regardless of contraception use, condom or other barrier use should be recommended with each sexual act. The risk of transmission and the legal implication of HIV non-disclosure should be discussed with the person. Current research confirms that PLWH whose viral load is consistently <200 copies/mL while adherent to ART do not transmit HIV via sexual contact ("undetectable = untransmittable" or "U=U");(15, 19-22) however, current sexual consent law in Canada requires PLWH to use condoms or disclose HIV status prior to intercourse, regardless of their viral load.(23) Condom use also reduces the risk of pregnancy and sexually transmitted infections (STIs). Barrier methods may reduce risk of HIV infection by approximately 69%,(24) but are associated with high rates of failure and are not welcomed by many men. No randomized trials comparing the clinical effectiveness of external (male) and internal (female) condoms for the prevention of HIV have been performed. Use of internal condoms can provide protection from acquisition and transmission of STIs, although data are limited.(25, 26) Internal condoms offer an option for individuals and couples who cannot or will not use the traditional external condom. Patients should be counselled about the greater effectiveness of condoms when used with a second method of protection.

Current evidence supports the safety and efficacy of intrauterine devices (IUDs) in PLWH, and this option should be considered, especially for those with CD4 >200 cells/mm3.(27) Cervical infections should be treated prior to the insertion of the IUD. Most studies have focused on non-hormonal IUDs (copper IUDs); several small studies have found the levonorgestrel-releasing IUDs to be safe.(28-30) For a more detailed discussion of recommendations for the use of IUDs among PLWH, see the Society of Obstetrician and Gynaecologists of Canada Committee's 2014 guidelines on Best Practices to Minimize Risk of Infection With Intrauterine Device Insertion (http://sogc.org/guidelines/best-practices-minimize-risk-infection-intrauterine-device-insertion/) and/or the WHO's guidance statement (https://extranet.who.int/iris/restricted/handle/10665/326653).

5.4 ART AND WEIGHT GAIN IN WOMEN

Evidence:
Various studies have suggested that sex assigned at birth may influence the frequency, presentation, and severity of some ART-related adverse events, including metabolic complications.(31) Pharmacokinetics

of antiretroviral drugs may differ between cisgender men and women,(32) due to factors such as body weight, plasma volume, hormones, gastric emptying time, plasma protein levels, cytochrome P (CYP) 450 activity, drug transporter function, and excretion activity.(33-35)

Several studies indicate that cisgender women experience metabolic complications associated with ART use differently than cisgender men. WLWH are more likely to experience increases in central fat and are at a higher risk of developing particular patterns of lipodystrophy than men living with HIV.(36) However, women are less likely to have triglyceride elevations on treatment.(37)

Weight gain and obesity are common in North America: 63% of Canadians over 18 years of age are overweight or obese, including 57% of women.(38) Obesity is highly associated with co-morbidities in the general population and in PLWH. For example, in the VACS Cohort, every 5 pound increase in weight was associated with a 14% increased risk of diabetes;(39) in the D:A:D cohort, every unit increase in body mass index (BMI) was associated with an 18% increase in the risk of cardiovascular disease.(40)

On average, women gain about 1.5 pounds (0.7 kg) per year from age 50-70 years independent of their initial body size or race/ethnicity.(41) Weight gain is multifactorial: in the context of aging, weight gain is mostly due to decreased lean body mass and reduced physical activity.(42, 43) In post-menopausal women, loss of estrogen and sleep and mood disorders also play a role.(43) Weight gain is especially important in older women, since obesity and increased central body fat are associated with increased risk of cardiovascular disease, which is the leading cause of death in post-menopausal women.

Initiation of ART often leads to weight gain. While some of this weight gain may be an appropriate "return-to-health" effect, excessive increases in weight may lead to obesity. Recent data suggest greater weight gain occurs on ART initiation among women than men, especially with the use of integrase strand transfer inhibitors and tenofovir alafenamide (AF).(44-47) Other factors associated with greater weight gain on ART include black race and lower baseline CD4 cell count.(44, 47)

The mechanisms by which certain ARV agents differentially contribute to weight gain are unknown and under investigation. In addition to HIV-related effects (CD4 nadir, level of viral load), social/environmental contributors, and genetic factors on weight gain, there may also be effects of newer, better-tolerated ARV agents, that better target the catabolic effects of HIV.

5.5 MENOPAUSE

Recommendation:

1. When systemic menopausal hormone therapy or non-hormonal medications are indicated for PLWH experiencing menopausal symptoms, potential drug interactions with ART should be considered. (B)

Evidence:
An increasing number of WLWH are living past menopausal age. In Canada in 2018, 22.2% of cisgender women newly diagnosed with HIV were over 50 years of age.(1) Aging with HIV is an emerging field,

and it is now expected that newly diagnosed individuals whose HIV is well controlled will have life expectancies similar to the general population.

In Canadian WLWH, the average age for the onset of menopause is 48 years, which is 3 years earlier than women in the general Canadian population.(48) Earlier menopause observed in PLWH may be multifactorial.(49) There are conflicting data on the effect of HIV on menopausal age and symptoms.(50) Factors that can influence menopausal symptoms, including smoking, stress, drug use, depression, low BMI, and race/ethnicity, are also relatively more prevalent among PLWH. Occasionally, symptoms of menopause may be difficult to distinguish from symptoms related to HIV, including fatigue, sleep disturbances, night sweats, achiness, and mental health effects.(50)

Sexual practices in menopausal WLWH are not well described. It is important for health care providers to discuss safer sex practices with PLWH of all ages. However, providers need to take into consideration that there are significant power imbalances for many WLWH that may compromise their ability to have safe sex and expose them to potential intimate partner violence.

There are currently no randomized controlled trials delineating the use of menopausal hormone therapy (MHT) in PLWH. As in the general population, MHT can be considered within 5-10 years of starting menopause in PLWH with severe vasomotor symptoms if the individual is below the age of 60. For those aged 60 years and over, the risk outweighs the benefits, and MHT is not recommended.(51, 52) Contraindications for MHT include unexplained vaginal bleeding, severe liver disease, breast or endometrial cancer, congestive heart failure, stroke, dementia, high risk of venous thromboembolism, hypertriglyceridemia, and severe migraine headaches. In individuals with a uterus, the proliferative effects of systemic estrogen on the endometrium must be countered by an appropriate dose of progestogen, to lower risk of cancer, i.e. combination MHT containing two hormones (estrogen and progestogen). For MHT recommendations, see: https://www.sigmamenopause.com/sites/default/files/pdf/publications/Final-Pocket%20Guide.pdf.

There may be drug interactions of MHT with ART(53, 54) (see https://hivclinic.ca/wp-content/uploads/2019/09/Hormonal-therapy_contraceptives-HRT_Eng.pdf). Levels of estradiol and progestogens may be increased by CYP3A4 inhibitors, especially cobicistat, potentially increasing MHT side effects and long-term thromboembolic risk. Ritonavir-boosted PIs and older non-nucleoside reverse transcriptase inhibitors (NNRTIs, such as efavirenz, etravirine, nevirapine) may change hormone levels, but the role of MHT dose adjustment has not been studied. Consultation with an HIV-experienced pharmacist, HIV gynecologist, or HIV specialist is recommended.

Hot flashes and night sweats related to menopause may also be managed by non-hormonal medications (e.g. venlafaxine, paroxetine, fluoxetine, gabapentin, or clonidine).(51, 52) As with MHT, drug interactions with ART should be considered (see DDI Booklet 2019_English.pdf (hivclinic.ca)) and expert guidance sought as necessary. For urogenital symptoms related to menopause, low-dose vaginal estrogen therapy should be considered.(55) It has limited systemic absorption and therefore has less systemic side effects/risks, lower interaction potential with ART, and has been shown to improve symptoms.

5.6 BONE HEALTH

Evidence:
Women have an increased risk of premature bone loss (osteopenia and osteoporosis), particularly during and after menopause, and this risk is exacerbated by HIV and ART.(56, 57) The prevalence of osteoporosis in WLWH is three times greater compared with HIV-uninfected women in the same age group in the United States.(58)

The pathogenesis of reduced bone mineral density (BMD) noted in PLWH is multi-factorial, with increased risk associated with some ARVs (tenofovir disoproxil fumarate [DF], efavirenz, PIs), as well as by HIV itself.(59) Traditional risk factors for osteoporosis, including smoking, menstrual irregularities (oligomenorrhea and amenorrhea), substance use, and low body weight, are more common in PLWH. Data from the Canadian Women's HIV Study demonstrated that BMD is compromised in WLWH compared to HIV-negative controls, even after adjusting for osteoporosis risk factors.(60)

Overall, women have lower bone density than men and start losing bone mass earlier, at the age of 40 years. Therefore, in WLWH, screening for risk of fragility fractures using the Fracture Risk Assessment tool (FRAX)(61) should start at the age of 40 years.(62) Those who had fractures, or with an intermediate or high risk for fragility fracture by FRAX (10-year risk >10%) should be referred for bone density screening via dual-energy x-ray absorptiometry (DXA) scan,(62) as should all post-menopausal women and all PLWH over the age of 50 years. In BC, as per provincial guidelines for the general population, the Medical Services Plan (MSP) covers DXA scans every 3 years starting at age 50, or any age if there is a fragility fracture or high osteoporosis risk, and accepts HIV as a risk factor for early bone loss. Replacement with vitamin D 1000-2000 IU/day and calcium supplementation should also be considered, especially for WLWH aged 40 and up and those receiving tenofovir DF.(62) For more information, see **Section 7.4**, page 82.

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6 SPECIAL CONSIDERATIONS FOR TRANSGENDER† INDIVIDUALS LIVING WITH HIV

Recommendations:

1. Endocrine therapy for transgender individuals living with HIV should be provided in consultation with an endocrinologist or other clinician who has experience providing endocrine care to transgender individuals. (D)

2. Selection of an ART regimen for transgender individuals living with HIV should take into account the potential for drug-drug interactions between certain ARVs and hormonal agents used for gender-affirming therapy. (B)

3. Transmasculine individuals who have not had bilateral mastectomy (A) and transfeminine individuals between the ages of 40 and 74 who have taken estrogen-based hormone therapy for more than 5 years (C) should be screened according to the BC Cancer breast screening policy for cisgender (non-transgender) persons.

Evidence:

Transgender populations are disproportionately affected by HIV. In a systematic review and meta-analysis among the United States (US) transgender population between 2006 and 2017, the estimated prevalence of HIV infection overall was 9.2% (compared to 13.3 per 100,000 in the US general population in 2018) and was higher among transgender women (14.1%, vs. 4.8 per 100,000) than transgender men (3.2%, vs. 22.1 per 100,000).(1, 2) Numerous challenges can affect health outcomes for transgender people, including socioeconomic factors, mental health issues, substance use, abuse and trauma, stigma, discrimination, social rejection, and exclusion.(3, 4) Lack of knowledge of transgender issues among health care providers and prior negative experiences in the health care system may constitute barriers to the transgender person's ability to access and maintain HIV care. Providers should be aware that transgender people may prioritize other health concerns over HIV (e.g. gender-affirming and non-discriminatory care, hormone therapy and its side effects, mental health care including trauma recovery), potentially leading to challenges with adherence to antiretroviral therapy (ART).(4, 5)

In BC, the care of transgender individuals is provided through a decentralized community-based model of care. While HIV treatment and gender-affirming endocrine therapy may be administered by different providers, transgender people living with HIV (PLWH) should have access to all facets of health care in a safe, welcoming, and respectful clinic environment. For information on the care of transgender individuals, clinicians can refer to Gender-affirming Care for Trans, Two-spirit, and Gender Diverse Patients in BC: A Primary Care Toolkit (September 2019) (http://www.phsa.ca/transcarebc/Documents/

†Note: In this document, *transgender* includes any person whose gender identity or expression is different from their sex assigned at birth. *Transfeminine* is used to mean people who were assigned male sex at birth and *transmasculine* is used to mean people who were assigned female sex at birth and both have gender identity or expression that do not align with their sex assigned at birth.

HealthProf/Primary-Care-Toolkit.pdf). Additional resources for primary care providers are available at: http://www.phsa.ca/transcarebc/health-professionals/clinical-resources.

Gender-affirming endocrine therapy, which allows the acquisition of secondary sex characteristics aligned with the individual's gender identity, should be provided in consultation with an endocrinologist or other clinician who has experience and expertise in this area. The general approach of feminizing hormone therapy is to combine an estrogen (transdermal, injectable [subcutaneous or intramuscular], or oral 17-beta estradiol) with an androgen antagonist (spironolactone, cyproterone acetate, bicalutamide, dutasteride), and in some cases a progestin (micronized progesterone or medroxyprogesterone).(6) Masculinizing hormone therapy involves the use of one of several forms of testosterone (e.g. injected, transdermal patch or gel, intranasal).(6) There is considerable variation in the medications that are used for gender affirmation depending on provider and patient preference.

Estradiol, cyproterone, bicalutamide, dutasteride, progestins, and testosterone are substrates of CYP3A4 and may have clinically significant drug interactions with certain ARVs.(7, 8) No significant drug interactions are expected between ARVs and spironolactone or finasteride. Estradiol levels may be increased with concomitant cobicistat, increased or decreased with ritonavir, and decreased with efavirenz, etravirine, or nevirapine. Levels of cyproterone, bicalutamide, dutasteride, progestins, and testosterone may be increased with concomitant cobicistat or ritonavir, and decreased with concomitant efavirenz, etravirine, or nevirapine. In transgender individuals receiving endocrine therapy, ART should be chosen to include a non-interacting agent such as doravirine, rilpivirine, or an unboosted integrase inhibitor (raltegravir, dolutegravir, or bictegravir). Otherwise, hormone efficacy and toxicity should be monitored and the hormone doses should be adjusted as necessary.(7)

BC Cancer provides guidance for healthcare professionals regarding breast/chest screening for transgender, gender diverse, and non-binary people (http://www.bccancer.bc.ca/screening/Documents/Breast-Screening-Transgender-Patients-Provider-Guide.pdf). Transmasculine individuals who have not had bilateral mastectomy and transfeminine individuals between the ages of 40 and 74 who have taken estrogen-based hormone therapy for more than 5 years should be screened according to the BC Cancer breast screening policy for cisgender (non-transgender) persons (http://www.bccancer.bc.ca/screening/health-professionals/breast/eligibility). Transfeminine individuals who have never taken estrogen-based hormone therapy or have taken hormones for fewer than five years do not need to be screened regularly for breast cancer.

For information regarding cervical cancer screening for transgender PLWH with a cervix, see Section 7.10, page 93, of this document. For further guidelines on cervical cancer screening among transgender individuals, see the BC Cancer website: http://www.bccancer.bc.ca/screening/Documents/CCSP_GuidelinesManual-ScreeningForCancerOfTheCervix.pdf.

For Trans Care BC recommendations regarding sexual health screening and pelvic examinations, see: http://www.phsa.ca/transcarebc/Documents/HealthProf/Sexual_Health_Screening_and_Pelvic_Exam.pdf .

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7 COMMON NON-INFECTIOUS CO-MORBIDITIES

7.1 INTRODUCTION

A number of conditions not traditionally associated with AIDS, including cardiovascular and renal disease, are exacerbated in the presence of uncontrolled HIV replication.(1) Therefore, despite the potential for long-term complications due to chronic antiretroviral therapy (ART), the benefits outweigh the potential risks in people living with HIV (PLWH) who are appropriately treated and monitored.(2) To this end, clinical and laboratory assessment of relevant co-morbid conditions should be performed at baseline before initiation of ART and during follow-up. Screening for non-infectious comorbid conditions is described in **Appendix 3**, page 114.

The frequency of lab monitoring for antiretroviral toxicity depends on the known potential toxicities of specific drugs, concomitant medications, and underlying co-morbid conditions. Lab monitoring may occur every 4 weeks after initiation of therapy, decreasing to up to every 6 months after stabilization of the patient on their antiretroviral (ARV) regimen.(3) In most cases, the timing of safety laboratory monitoring can be coordinated with monitoring of HIV RNA and CD4 cell counts. For details regarding laboratory monitoring for individuals receiving ART, see Chapter 3 of the BC-CfE Guidelines for Antiretroviral ARV Treatment of Adult HIV Infection | (bccfe.ca).

7.2 CARDIOVASCULAR DISEASE

Recommendations:

1. All PLWH should be screened for risk of cardiovascular disease at least annually, and modifiable cardiovascular risk factors should be addressed where possible. (D)
2. Blood pressure should be measured at least annually and at each visit (at least every 6 months) if abnormal. (D)
3. Assess lipids (total, HDL, and LDL cholesterol, and triglycerides) and/or apolipoprotein B at baseline and every 6-12 months once patient begins antiretroviral therapy. (B)
4. An electrocardiogram (ECG) should be considered at baseline and periodically (at intervals determined by the degree of risk) in patients taking protease inhibitors and/or rilpivirine with other PR- or QTc-prolonging drugs. (D)

Evidence:

Cardiovascular disease (CVD) is a leading cause of morbidity and mortality in the general population. HIV infection is associated with a doubling of the risk of CVD, including acute myocardial infarction (MI), stroke, peripheral arterial disease, heart failure, and sudden cardiac death.(4-6) Globally, the burden of HIV-associated CVD has tripled over the last 20 years.(4)

The mechanisms underlying the increased CVD risk in PLWH include a preponderance of traditional risk factors in this population, including smoking, hypertension, dyslipidemia, diabetes, and metabolic syndrome.(4, 5) In addition, uncontrolled HIV infection, including during ART interruption, is associated with chronic inflammation and an increased risk of cardiovascular events.(1, 7) Even in the setting of controlled HIV viremia, underlying chronic vascular inflammation directly contributes to accelerated atherosclerosis and endothelial dysfunction. Elevated levels of some inflammatory biomarkers, notably high-sensitivity C-reactive protein (hsCRP), are independently associated with a higher risk of MI in PLWH, as in the general population.(8, 9) However, the interpretation of hsCRP and other inflammatory biomarkers can be complicated in the setting of the chronic inflammatory state associated with HIV infection. Although ART reduces the levels of these biomarkers, they can remain elevated compared with those of HIV-negative individuals. The clinical utility of these biomarkers for initiation or monitoring therapy in PLWH is unknown.

While virally suppressive ART reduces risk of clinical CVD events,(1) specific ARV agents can be associated with increased CVD risk. In the D:A:D observational cohort from 1999 to 2005, the rate of CV events increased by 16% per year of exposure to ART regimens including older protease inhibitors (PIs).(10) However, more recently, the rate of MI in PLWH has plateaued, attributable at least in part to the use of contemporary PIs; in the D:A:D study from 2009 to 2016, use of darunavir/ritonavir was associated with an increase in CVD risk (59% per 5 years additional use), while use of atazanavir/ritonavir was not.(11) Although rates of MI are declining in recent years, PLWH receiving newer ART regimens remain at an increased risk of other forms of CVD, notably atrial fibrillation and heart failure.(5) The association between recent use of abacavir and acute MI remains controversial, but most current guidelines recommend avoidance of this agent in people with established CVD or who are at a high risk for CVD.(5, 12) Some ARV agents such as efavirenz may contribute to CVD risk through their detrimental effect on serum lipids (especially triglycerides and LDL cholesterol), while other have beneficial effects on lipid profiles, including tenofovir DF (compared to tenofovir AF) and unboosted integrase inhibitors.(13-16)

The Canadian Cardiovascular Society Guidelines (https://www.onlinecjc.ca/action/showPdf?pii=S0828-282X%2816%2930732-2) recognizes HIV as a significant risk factor for premature CVD and an indication for screening for cardiovascular risk factors, including lipids, regardless of age.(17) Screening for lipids (total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides) and apolipoprotein B (apoB) can be done non-fasting, except in individuals with a history of triglycerides >4.5 mmol/L, where these tests should be performed in a fasting state. ApoB measurement is subject to less laboratory error than LDL cholesterol, particularly in patients with hypertriglyceridemia (as often seen in HIV). LDL cholesterol is currently recommended as the primary treatment target, but apoB and/or non-HDL cholesterol are alternatives and may be the preferred treatment targets in the future.(17) Lipids and apoB should be measured annually, and monitoring frequency should be increased to every 6 months if abnormalities are detected.

Despite the impact of ART and HIV infection itself, traditional CVD risk factors (including age and smoking) remain the most important contributors to CVD in PLWH.(17, 18) A modified Framingham Risk Score (FRS) (http://www.ccs.ca/en/guidelines/guideline-resources), where the 10-year FRS percentage

is doubled for a family history of premature CVD, is the recommended tool for assessing total 10-year CVD risk in the general population;(17) however, the FRS may underestimate cardiovascular risk in PLWH.(18) Alternative methods of risk assessment are to calculate cardiovascular age using the Canadian Life Expectancy Model (CLEM) (http://myhealthcheckup.com/cvd/?lang=en) (17) or the American College of Cardiology/American Heart Association's (ACC/AHA) 10-year Cardiovascular Risk Assessment (https://www.merckmanuals.com/medical-calculators/ACCAHA2013.htm).(19) Both the FRS and the CLEM have been validated and shown to accurately estimate risk in the general Canadian population but not among South Asian, First Nations, or new immigrant populations.(17)

Regardless of underlying cardiovascular risk, modifiable risk factors should be aggressively addressed in all PLWH as in the general population, including smoking, sedentary lifestyle, and excess weight.(17) Smoking cessation is particularly critical and has been demonstrated to reduce clinical CV events in a large population of PLWH.(2, 20) Dyslipidemia, where present, should be managed according to current general population guidelines.(17) Dietary modification has been shown to be effective in the setting of HIV-associated hypertriglyceridemia;(21) a switch to a more lipid-friendly ART regimen may also be a consideration.(5) When needed, statins can be used safely for the treatment of dyslipidemia in HIV,(22) but potentially significant drug-drug interactions between lipid-lowering agents and antiretrovirals (e.g. statins and PIs) must be taken into account (www.hiv-druginteractions.org) (DDI Booklet 2019_ENG DIGITAL.pdf (hivclinic.ca)). Of note, PLWH may not reach desirable lipid targets with conventional statin therapy and combination therapy may be necessary.(23, 24)

Some older HIV PIs (specifically saquinavir and lopinavir/ritonavir) were associated with PR interval prolongation or QTc interval prolongation.(25-27) Case reports have also described QTc prolongation and torsades de pointes in association with atazanavir(28) and efavirenz.(29) Cardiac conduction abnormalities may become clinically significant when a ritonavir-boosted PI is co-administered with one or more QTc-prolonging drugs such as methadone, quetiapine, macrolides, quinolones, and/or azoles (for a full list, see the CredibleMeds website at https://www.crediblemeds.org/index.php), or PR-prolonging drugs, such as digitalis, calcium channel blockers, anti-arrhythmics, and beta-blockers. Rilpivirine was associated with QTc prolongation at daily doses of 75 mg or 150 mg, although this does not appear to be a problem at the 25 mg daily dose currently in use.(30-32) An electrocardiogram (ECG) should be considered at baseline before starting a ritonavir-boosted PI and/or rilpivirine with one or more PR- or QTc-prolonging drugs. A repeat ECG should be performed approximately five half-lives after starting the relevant drug, i.e. approximately 2 days after starting atazanavir/ritonavir, 3 days after starting darunavir/ritonavir, or 10 days after starting rilpivirine. In addition, an ECG should be done after the addition or dose increase of any other QTc-prolonging drug and at times of increased risk (e.g. hypokalemia, hypomagnesemia). Repeat ECG monitoring should be performed at intervals determined by the degree of risk, i.e. whether the QTc is short (<0.41 seconds), borderline (0.42-0.44 seconds), or prolonged (>0.45 seconds).(33)

7.3 INSULIN RESISTANCE (IR) AND DIABETES MELLITUS (DM)

Recommendations:

1. Fasting blood glucose (FBG) and/or glycated hemoglobin (HbA1C) should be performed in all PLWH at baseline and at 6- to 12-month intervals during antiretroviral therapy. Abnormalities in fasting glucose and/or HbA1C should be evaluated and managed according to the Diabetes Canada guidelines (http://guidelines.diabetes.ca/). (A)

2. Initial management of blood glucose abnormalities in PLWH involves lifestyle changes (weight loss, diet, exercise). (A)

3. Oral anti-glycemic agents and injectable anti-glycemic agents should be used as required, keeping in mind drug interactions with some antiretrovirals. (A)

Evidence:

HIV and its treatment increase the risk of insulin resistance (IR) and diabetes mellitus (DM) by approximately 1.5- to 4-fold compared to the general population,(34, 35) and the risk is greater with hepatitis C co-infection.(36) IR is associated with use of older nucleoside reverse transcriptase inhibitors (NRTIs) and protease inhibitors (PIs).(37) Integrase inhibitors may be associated with weight gain, which in turn exacerbates the risk of diabetes, particularly in PLWH; however, an association between integrase inhibitors and clinical metabolic abnormalities has yet to be confirmed.(38, 39) Traditional risk factors for DM remain relevant in PLWH.

HbA1C may be monitored as an alternative to fasting blood glucose, particularly if fasting status is difficult to ascertain; however, HbA1C can underestimate glycemia in PLWH, leading to under-diagnosis, especially in the setting of macrocytosis, lower CD4 cell counts, or certain antiretrovirals.(40-42) Fasting glucose and HbA1C should be measured annually in PLWH, with frequency of monitoring increased to every 6 months if abnormalities are detected.

In PLWH with type 2 diabetes, HbA1C should be measured every 3 months and targets should be established as per the Diabetes Canada Guidelines.(43) HbA1C targets are individualized; in most cases the target is 7%. In type 2 diabetics with CD4<500 cells/mm^3 or mean corpuscular volume (MCV) >95 fL, glucose levels should be used instead of HbA1C to guide management.

As in the general population, initial management of blood glucose abnormalities in PLWH involves lifestyle changes: maintaining healthy weight, healthy diet, and physical activity.(44) Depending on the degree of hyperglycemia at diagnosis, antihyperglycemic agents should be started concomitantly or if blood sugar targets are not met within 3 months of instituting healthy behaviour interventions.(45) Of note, in the presence of dolutegravir, metformin concentrations are increased by 79%, with a potential for increased adverse events.(46) In patients taking dolutegravir, metformin should be started at a low dose and not prescribed in doses greater than 1000 mg daily. Bictegravir increases metformin levels by 39% and no dose adjustment is required for co-administration.(47) In individuals with established cardiovascular

disease with suboptimal glycemic control there is a clear role for sodium-glucose cotransporter-2 (SGLT-2) inhibitors and/or glucagon-like peptide-1 (GLP-1) receptor agonists;(45) some precautions should be noted with respect to potential drug interactions with antiretrovirals (TS_Antidiabetic_2019_Oct.pdf (liverpool-hiv-hep.s3.amazonaws.com); DDI Booklet 2019_English.pdf (hivclinic.ca).

7.4 BONE

Recommendations:

1. Clinicians should undertake preventive measures for bone loss in all PLWH, including weight-bearing exercises, maintaining ideal weight, reducing smoking and alcohol consumption, and optimizing vitamin D (1000-2000 IU/day) and calcium intake (in the form of diet and/or supplements if necessary). (D)

2. Screening for risk of fragility fractures using the Fracture Risk Assessment (FRAX) tool (https://www.sheffield.ac.uk/FRAX/tool.aspx?country=19) should start at the age of 40 years for cisgender women and 50 years for all PLWH. (D)

3. Clinicians should consider performing a baseline dual energy X-ray absorptiometry (DXA) scan to assess bone mineral density for: cisgender women living with HIV who are post-menopausal; all PLWH aged 50 years and older; and PLWH of any age with a history of fragility fractures, >10% 10-year risk of major osteoporotic fracture by FRAX, and/or significant risk factors for osteoporosis (https://osteoporosis.ca/health-care-professionals/clinical-practice-guidelines/osteoporosis-guidelines/). (B) DXA scan should be repeated at intervals according to local provincial recommendations. (B)

4. If decreased bone density is diagnosed, secondary causes such as hypogonadism, alcoholism, glucocorticoid exposure, vitamin D deficiency, hyperparathyroidism, hyperthyroidism, renal phosphate wasting, and idiopathic hypercalciuria should be investigated and treated appropriately, including referral to a specialist if necessary. (D)

Evidence:

PLWH are at a greater risk of fractures than non-infected individuals.(48) The loss of bone density associated with normal aging is accelerated by HIV-associated chronic inflammation and vitamin D deficiency and by exposure to antiretrovirals.(49) The role of specific antiretrovirals in causing bone loss is controversial; however, the evidence points to tenofovir DF and ritonavir-boosted PIs as the leading culprits.(49, 50) Efavirenz has also been implicated as a contributor to low bone mass, mediated through its effect on vitamin D metabolism.(51) Other risk factors for low bone mineral density and fractures in PLWH include older age, lower body mass index (BMI), frailty, smoking, alcohol and substance use, low testosterone, lower CD4 cell count, and hepatitis C co-infection.(50, 52, 53)

Consensus guidelines are available for screening, assessing, monitoring, and treating low bone mineral density (BMD) in PLWH.(54) The risk of low BMD and fragility fractures should be assessed periodically

(e.g. at 1-2 year intervals) in all adults living with HIV. The 10-year risk of fracture can be assessed using the WHO Fracture Risk Assessment tool (https://www.sheffield.ac.uk/FRAX/tool.aspx?country=19). Of note, this instrument has not been validated for use in PLWH and may underestimate actual fracture risk;(55) this may be partially corrected by considering HIV to be a "secondary cause" of osteoporosis when using the FRAX calculator.(54, 55) Particular attention should be paid to modifiable risk factors such as lifestyle (e.g. smoking, alcohol intake), nutrition (vitamin D, calcium, and protein intake), and risk of falls.(49) BMD should be assessed with dual energy X-ray absorptiometry (DXA) scan in men living with HIV >50 years of age, post-menopausal women, and PLWH of any age with major risk factors, e.g. previous fragility fractures or at an intermediate or high risk for future fractures (>10% by FRAX).(49, 54) When using DXA scan data to assess BMD in PLWH, clinicians should use caution in the interpretation of T-scores, and the Z-score is preferable in those <50 years of age.(54, 56) A diagnosis of decreased bone density should prompt investigation into causes of secondary osteoporosis (e.g. hypogonadism, alcoholism, glucocorticoid exposure, vitamin D deficiency, hyperparathyroidism, hyperthyroidism, renal phosphate wasting, idiopathic hypercalciuria).(57) Positive findings should be treated appropriately, including referral to a specialist if necessary.

Preventive measures for bone loss should be implemented in all PLWH, regardless of age, following the recommendations for the general population (https://osteoporosis.ca/health-care-professionals/clinical-practice-guidelines/osteoporosis-guidelines/). These measures include regular weight-bearing exercises, maintaining ideal weight, reducing smoking and alcohol consumption, and optimizing vitamin D and calcium intake (in the form of diet and supplements if necessary). Falls prevention strategies should be implemented for individuals with frailty or other conditions associated with a high risk of falling (https://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/bc-guidelines/osteoporosis). Most PLWH have low vitamin D levels, as does the general North American population; therefore, there is insufficient evidence to support routine measurement of vitamin D levels in PLWH.(58) While there is no consensus regarding the optimal dose in the setting of HIV, supplementation with vitamin D at doses of 1000-2000 international units (IU) daily is inexpensive, safe, and not associated with known interactions with antiretroviral drugs. If dietary calcium intake is inadequate, a calcium supplement should be considered, taking into consideration potential interactions with antiretrovirals.

7.5 RENAL DISEASE

Recommendations:

1. It is recommended that laboratory assessment of renal function (i.e. serum creatinine, estimated glomerular filtration rate [eGFR], serum phosphate, urinalysis for protein and sediment, and spot urine for albumin to creatinine ratio [UACR]) should be performed in all PLWH at baseline and every 3-4 months after starting antiretrovirals, increasing to 6-month intervals when stable (depending on degree of risk). (D)

2. Blood pressure should be measured at least annually and at each visit (at least every 6 months) if abnormal. (D)

3. In case of renal dysfunction, clinicians should adjust doses of medications, including antiretrovirals that are cleared by the kidney. (B) An exception is tenofovir DF, which should be avoided in patients with or at high risk of renal disease and replaced with another agent in the presence of clinically significant renal dysfunction. (B)

Evidence:

Renal dysfunction is frequently seen in PLWH, especially as they age. The risk for renal disease is increased by black race, age over 50 years, past or family history of kidney disease, advanced HIV disease (low CD4 nadir), nephrotoxic medication use including recreational drugs (e.g. cocaine, heroin, ketamine, methamphetamine, MDMA [ecstasy], inhaled solvents), and certain co-morbidities (including diabetes mellitus, hypertension, hepatitis B or C, and other liver disease).(59) Classic HIV-associated nephropathy (HIVAN), due to direct infection of renal epithelial cells with HIV, is relatively uncommon in British Columbia. It is seen almost exclusively in Black individuals of West African or Haitian descent in association with advanced HIV disease. Despite a small potential for nephrotoxicity, overall large studies show that current ART is beneficial for renal function.(1, 60)

Numerous forms of acute and chronic renal disease are seen in PLWH:(59)

- HIV-related, e.g. thrombotic microangiopathy, immune complex glomerulonephritis, IgA nephropathy
- Secondary to co-morbid conditions, e.g. hepatitis B/C, hypertension, diabetes mellitus
- Related to nephrotoxic medications (notably nonsteroidal anti-inflammatory drugs) including some antiretrovirals, notably tenofovir DF and some ritonavir-boosted PIs(61-63)
- Drug interactions, e.g. ritonavir-boosted PIs/statins (rhabdomyolysis and myoglobinuria)

Certain etiologies of renal disease may also be related to ARVs,(59) specifically:

- Risk of tubular dysfunction and renal phosphate wasting with tenofovir DF, especially in patients with other risk factors for chronic kidney disease at baseline
- Other NRTIs (didanosine, stavudine, and lamivudine) rarely associated with tubular disorders
- Nephrolithiasis risk with indinavir and, less commonly, with atazanavir(64-66)—patients should be advised to maintain adequate hydration to prevent kidney stones during treatment with atazanavir or indinavir (the latter agent is not recommended in current treatment guidelines)
- Rarely, acute interstitial nephropathy with reversible acute renal failure, which has been described in association with hypersensitivity reactions to abacavir, efavirenz, and atazanavir(67)

Establishing the etiology of renal dysfunction in PLWH can be difficult as it is often multi-factorial. Referral to a nephrologist and possibly renal biopsy may be required for a definitive diagnosis, especially in cases where drug-related nephrotoxicity is suspected. Any renal function abnormalities identified at screening should be investigated and managed appropriately as in the general population. Some ARVs (specifically all NRTIs except abacavir) are renally cleared and may require dosage adjustment if renal function is abnormal.(59) For some drugs with low nephrotoxic potential (e.g. lamivudine), the beneficial effect of dose adjustment has not been proven. However, tenofovir DF is renally cleared and is also a nephrotoxin; this drug should be avoided in patients with renal disease or at high risk. If renal dysfunction occurs during ART, tenofovir DF should be discontinued if possible and replaced with another agent (e.g. abacavir if HLA-B*5701 negative or tenofovir alafenamide [AF] if eGFR >30 mL/min) rather than dose-

reduced. For further information, refer to the BC-CfE Guidelines for Antiretroviral ARV Treatment of Adult HIV Infection | (bccfe.ca).

Certain ARV agents (bictegravir, dolutegravir, rilpivirine) and pharmacokinetic enhancers (cobicistat) affect renal tubular creatinine transporters resulting in decreased tubular creatinine secretion and increased serum creatinine levels.(31, 32, 68-74) This is manifested as a factitious increase in serum creatinine (mean increase ~10-12 µmol/L) during the initial 2-8 weeks of therapy, without an effect on true glomerular filtration rate. After the initial increase, serum creatinine levels remain stable at the new higher level as long as the agent is continued. Decreases in eGFR that are >25% of the baseline level, that start later or continue to progress after the first 2-8 weeks of therapy, or that are accompanied by signs of renal tubular dysfunction (e.g. proteinuria) require further investigation to rule out true renal function impairment, and nephrology referral should be considered.(74)

7.6 HYPOGONADISM

Recommendations:

1. Cisgender men living with HIV presenting with symptoms of hypogonadism should be assessed with a morning serum total testosterone level; an abnormal testosterone level should be confirmed with repeat testing. (B) An estimated bioavailable testosterone measurement may be helpful to assess certain individuals, including obese cisgender men with borderline low total testosterone levels. (B)

2. Testosterone replacement is indicated only for symptomatic cisgender men with total testosterone levels less than 10 mmol/L (B) and should be prescribed in consultation with a specialist. (D)

3. Endocrine therapy for transgender individuals living with HIV should be provided in consultation with an endocrinologist or other clinician who has experience providing endocrine care to transgender individuals. (D)

Evidence:
In the early ART era, hypogonadism was identified as an important contributor to loss of lean body and muscle mass, the hallmarks of AIDS-associated wasting, as well as decreased bone mineral density.(71) While less prevalent now, low testosterone levels are still present in a significant minority of cisgender men living with HIV.(75)

Symptoms suggestive of testosterone deficiency include decreased libido, erectile dysfunction, hot flashes and sweats, weight loss, reduced muscle strength or exercise capacity, fragility fractures, sleep disturbance, fatigue, and depression. Cisgender men living with HIV presenting with one or more of these symptoms should be screened with a morning free testosterone level, and low levels should be confirmed on repeat testing.(76) An estimated bioavailable testosterone measurement may be helpful to assess certain individuals, specifically obese cisgender men with borderline low total testosterone levels. Normal serum testosterone levels in cisgender women are unknown.

Confirmed low testosterone levels may necessitate further investigation (including luteinizing hormone, follicle-stimulating hormone, prolactin, prostate-specific antigen) to distinguish primary (testicular) vs. secondary (pituitary/hypothalamic) hypogonadism and to rule out other clinical conditions.(77) Testosterone replacement therapy (TRT) is indicated only for cisgender men with symptomatic low testosterone levels and should be prescribed according to current guidelines, preferably in consultation with an endocrinologist or other specialist.(76, 78) In cisgender men living with HIV with hypogonadism, TRT has been shown to improve mood, energy, libido, muscle strength, and body composition (specifically, decreasing fat and increasing muscle mass), without adverse effects on viral load or CD4 cell count. However, there are no reliable data demonstrating that TRT improves muscle mass, in excess of that achieved by physical exercise, or overall physical function in cisgender men living with HIV. The benefits of longer term TRT (>3-6 months) in this population have not been studied.(76)

Potential side effects of TRT include acne, male pattern balding, and sleep apnea. More serious potential adverse effects include myocardial infarction (due to erythrocytosis) and prostate cancer. TRT is contraindicated in men with acute coronary syndrome or prostate cancer. The long-term safety of TRT is unknown; the need for ongoing TRT should be reassessed at least every 6 months.(76, 78)

7.7 NEUROCOGNITIVE IMPAIRMENT

Recommendations:

1. ART to suppress plasma viral load should be started early and administered continuously to prevent or minimize HIV-related neurocognitive impairment. (B)

2. In PLWH presenting with cognitive complaints that affect their daily functioning, an investigation should be done to rule out relevant underlying conditions. (B)

Evidence:
HIV can affect the central nervous system (CNS), impacting cognitive function (e.g. memory, reasoning, planning, solving problems, attention, concentration) and activities of daily living. Fortunately, the incidence of severe cognitive impairment in the form of HIV-associated dementia has declined significantly since the advent of ART. However, milder forms of neurocognitive impairment remain prevalent, even in the presence of virologic suppression, and can have a significant impact on quality of life and adherence to HIV medications.(79)

PLWH with impairment in two or more cognitive domains and mild to moderate impairment in daily functioning, in the absence of confounding conditions, may be diagnosed with mild neurocognitive disorder.(80) Potential underlying conditions that need to be ruled out include:(81, 82)

- Psychiatric conditions, e.g. depression
- Alcohol and other substance use
- CNS infections, e.g. encephalitis, meningitis, neurosyphilis
- CNS lymphoma
- Cerebrovascular disease

- History of head trauma
- Endocrine disorders, e.g. thyroid disease, hypogonadism
- Nutritional deficiencies
- Side effects of ARVs or other medications

PLWH presenting with significant cognitive complaints (affecting their work performance, housekeeping, and/or social functioning) should have their plasma HIV viral load assessed and ART started or adjusted as necessary to ensure good adherence and consistent viral suppression. Those already receiving suppressive ART should have investigations to rule out the above conditions, including brain computed tomography (CT)/magnetic resonance imaging (MRI) and lumbar puncture for cerebrospinal fluid (CSF) examination if appropriate.(82) This should be done in consultation with a neurologist. A full evaluation by a neuropsychologist, if available, may be needed to delineate the pattern and extent of the neurocognitive deficit.

In the absence of relevant underlying conditions, neurocognitive impairment in HIV may be related to CSF viral "escape", i.e. presence of detectable HIV RNA in CSF despite undetectable viral load in plasma. Limited evidence exists that adjusting the ART regimen to include agents with better CSF penetration (e.g. zidovudine, nevirapine, abacavir, emtricitabine, darunavir/ritonavir, raltegravir) can stabilize or improve neurocognitive function in this setting.(79, 82) Referral to a physician with expertise in the management of HIV is advised in these situations. Full suppression of plasma viral replication remains the most important target, for both prevention and treatment of HIV-related cognitive disorders.

7.8 LUNG DISEASE

Recommendations:

1. Smoking cessation should be strongly encouraged in all PLWH because they are at a higher risk for chronic obstructive pulmonary disease (COPD) and lung cancer than smokers who do not have HIV. (A)

2. A chest X-ray should be performed at baseline in all PLWH. (D) Once infection has been treated or ruled out, patients with persistently abnormal chest X-ray findings should be investigated and referred to a respiratory specialist if necessary. (D)

3. PLWH of any age presenting with persistent respiratory complaints should be assessed via spirometry, especially those with additional risk factors such as smoking. (B)

4. COPD should be managed according to current Canadian Thoracic Society guideline (https://cts-sct.ca/guideline-library/). (A) Concomitant use of inhaled steroids with ritonavir or cobicistat should be avoided if possible. (B)

Evidence:
Compared to the general population, PLWH have a greater risk for chronic obstructive pulmonary disease (COPD) and are prone to develop it at a younger age, even taking into account the relatively high

rates of smoking in this population.(83, 84) COPD should be managed according to current Canadian Thoracic Society guidelines (available at https://cts-sct.ca/guideline-library/), including an aggressive plan for smoking cessation. The use of all inhaled steroids should be avoided if possible in patients receiving ritonavir or cobicistat as part of their ART regimen, due to the risk of adrenal suppression and iatrogenic Cushing's syndrome.(85, 86) Beclomethasone cannot be recommended as a "safer" alternative in this setting; a systematic review showed this agent has no clinical effect in COPD.(87) If combination inhaled steroids/long-acting beta-agonist (LABA) inhalers are necessary for the management of severe COPD symptoms, consideration should be given to switching patients off of ARV regimens containing ritonavir or cobicistat. Salmeterol is not recommended with concomitant ritonavir or cobicistat in PLWH with COPD because of elevated salmeterol levels that may increase the risk of cardiovascular adverse events.(88) Formoterol can be associated with QT prolongation and should be used with caution in patients receiving QT-prolonging ARVs (rilpivirine, ritonavir-boosted lopinavir or atazanavir); however, other single-agent LABAs (e.g. indacaterol) and long-acting muscarinic antagonists (LAMAs, e.g. aclidinium, glycopyrronium, tiotropium) can be used safely in this setting.(88)

A chest X-ray should be performed at baseline in all PLWH. As HIV confers an increased risk of lung cancer, HIV care providers should have a low threshold for performing chest CT in the presence of significant respiratory symptoms, particularly in smokers.(89-91) After appropriate management of infectious etiologies, consultation with a respiratory specialist is advisable to investigate persistent symptoms or abnormal imaging findings.

7.9 LIVER DISEASE/CIRRHOSIS

Recommendations:

1. Liver enzymes and liver function should be assessed in all PLWH at baseline and every 3-4 months after starting ART, increasing to 6-month intervals when stable. (D)

2. All PLWH who are co-infected with hepatitis C virus and have cirrhosis, all who are co-infected with hepatitis B virus (regardless of fibrosis stage), and all who have cirrhosis from another etiology should be screened for hepatocellular carcinoma every 6 months using ultrasound. (B)

3. All PLWH with cirrhosis should be referred for a baseline gastroscopy to screen for esophageal varices. (B)

Evidence:

Chronic liver disease is a leading cause of morbidity and mortality among PLWH.(92-94) Due to shared routes of transmission, a significant proportion of PLWH are co-infected with hepatitis B and/or C virus (HBV and/or HCV);(93, 94) see also **Section 4.1**, page 41. Other important etiologies of liver disease in PLWH include alcohol-associated hepatitis, non-alcoholic steatohepatitis (NASH), and drug-induced hepatotoxicity.(93-95) Due to HIV being well-controlled with ART, opportunistic infections of the liver are now uncommon.

PLWH who are co-infected with HBV and/or HCV have a relatively rapid rate of progression to cirrhosis, hepatic decompensation, and hepatocellular carcinoma compared to HIV-negative individuals with viral hepatitis.(96-100) HCV and HBV in PLWH should be managed according to current guidelines to prevent cirrhosis (101-103) (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4947683/pdf/CJIDMM2016-4385643.pdf; https://www.cmaj.ca/content/cmaj/190/22/E677.full.pdf; https://canlivj.utpjournals.press/doi/full/10.3138/canlivj.2018-0008).

PLWH with confirmed cirrhosis should undergo routine hepatocellular carcinoma surveillance with ultrasound every 6 months (see **Table 7.1**, page 91).(101-104) If signs of decompensation (e.g. ascites) are present, these individuals should also undergo a baseline gastroscopy to screen for varices.(105) Serum alpha-fetoprotein (AFP) monitoring lacks adequate sensitivity and specificity for hepatocellular carcinoma surveillance and is no longer recommended. Cirrhosis in PLWH should be managed in collaboration with experts in liver diseases.

7.10 CANCER

Recommendations:

1. In PLWH, screening for breast, colorectal, and prostate cancer should follow current provincial recommendations for the general population. (A)

2. PLWH may be at an increased risk for lung cancer, HPV-related cancers (oropharyngeal, cervical, anal), lymphoma, and hepatocellular cancer as compared to the general population. Increased surveillance for these cancers is recommended. (D)

3. Annual cervical cancer screening should be offered to all PLWH with a cervix between ages 25-69. (C) If Pap smear results are abnormal, the individual should be referred for colposcopy and directed biopsy, as recommended by BC Cancer, with further treatment as indicated by results. (A)

4. After three or more consecutive normal cervical Pap results in individuals who are actively engaged in HIV care and have a CD4 count >500 cells/mm^3, less frequent screening can be considered on a case-by-case basis. (C)

5. Annual digital rectal examination is recommended as a screening test for anal cancer for all PLWH. (D) We do not currently recommend routine anal cytology (anal Paps) for anal cancer screening in PLWH. (D)

Evidence:

The incidence of AIDS-defining cancers, Kaposi's sarcoma, and non-Hodgkin's lymphoma has markedly decreased in the highly active ART era (with the exception of invasive cervical cancer which has remained relatively unchanged), while non-AIDS-defining cancers have become more common.(106-108) This is attributable at least in part to the increasing risk of malignancy as the PLWH population ages.

In general, PLWH are not at a greater risk of common cancers (e.g. breast, colorectal, ovary, prostate) than their age-matched HIV-negative counterparts.(106-110) Screening for these cancers in PLWH should follow current provincial recommendations for the general population.

However, even after controlling for relevant risk factors such as smoking, PLWH are at a higher risk for lung cancer(89, 90, 106, 109, 111) (see **Section 7.8**, page 87) and cancers attributable to infectious etiologies, specifically:

- Anogenital and oropharyngeal cancers, secondary to human papilloma virus (HPV) (108) – see below.
- Lymphoma, secondary to Epstein-Barr Virus (EBV)(112)
- Hepatocellular cancer, related to hepatitis B and C viruses (HBV and HCV)(113) – see **Section 4.1**, page 41.

While many guidelines for cervical cancer screening have changed in recent years in response to evidence supporting the safety of initiating screening at a later age and longer intervals between screening,(114) abnormal cervical cytology is more than ten times more prevalent in PLWH compared with the general population.(110) The prevalence of genital tract HPV is double the population norm among PLWH and invasive cervical cancer is three times the norm. Therefore, we continue to recommend annual Pap smears in all PLWH with a cervix. Risks for cervical cancer are associated with level of immune compromise, but well-controlled HIV does not fully eliminate additional cervical cancer risk. More frequent screening improves the sensitivity of Pap smears. Less frequent screening (i.e. less than annually) for cervical cancer may be considered on a case-by-case basis in individuals who are actively engaged in HIV care and have a CD4 count >500 cells/mm^3 after three or more consecutive normal Pap test results.(114)

Screening should be considered starting at age 21 if sexually active, with clinical judgement. Continuing cervical cancer screening after the age of 69 years should be considered based on clinical judgement of individual risks. BC guidelines recommend that people above age 70 years continue to be screened if they have not had 3 consecutive normal Paps within the last 10 years; if they do not meet this criterion, then they should be screened until they have 3 normal Paps (https://www.healthlinkbc.ca/health-topics/hw27039). The following risks should be considered in determining cervical cancer screening frequency and age of initiation or discontinuation:

a. Prior abnormal Pap test result(s)
b. Lack of prior documented normal prior Pap test results (e.g. for new immigrants)
c. Known HPV infection
d. Duration of HIV infection; perinatal HIV infection
e. ART adherence and HIV viral load
f. Evidence of immune compromise (higher risk with CD4 count <500 cells/mm^3)
g. Other risks for cervical cancer, such as smoking, family history of cancer
h. Age of sexual debut for youth

PLWH over age 65 remain at an elevated risk of abnormal vaginal and cervical cytology. Those who have had hysterectomy for benign reasons remain at risk for vaginal intraepithelial neoplasia.(114) If

Pap smear results are abnormal, the individual should be referred for colposcopy and directed biopsy, as recommended by BC Cancer, with further treatment as indicated by results.

Anal cancer is an HPV-associated condition with an annual prevalence of only 1.7 per 100,000 in the Canadian general population; however, anal cancer rates are up to 100 times higher among PLWH, particularly among men who have sex with men.(115) As a potential screening test, anal canal cytology ("anal Pap") has a high sensitivity for detecting abnormalities but very low specificity; since evidence is lacking on how to appropriately manage abnormal results or treat precancerous lesions, the utility of routine anal Pap testing is uncertain.(116, 117) High-resolution anoscopy (HRA) with directed biopsy is required to follow up abnormal anal Pap results, but capacity for such follow-up in Canada is lacking, as HRA is available in only five specialized clinics in the country (one in BC).(117) Furthermore, there is currently limited proof that screening prevents anal cancer or associated mortality.(116, 117) Anal cancer screening is not a standardized clinical procedure internationally, and at present there are no official Canadian guidelines or anal cancer screening programs.(117) Annual digital rectal examination is recommended as a screening test for anal cancer for all PLWH, consistent with BC guidelines for the general population (Screening (bccancer.bc.ca)), and US guidelines for PLWH (Human Papillomavirus Disease | NIH (hiv.gov)). We do not currently recommend routine anal cytology (anal Paps) for anal cancer screening in PLWH.

See **Section 4.2.1**, page 46, for recommendations on HPV vaccination.

Recommendations for cancer screening in PLWH are summarized in **Table 7.1** below.

Table 7.1 Recommendations for cancer screening in PLWH

Cancer	Population	Screening test	Baseline	Screening interval	Comments
Anal	All PLWH	Digital rectal exam	✓	1-3 years	Anal Pap test may be considered where available, but not standard of care
Breast	Cisgender women; transfeminine individuals aged 40-74 years on endocrine therapy >5 years; transmasculine individuals who have not had bilateral mastectomy	Mammography	Follow standard BC guidelines*	Follow standard BC guidelines*	See also *Section 6*

Cancer	Population	Screening test	Baseline	Screening interval	Comments
Cervical†	All individuals with a cervix	Pap test	✓	Annually. Consider less frequent testing after 3+ consecutive normal Pap tests.	Patients with abnormal Pap test should be referred for colposcopy†. See also *Section 6*
Colorectal	All individuals aged 50-74 years	Fecal immu-no-chemical test (FIT)	Follow standard BC guidelines‡	2 years‡	Patients with abnormal FIT test should be referred for colonoscopy‡
Hepatocellular	Hepatocellular HCV Ab+	Abdominal ultrasound	✓§	Not required (unless cirrhosis present)	See also *Sections 4.1* and *7.9*
	HCV Ab+ with cirrhosis; or HB-sAg+ regardless of fibrosis stage		✓	6 months	See also *Sections 4.1* and *7.9*
Lung	All	Chest X-ray	✓	Not required	Chest CT if symp-tomatic, especially in smokers; see also *Section 7.8*
Prostate	Cisgender men and transfemi-nine individuals aged >50 years	Digital rectal exam	✓	1-3 years	Use of the pros-tate-specific antigen (PSA) test for screening is not recommended¶,**

Adapted from 2019 EACS Guidelines. Available from https://www.eacsociety.org/media/2019_guidelines-10.0_final.pdf

* http://www.bccancer.bc.ca/screening/health-professionals/breast/eligibility
† http://www.bccancer.bc.ca/screening/health-professionals/cervix/eligibility
‡ http://www.bccancer.bc.ca/screening/colon/get-screened/who-should-get-screened
§ Consider baseline ultrasound in all HIV/HCV coinfected individuals; recommended if thrombocytopenia or cirrhosis present (Hull M, Shafran S, Wong A, Tseng A, Giguere P, Barrett L, et al. CIHR Canadian HIV Trials Network Coinfection and Concurrent Diseases Core Research Group: 2016 Updated Canadian HIV/Hepatitis C Adult Guidelines for Management and Treatment. Can J Infect Dis Med Microbiol. 2016;2016:4385643.)
¶ Bell N, Connor Gorber S, Shane A, Joffres M, Singh H, Dickinson J, et al. Recommendations on screening for prostate cancer with the prostate-specific antigen test. CMAJ. 2014;186(16):1225-34.
** Prostate Cancer Canada. Prostate Cancer Canada reminds men that early detection using 'Smart Screening' for prostate cancer can save lives. Oct. 27, 2014. Available from https://www.newswire.ca/news-releases/prostate-cancer-canada-reminds-men-that-early-detection-using-smart-screening-for-prostate-cancer-can-save-lives-516097371.html

7.11 MENTAL HEALTH

Recommendation:

1. Mental health should be proactively assessed during clinic visits, and identified conditions should be managed using a stepped-care approach. (D)

Evidence:

The populations at risk of HIV acquisition are also at heightened risk of anxiety, depression, and other mental health issues, including people who inject drugs(118) and cis- and transgender men who have sex with men (MSM).(119-121) Sexual minorities and transgender individuals carry a disproportionate burden of mental health challenges as indicated by higher rates of self-reported depression, anxiety, self-harm, suicidality, and substance use disorders when compared to their heterosexual counterparts.(119-122) In this sense the intersecting burdens of mental illness, substance use disorders, and experiences of discrimination related to sexuality among these populations impart an increased vulnerability towards HIV acquisition.(123)

Cisgender women living with HIV also experience high rates of anxiety, depression, and post-traumatic stress disorder (PTSD).(124, 125) For example, among BC participants (97% of whom were cisgender women) in the Canadian HIV Women's Sexual & Reproductive Health Cohort Study (CHIWOS), 56% experienced PTSD symptoms.(126)

Depression and other mental health issues among PLWH can interfere with retention in care and adherence to ART, and can have significant negative impacts on virologic suppression, health outcomes, and quality of life.(127-129)

Mental health should be proactively assessed during clinic visits, and identified conditions should be managed using a stepped-care approach (for example, see Section E of https://whai.ca/wp-content/uploads/2020/07/CEP_HIVCliniciansTool.pdf). Health care providers should refer to Canadian clinical practice guidelines for the management of depression, anxiety, and PTSD.(130, 131) Healthy coping behaviours such as self-care, stress management, cognitive behavioural therapy, and maintaining social support networks (including peer support) have been linked to better mental and physical quality of life among PLWH and should be offered.(132) Spirituality, culturally safe practices, and prayer are also coping tools that some PLWH may use to combat stress and distress and should be encouraged as relevant and appropriate.(132)

Of note, adverse effects of certain antiretroviral medications can contribute to mental health issues in PLWH. Efavirenz is commonly (~50%) associated with a wide range neuropsychiatric symptoms (sleep disturbances, somnolence, insomnia, abnormal dreams, dizziness, depression, anxiety, confusion, abnormal thinking, impaired concentration, amnesia, agitation, depersonalization, hallucinations, euphoria) and a two-fold increased risk of suicidality.(133, 134) Less commonly, integrase inhibitors can be associated with insomnia, sleep disturbances, abnormal dreams, and depression.(135-138)

A comprehensive overview of mental health issues in PLWH and of their consequences and management is outside the scope of this guideline. For a recent in-depth review of mental health issues in women living with HIV, including those of trans experience, see: https://journals.sagepub.com/doi/10.1177/2325958220985665.

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8 SPECIAL CONSIDERATIONS FOR INDIVIDUALS WITH ADVANCED HIV – OPPORTUNISTIC INFECTION & PROPHYLAXIS

Despite efforts to expand HIV testing and the accessibility of effective antiretroviral therapy (ART) in British Columbia, just under 20% of people living with HIV (PLWH) are diagnosed at an advanced stage of HIV disease.(1) Others may not access medical care including ART or are unable to adhere to their ART regimen consistently. Such individuals may develop low CD4 cell counts, which places them at risk for opportunistic infections (OIs), and indeed an OI is often the presenting feature that brings them into medical care. Once the acute OI has been treated, primary prophylaxis for other common OIs may be appropriate if the CD4 cell count remains low. Following immune reconstitution with ART, primary prophylaxis can often be discontinued once the patient is clinically stable and has established consistent adherence. Indications for prophylaxis, agents of choice, and criteria for discontinuing and restarting primary prophylaxis for *Pneumocystis jirovecii* pneumonia (PJP), Toxoplasma, *Mycoplasma (M.) tuberculosis*, and *Mycobacterium avium* complex (MAC) are shown in **Table 8.1**. Also refer to the BC CfE Opportunistic Infection Therapeutic Guidelines.

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Table 8.1: Prophylaxis to prevent first episode of opportunistic disease and criteria for when to discontinue or restart primary prophylaxis for adults and adolescents living with HIV

Pathogen*	Indication	First choice	Alternative	Criteria for discontinuing primary prophylaxis	Criteria for restarting primary prophylaxis
Pneumocystis jirovecii pneumonia (PCP or PJP)	• CD4 cell count <200 cells/mm^3; **or** • CD4 cell count <14%; **or** • CD4 cell count >200 but <250 cells/mm^3 if monitoring CD4 cell count every 1-3 months is not possible	Trimethoprim-sulfamethoxazole (TMP-SMX)*: • 1 double strength (DS) per os (by mouth) (PO) daily; **or** • 1 single strength (SS) PO daily	• TMP-SMX* 1 DS PO 3 times a week; **or** • Dapsone* 100 mg PO daily or 50 mg PO bid; **or** • Dapsone 50 mg PO daily + (pyrimethamine 50 mg + leucovorin 25 mg) PO weekly; **or** • Atovaquone 1500 mg PO daily; **or** • Aerosolized pentamidine 300 mg via Respirgard® II nebulizer every month	• CD4 cell count >200 cells/mm^3 for >3 months in response to antiretroviral therapy (ART); **or** • CD4 cell count 100-200 cells/mm^3 for >3 months in response to ART and HIV RNA <40 copies/mL x 3-6 months	• CD4 cell count <200 cells/mm^3, if HIV RNA >40 copies/mL; **or** • CD4 <100 cells/mm^3 regardless of HIV RNA

Pathogen*	Indication	First choice	Alternative	Criteria for discontinuing primary prophylaxis	Criteria for restarting primary prophylaxis
Toxoplasma gondii encephalitis	Toxoplasma IgG positive patients with CD4 cell count <100 cells/mm^3 Seronegative patients receiving PJP prophylaxis not active against toxoplasmosis should have Toxoplasma serology retested if CD4 cell count declines to <100 cells/mm^3. Prophylaxis should be initiated if seroconversion occurred	Trimethoprim-sulfamethoxazole (TMP-SMX)*, 1 DS PO daily	• TMP-SMX* 1 DS PO 3 times a week; **or** • TMP-SMX 1 SS PO daily; **or** • Dapsone* 50 mg PO daily + (pyrimethamine 50 mg + leucovorin 25 mg) PO weekly; **or** • Atovaquone 1500 mg PO daily	• CD4 cell count >200 cells/mm^3 for >3 months in response to ART; **or** • CD4 cell count 100-200 cells/mm^3 for >3 months in response to ART and HIV RNA <40 copies/mL x 3-6 months	CD4 cell count < 100-200 cells/mm^3
Mycobacterium tuberculosis infection (TB) [Treatment of latent TB infection (LTBI)]	• (+) diagnostic test for LTBI, no evidence of active TB, and no prior history of treatment for active or latent TB; **or** • Close contact with a person with infectious pulmonary TB and no evidence of active TB, regardless of screening diagnostic test result for LTBI; **or** • History of untreated or inadequately treated healed TB (i.e. old fibrotic lesions), regardless of diagnostic tests for LTBI and no evidence of active TB	Isoniazid (INH) 300 mg PO daily or 900 mg PO twice a week for 9 months – both plus pyridoxine 25 mg PO daily	• Rifampin (RIF) 600 mg PO daily x 4 months; **or** • Rifapentine (900 mg for weight >50 kg; 750 mg for 32-49 kg) plus INH 15 mg/kg (900 mg maximum) plus pyridoxine 50 mg, all once weekly for 12 weeks (only available under the direction of BCCDC TB clinic; and only compatible with efavirenz- or raltegravir-based ART) (For persons exposed to drug-resistant TB, consult BCCDC TB clinic)	Not applicable	Not applicable
Disseminated *Mycobacterium avium* complex (MAC) disease	Primary prophylaxis is no longer recommended if ART therapy is to be initiated promptly. CD4 cell count <50 cells/mm^3 after ruling out active MAC infection¶	• Azithromycin 1200 mg PO once weekly; **or** • Clarithromycin 500 mg PO bid; **or** • Azithromycin 600 mg PO twice weekly	Rifabutin 300 mg PO daily (dosage adjustment based on drug-drug interactions with ART); rule out active TB before starting RFB	CD4 cell count >100 cells/mm^3 for >3 months in response to ART	CD4 cell count <50 cells/mm^3 and not taking a fully suppressive ART regimen

Adapted from http://aidsinfo.nih.gov/guidelines 2013.

* Screening for Glucose-6-phosphate Dehydrogenase (G6PD) deficiency for patients with a predisposing racial or ethnic background may be relevant to prevent hemolysis after exposure to oxidant drugs such as dapsone and trimethoprim-sulfamethoxazole.
¶ For asymptomatic patients, MAC prophylaxis can be started after drawing a mycobacterial blood culture. Symptomatic patients should wait for the results of blood culture before starting MAC prophylaxis.
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9 HEALTH SERVICES TO OPTIMALLY ENGAGE PEOPLE LIVING WITH HIV (PLWH) IN EFFECTIVE PRIMARY CARE

Chapter Summary:

1. Optimal HIV management is facilitated by healthcare delivery models that are focused on long-term engagement and relationship-building between healthcare providers and their clients.
2. Actively linking individuals newly diagnosed with HIV to clinicians who are familiar with the HIV management is preferred to passive referrals or simply providing patients information. In BC, regional public health nursing teams may be helpful in linking newly diagnosed individuals to care.
3. Peer support or peer-navigation may also be helpful for linking or retaining some PLWH in care
4. Formal case management to link and/or retain PLWH in care may be needed for some individuals.
5. PLWH may face additional challenges such as housing instability and food insecurity, which should be addressed through referrals to specific social services.
6. Outreach support, such as those provided by public health nursing teams though health authorities, are a helpful resource in assisting PLWH to remain engaged in care.

Engaging people living with HIV (PLWH) in healthcare and ensuring client retention are key elements to providing successful treatment, ensuring adherence to antiretroviral treatments, and preventing onward disease transmission.(1, 2) However, PLWH may encounter a variety of challenges to accessing consistent and effective care. Some factors are patient-dependent, such as negative emotions associated with diagnosis(1) and a lack of adequate social supports.(1, 2) Other factors are associated with health services themselves, such as negative healthcare experiences(1) and lack of culturally sensitive care for Indigenous people and other cultural minorities.(3)

Healthcare providers and staff who are perceived to be supportive and collaborative are important to establishing rapport with PLWH, and these positive relationships can, in turn, improve linkage to healthcare.(1, 4, 5) Moreover, supportive providers may be seen by patients as members of their supportive social network and as proxies for absent friends and family.(1) In addition, providing appropriate education around HIV, through programmes tailored for PLWH or by care providers trained/competent in providing patient education, improves patient empowerment and understanding of antiretroviral therapy (ART).(6, 7) Patients also highly value confidentiality as the fear of incidental disclosure when seeking services is a concern for many PLWH accessing care.(7) Client-centred healthcare that accounts for patient preferences and is culturally sensitive and confidential underpins the effective delivery of HIV services.(3, 5, 8, 9)

In BC, all residents are eligible for care and treatment of HIV free of charge. Care providers who are faced with challenges of caring for visitors without health insurance and/or persons residing in Canada illegally should contact the BC-CfE to advocate on the person's behalf for coverage of the cost of medical treatment.

9.1 CHRONIC DISEASE MODEL OF CARE

As HIV is now conceptualized as a chronic, manageable condition, its optimal management is facilitated by care models that are focused on long-term engagement and relationship-building between healthcare providers and their clients. The Chronic Care Model, first formulated by Wagner et. al. in 1996(10) and recently revisited,(11) addresses relational aspects of care (**Figure 9.1**). At its core, the Chronic Care Model postulates that an informed and activated client, when partnered with a proactive and prepared healthcare team, will achieve optimal outcomes for chronic disease management. HIV care has been evaluated in terms of how well it incorporates aspects of the Chronic Care Model;(12-14) however, we are not aware of studies which have evaluated different service delivery models in terms of clinical outcomes. Many aspects of care related to the Chronic Care Model have recently been identified as priorities for PLWH in high-income countries.(7) These include: a strong healthcare professional-patient relationship, HIV specialist knowledge, continuity of care, ease of access to services, access to high quality information and support, effective co-ordination between HIV specialists and other healthcare professionals, and patient involvement in decisions about treatment and care. Other studies have shown that better physician-patient relationships are associated with higher rate of adherence to ART.(15)

Quality improvement involves routine data collection and cycles of planning, change, and feedback to improve processes and outcomes. Incorporating quality improvement methods in HIV care can provide useful feedback throughout cycles of change, including the implementation of an intervention, and help close gaps in care.(16) For more information on best practices for quality improvement and evaluation of HIV care and services, please consult the resources available on the HIV Continuum of Care Collaborative website (http://stophivaids.ca/hiv-continuum-collaborative/).

9.2 ACTIVE REFERRAL FOLLOWING DIAGNOSIS

Upon diagnosis, active guidance to set up initial clinic appointments rather than passive methods (e.g. handing out brochures) improves linkage,(1) as does scheduling clinic orientation visits.(17) In BC, regional public health teams may be helpful in linking newly diagnosed individuals to clinicians who are familiar with the management of HIV infection. A list of contact numbers can be found in the **Appendix 4**, page 116. As well, The Canadian AIDS Treatment and Information Exchange (http://catie.ca, 1-800-263-1638) is a national organization that provides useful support and information regarding HIV treatment and related topics in languages accessible to most clients.

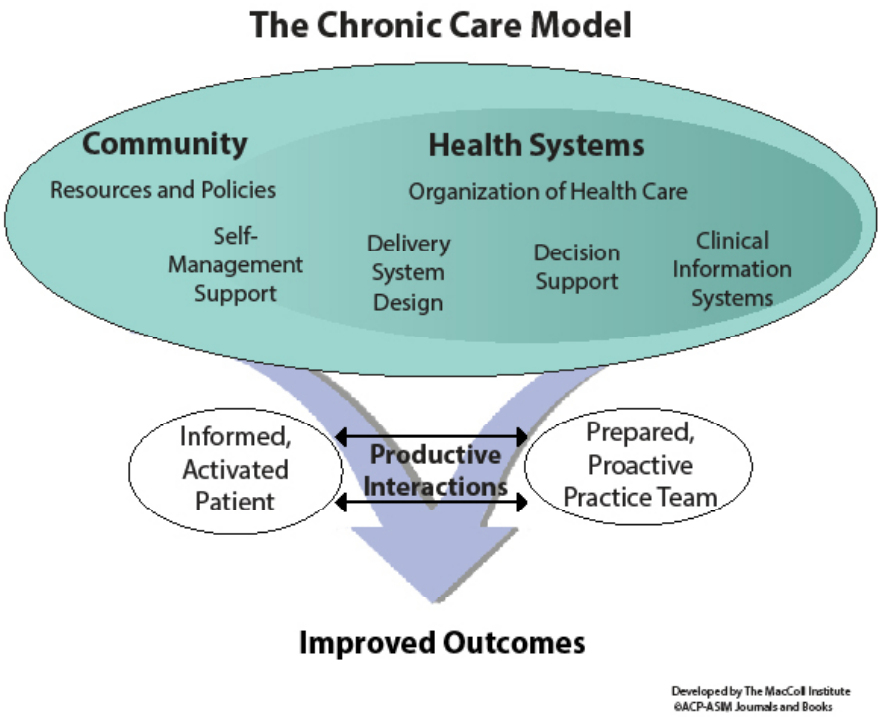

Figure 9.1: The Chronic Care Model

9.3 ADDRESSING SOCIAL DETERMINANTS OF HEALTH

PLWH may face additional challenges such as housing instability and food insecurity. Stable housing among PLWH has been associated with a variety of positive clinical outcomes, including adherence to ART and improvement in overall health status,(18, 19) As well, evidence from randomized trials has demonstrated that receiving assistance or other services that improve housing status has a direct impact on improved medical care and health outcomes for formerly homeless or inadequately housed PLWH.(20, 21) Food insecurity has been associated with a lack of virologic suppression among PLWH receiving ART, with 37% of those with unsuppressed viral load reporting food insecurity;(22) food insecurity has also been associated with increased mortality among PLWH who use injection drugs in studies conducted in BC(23) and New York.(22) Clinicians should actively ask PLWH about these issues and have connections to social work supports and community organizations so that they can actively assist patients in accessing appropriate programs and services.

9.4 PEER-SUPPORT AND PATIENT OR PEER NAVIGATION

Stigma, isolation, and marginalization are common realities in the lives of PLWH. Ensuring access to social and emotional support for affected individuals is a crucial part of HIV primary care. Peer support programs can help to improve linkages and retention in care. AIDS service organizations (ASOs) are excellent starting points for many of these services. Please refer to the Contact List (**Appendix 4**, page 117 for a list of provincial organizations, providing support for PLWH).

Patient navigators, who may be peers with lived experience, assist in relationship-building and non-medical support. Peer navigators may accompany clients to appointments, guide clients through the healthcare system, teach skills in communicating with providers, and provide non-clinical services such as transportation.(17, 24) Peers may also provide basic information on HIV medications and support treatment adherence, including reinforcing messages regarding treatment as prevention or U=U. Peers can also provide education regarding sexually transmitted infections and other related topics. Moreover, peers can connect patients with community organizations and provide referrals to services and support groups, including addiction and mental health support. Patient and peer navigators have been found to improve linkage to and retention in healthcare by supporting clients in navigating complex medical systems to meet their care needs.(24, 25) Guidelines for peer navigation services have been published by the Canadian AIDS Treatment Information Exchange.(26) In BC, several community-based organizations provide peer navigation or peer support services, including Vancouver Island PWA Society (https://vpwas.com/programs/peer-support/) and AIDS Vancouver (https://www.aidsvancouver.org/peer-navigation-program). Health care providers should contact their regional health authority's HIV program if they have clients who could benefit from peer navigation or support.

9.5 CASE MANAGEMENT

Case management has been shown to be effective in both initial linkage to care(27) and subsequent retention in care(28, 29) and often comprises a variety of interventions. Case management may consist of assistance from a healthcare worker to link PLWH to HIV care providers with time-limited follow-up to ensure that linkage and retention have occurred. Case management may also include referring clients to appropriate providers, assisting clients to prioritize personal needs, introducing HIV resources, helping to complete forms, and teaching skills about disclosure to support networks.(17) Case management activities may overlap with patient/peer navigation.(24)

9.6 OUTREACH SERVICES

Intensive outreach services (e.g. home visits or mobile van outreach) were also found to increase retention and ART adherence, though the programs could be resource-intensive and lack long-term stability.(6, 17) Outreach services can be provided by medical professionals or by peers. These programs may work better when integrated with other social services.(6) In BC, all regional health authorities have outreach nursing teams to assist PLWH who have not engaged in HIV care following diagnosis or who have fallen out of care. At Vancouver Coastal Health, these outreach personnel are known as STOP teams; they have different names in other regional health authorities. Contact information for these teams are found in **Appendix 4**, page 117.

The Re-Engagement and Engagement in Treatment for Antiretroviral Interrupted and Naïve populations (RETAIN) Initiative (http://bccfe.ca/stop-hiv-aids/retain) is a partnership between the BC-CfE, Medical Health Officers from each health authority, and HIV outreach personnel throughout British Columbia. The BC-CfE sends routine alerts to physicians regarding their patients who are at least 2 months late in refilling their ART prescription. Additionally, alerts have been launched for physicians linked to

patients newly diagnosed with HIV who have not yet accessed ART. Both of these alerts include contact information for local public health support.

A core component of RETAIN is the routine province-wide coordination of public health support for PLWH who have interrupted ART or who have yet to initiate therapy. PLWH will be eligible for this outreach support if: 1) they have interrupted treatment for longer than 4 months, or 2) they have not yet started treatment more than 4 months after a high plasma viral load was reported. The BC-CfE provides routine referrals for such clients to each regional health authority on a monthly basis. An evaluation of the RETAIN program demonstrated that, among individuals who had interrupted treatment for >4 months, those who interrupted their treatment in the post-RETAIN era (i.e. after June 2016) were more likely to re-start ART (adjusted hazard ratio 1.50; 95% CI 1.34 - 1.69), compared to earlier time periods.(30)

9.7 OTHER SUPPORTS

In addition, supports such as counselling and use of motivational interviewing methods may improve retention and adherence to medication.(17, 31) Motivational interviewing techniques can be delivered by mental health clinicians or by trained peer outreach workers.(32)

Interventions using phone text messaging can help to provide remote clinic support for individuals receiving ART.(6) In BC, the WelTel intervention has been shown to improve adherence to ART and virologic suppression among women with an unsuppressed viral load at the Oak Tree Clinic.(33, 34)

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APPENDIX 1: SIGNS AND SYMPTOMS ASSOCIATED WITH HIV SEROCONVERSION SYNDROME/ACUTE RETROVIRAL SYNDROME AND THEIR FREQUENCY IN SYMPTOMATIC INDIVIDUALS

- Fever (80%)
- Tired or fatigued (78%)
- Malaise (68%)
- Arthralgias (54%)
- Headache (54%)
- Loss of appetite (54%)
- Rash (51%)
- Night sweats (51%)
- Myalgias (49%)
- Nausea (49%)
- Diarrhea (46%)
- Fever and rash (46%)
- Pharyngitis (44%)
- Oral ulcers (37%)
- Stiff neck (34%)
- Weight loss (>5 lb; 2.5 kg) (32%)
- Confusion (25%)
- Photophobia (24%)
- Vomiting (12%)
- Infected gums (10%)
- Sores on anus (5%)
- Sores on genitals (2%)

Adapted from HIV Clinical Resource, New York State Department of Health AIDS Institute (http://www.hivguidelines.org/clinical-guidelines/adults/diagnosis-and-management-of-acute-hiv-infection/) with data from Hecht FM, Busch MP, Rawal B, Webb M, Rosenberg E, Swanson M, et al. Use of laboratory tests and clinical symptoms for identification of primary HIV infection. AIDS. 2002;16(8):1119-29.

APPENDIX 2: AIDS-DEFINING CONDITIONS

(Require concurrent positive HIV serology to be diagnostic of AIDS)

- Bacterial pneumonia, recurrent
- Candidiasis (esophageal, bronchi, trachea, or lungs)
- Cervical cancer, invasive
- Coccidioidomycosis (disseminated or extrapulmonary)
- Cryptococcosis (extrapulmonary)
- Cryptosporidiosis (chronic intestinal)
- Cytomegalovirus disease (other than liver, spleen, nodes)
- Cytomegalovirus retinitis (with loss of vision)
- Encephalopathy, HIV-related (dementia)
- Herpes simplex virus (chronic ulcers or bronchitis, pneumonitis or esophagitis)
- Isosporiasis, chronic intestinal
- Kaposi sarcoma
- Lymphoma (Burkitt, immunoblastic, primary in brain)
- *Mycobacterium avium* complex or M. kansasii (disseminated or extrapulmonary)
- Mycobacterium of other species (disseminated or extrapulmonary)
- *Mycobacterium tuberculosis* (pulmonary, disseminated or extrapulmonary)
- *Pneumocystis jiroveci* (formerly *carinii*) pneumonia
- Progressive multifocal leukoencephalopathy
- *Salmonella* septicemia, recurrent
- Toxoplasmosis of brain
- Wasting syndrome due to HIV

Adapted from *Canadian Guidelines on Sexually Transmitted Infections*, Public Health Agency of Canada (http://www.phac-aspc.gc.ca/std-mts/sti-its/cgsti-ldcits/section-5-8-eng.php#table-3) with data from Health and Welfare Canada. Revision of the CDC surveillance case definition for acquired immunodeficiency syndrome. *CDWR* 1987;13-38:169–177; and from Revision of the surveillance case definition for AIDS in Canada. *CCDR* 1993;19-15:116–117.

APPENDIX 3: SCREENING FOR NON-INFECTIOUS CO-MORBID CONDITIONS IN PEOPLE LIVING WITH HIV (PLWH)

	Assessment	Pre-ART baseline	Follow-up on ART*	Comments
General Medical History	Personal and family history of relevant co-morbid conditions (e.g. premature cardiovascular disease, hypertension, diabetes, osteoporosis, liver disease, chronic kidney disease)	+	Update at least annually	
	Concomitant medications	+	Update at each visit	
	Lifestyle (smoking, alcohol, recreational drugs, diet, exercise)	+	Update at least annually	
Cardiovascular disease	Risk assessment (Framingham risk score) (http://www.ccs.ca/en/guidelines/guideline-resources)	+	At least annually	• Framingham Risk Score may underestimate risk in HIV • Consider using Canadian Life Expectancy Model (CLEM) (http://myhealthcheckup.com/cvd/?lang=en) or the American College of Cardiology/ American Heart Association (ACC/ AHA) 2013 10-year Cardiovascular Risk Assessment (https://www.merckmanuals.com/medical-calculators/ACCAHA2013.htm) • Manage hypertension and dyslipidemia per general population guidelines; assess for potential drug interactions with ART • Address modifiable risk factors where possible • Monitor ECG if receiving protease inhibitors and/or rilpivirine with concomitant agents associated with cardiac conduction abnormalities
	Blood pressure	+	At least annually	
	Fasting lipids (total, HDL, and LDL cholesterol, triglycerides) and apolipoprotein B	+	Annually; every 6 months if abnormal	
Diabetes	Fasting blood sugar and/or HbA1C	+	Annually; every 6 months if abnormal; every 3 months if diabetic	• HbA1C can underestimate glycemia in PLWH • Manage blood glucose abnormalities per Diabetes Canada guidelines, with lifestyle changes first (weight loss, diet, exercise) • NB potential drug interactions with ART

	Assessment	Pre-ART baseline	Follow-up on ART*	Comments
Bone disease (osteopenia/ osteoporosis)	Osteoporosis risk assessment (family history, exercise, weight, smoking, alcohol, calcium and vitamin D intake)	+	At each visit (at least annually)	• FRAX not validated for use in PLWH • Recommend supplementation with Vitamin D 1000-2000 IU/day for prevention • Recommend calcium supplementation if dietary intake inadequate • Perform DXA in PLWH of any age with a history of fragility fractures, significant risk factors for osteoporosis, or intermediate or high 10-year risk of fracture by FRAX (>10%)
	Fracture risk assessment (FRAX) https://www.sheffield.ac.uk/FRAX/tool.aspx?country=19	+ in cisgender women >40 years and all PLWH >50 years	At least annually in cisgender women >40 years and all PLWH >50 years	
	DXA scan	+ or post-menopausal cisgender women, and all PLWH >50 years	Intervals determined by BC guidelines	
Renal disease	Risk assessment including nephrotoxic medications	+	At least annually	• Increased risk for renal disease associated with family history, black race, age >50 years, advanced HIV disease (low CD4 nadir), diabetes, hypertension, hepatitis B/C, other liver disease, concomitant nephrotoxic medications including NSAIDs and some recreational drugs • Increased risk of renal toxicity with certain antiretrovirals, particularly tenofovir DF • Diagnosis of abnormalities may require referral to a nephrologist and possible renal biopsy
	Blood pressure	+	At least annually	
	Serum creatinine and eGFR; serum phosphate; urinalysis; spot urine for albumin to creatinine ratio	+	Every 3-4 months initially, then every 6 months when stable	
Hypogonadism	Morning serum total testosterone	+ Only in symptomatic cisgender men	Only in symptomatic cisgender men	• Symptoms may include decreased libido, erectile dysfunction, reduced bone mass or low trauma fractures, hot flashes or sweats, weight loss, reduced muscle strength or exercise capacity, sleep disturbance, fatigue, or depression
Lung disease	Chest X-ray	+	If symptomatic	• Encourage smoking cessation • Chest CT in presence of persistently abnormal chest X-ray or significant symptoms, especially in smokers
Liver disease	AST, ALT, total bilirubin, albumin	+	Every 3-4 months initially, then every 6 months when stable	
	Abdominal ultrasound	+ (if HBV+ or HCV+ or cirrhosis)	Every 6 months if HBV+ (any stage fibrosis) or HCV+ with cirrhosis or cirrhosis of other etiology	

* Frequency of laboratory monitoring may be adjusted according to history of relevant co-morbid conditions, potential toxicities of specific antiretroviral drugs and concomitant medications, previous or ongoing laboratory abnormalities, and clinical status.

ART, antiretroviral therapy
ALT, alanine aminotransferase
AST, aspartate aminotransferase
CT, computed tomography
DXA, dual energy absorptiometry
ECG, electrocardiogram
eGFR, estimated glomerular filtration rate
FRAX, Fracture risk assessment
HbA1C, glycated hemoglobin
HBV, hepatitis C virus
HCV, hepatitis C virus
HDL, high-density lipoprotein
LDL, low-density lipoprotein
NSAIDs, non-steroidal anti-inflammatory drugs
PLWH, people living with HIV

APPENDIX 4: CONTACT LIST

Revised January 2021

Resource	Local Number	Other Number	Website
BC Centre for Excellence in HIV/AIDS For HIV treatment and management or guideline inquiries	604-806-8477	**HIV/AIDS Treatment Program Information Line** 604-806-851 **Drug Resistance Testing** 1-800-517-1119	www.bccfe.ca
REACH Telephone Line Rapid Expert Advice and Consultation in HIV – a 24-hour line available to connect all physicians, nurses, and pharmacists in BC to infectious disease specialists, GP HIV specialists, or HIV-experienced pharmacists	604-681-5748	1-800-665-7677	N/A
RACE Telephone Line Rapid Access to Consultative Expertise – a provincial shared care telephone advice line for family physicians. When calling, request BC-CfE for HIV primary care.	604-696-2131	1-877-696-2131	N/A
St. Paul's Hospital Pharmacy To reach an HIV-experienced pharmacist if you practice in British Columbia		1-888-511-6222	N/A
BC Centre for Disease Control For HIV testing and other STI inquiries	604-707-5600	N/A	www.bccdc.ca
Oak Tree Clinic Inquiries regarding specialized HIV care for HIV-positive women, pregnant women, partners, children, and youth	604-875-2212	1-888-711-3030	www.bcwomens.ca/health-professionals/refer-a-patient/oak-tree-clinic-hiv-care
Trans Care BC Supports the delivery of equitable and accessible care, surgical planning, and peer and community support for trans people across BC	604-675-3647	1-866-999-1514	http://www.phsa.ca/our-services/programs-services/trans-care-bc

Provincial and Regional HIV/AIDS Service Organizations

Organization	Local Number	Other Number	Website
Cool Aid Community Health Centre (Victoria)	250-385-1466	N/A	https://coolaid.org/
Pacific AIDS Network (PAN)	604-569-1998	N/A	https://pacificaidsnetwork.org/ https://pacificaidsnetwork.org/about/members/ (with links to regional service organizations)
Viva Women	N/A	N/A	vivawomen@gmail.com
YouthCO HIV & Hep C Society	604-688-144	1-877-968-8426	http://www.youthco.org/

Regional Health Authority Contacts/ Communicable Disease Nursing Contacts

Fraser Health Authority (FHA)	Telephone Number	Additional Info
All FHA	604-777-6705	Frequently monitored (Monday through Friday)

Vancouver Island Health Authority (VIHA)	BC Toll Free Number	Local Number
Central Island	1-866-770-7798	250-740-2616
North Island	1-877-887-8835	250-331-8555
South Island	1-866-665-6626	250-388-2225

Interior Health Authority	Telephone Number
Communicable Disease Unit	1-866-778-7736

Northern Health Authority	Telephone Number	Additional Info
Northwest	1-250-631-4228	Ask for the Designated Nurse
Northern Interior	1-778-349-2793	-
Northeast	1-250-719-6500	Ask for the Designated Nurse

Vancouver Coastal Health (VCH)	Telephone Number	Additional Info
VCH Communicable Disease Control	604-675-3900	Ask for Communicable Disease Nurse on call

APPENDIX 5: OTHER GUIDELINES RELATED TO THE CARE OF PEOPLE LIVING WITH HIV (PLWH)

Topic/Title	URL	Issuing Agency
Antiretroviral Therapy & HIV Care Therapeutic Guidelines		
Therapeutic Guidelines: Management of Acute HIV Infections (May 2018)	http://bccfe.ca/sites/default/files/uploads/Guidelines/Management-of-Acute-HIV-Infections-[16-MAY-2018].pdf	BC Centre for Excellence in HIV/AIDS
Therapeutic Guidelines for Antiretroviral (ARV) Treatment of Adult HIV Infection (2020)	http://bccfe.ca/therapeutic-guidelines/guidelines-antiretroviral-arv-treatment-adult-hiv-infection	BC Centre for Excellence in HIV/AIDS
HIV Treatment and Management online course	http://education.bccfe.ca	BC Centre for Excellence in HIV/AIDS Clinical Training and Education Program
Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults: 2020 Recommendations of the International Antiviral Society–USA Panel	https://www.iasusa.org/2020/11/12/antiretroviral-drugs-treatment-prevention-hiv-infection-adults-2020-recommendations-of-the-international-antiviral-society-usa-panel/	International Antiviral Society - USA
Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV (2019)	https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/AdultandAdolescentGL.pdf	Department of Health & Human Services, USA
EACS Guidelines (October 2020)	https://www.eacsociety.org/files/guidelines-10.1_finaljan2021_1.pdf	European AIDS Clinic Society
Primary Care Guidance for Persons With Human Immunodeficiency Virus: 2020 Update by the HIV Medicine Association of the Infectious Diseases Society of America	https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa1391/5956736?login=true	Infectious Diseases Society of America. IAS medicine association
Psychotropic Drugs: Sedatives/Hypnotics, Antidepressants, and Antipsychotics	https://hivclinic.ca/wp-content/uploads/2019/06/Psychotropics_Eng.pdf	Canadian HIV and Viral Hepatitis Pharmacists Network (CHAP)
HIV Drug Interactions	https://www.hiv-druginteractions.org/	Liverpool HIV Pharmacology Group, University of Liverpool
Drug Interaction Tables, Immunodeficiency Clinic	https://hivclinic.ca/drug-information/drug-interaction-tables	Toronto General Hospital, University Health Network
Re-Engagement and Engagement in Treatment for Antiretroviral Interrupted and Naïve populations (RETAIN) Initiative	http://bccfe.ca/stop-hiv-aids/retain	BC Centre for Excellence in HIV/AIDS; Provincial Health Authorities; HIV outreach nursing staff
Seek and Treat for Optimal Prevention of HIV/AIDS (STOP HIV/AIDS)	http://stophivaids.ca/hiv-continuum-collaborative/	STOP HIV/AIDS

Topic/Title	URL	Issuing Agency
Post-exposure Prophylaxis Guidelines (Guidance for the use of post-exposure prophylaxis (PEP) for the prevention of HIV in British Columbia)	http://www.bccfe.ca/post-exposure-prophylaxis	BC Centre for Excellence in HIV/AIDS
Assessments & Laboratory Testing		
Adult BMI Calculator	http://www.cdc.gov/healthyweight/assessing/bmi/adult_bmi/english_bmi_calculator/bmi_calculator.html	US Centers for Disease Control and Prevention
HIV Testing Guidelines for the Province of British Columbia	https://www2.gov.bc.ca/assets/gov/health/about-bc-s-health-care-system/office-of-the-provincial-health-officer/hiv-testing-guidelines-bc.pdf	Office of the Provincial Health Officer
IGRA Testing Guidelines	http://www.bccdc.ca/resource-gallery/Documents/Communicable-Disease-Manual/Chapter%204%20-%20TB/TB_manual_IGRA_guidelines.pdf or http://www.bccdc.ca/resource-gallery/Documents/Communicable-Disease-Manual/Chapter%204%20-%20TB/CPS_TB_IGRA_PublicHealth.pdf	BC Centre for Disease Control
HIV Drug Resistance Mutations: 2019	https://www.iasusa.org/resources/hiv-drug-resistance-mutations/	International Antiretroviral Society-USA
Infectious Co-Morbid Conditions		
Sexually Transmitted Infections		
British Columbia Treatment Guidelines: Sexually Transmitted Infections in Adolescents and Adults 2014	http://www.bccdc.ca/resource-gallery/Documents/Communicable-Disease-Manual/Chapter%205%20-%20STI/CPS_BC_STI_Treatment_Guidelines_20112014.pdf	BC Centre for Disease Control
Sexually Transmitted Infections (Section I)	http://www.bccdc.ca/dis-cond/comm-manual/CDManualChap5.htm	BC Centre for Disease Control
Canadian Guidelines on Sexually Transmitted Infections (2014)	http://www.phac-aspc.gc.ca/std-mts/sti-its/cgsti-ldcits/index-eng.php	Public Health Agency of Canada. Expert Working Group for the Canadian Guidelines on Sexually Transmitted Infections.
Tuberculosis		
Interferon Gamma Release Assay Testing for Latent Tuberculosis Infection: Physician Guidelines	http://www.bccdc.ca/resource-gallery/Documents/Communicable-Disease-Manual/Chapter%204%20-%20TB/TB_manual_IGRA_guidelines.pdf	BC Centre for Disease Control
Canadian Tuberculosis Standards (2014)	https://cts-sct.ca/guideline-library/	Public Health Agency of Canada and Canadian Lung Association

Topic/Title	URL	Issuing Agency
Management of Hepatitis B Virus Infection: 2018 Guidelines from the Canadian Association for the Study of the Liver and Association of Medical Microbiology and Infectious Disease Canada	https://canlivj.utpjournals.press/doi/full/10.3138/canlivj.2018-0008	Canadian Association for the Study of the Liver and Association of Medical Microbiology and Infectious Disease Canada
Hepatitis B Guideline in *Chapter I – Communicable Disease Control Manual*	http://www.bccdc.ca/resource-gallery/Documents/Guidelines%20and%20Forms/Guidelines%20and%20Manuals/Epid/CD%20Manual/Chapter%201%20-%20CDC/BCCDC%20HBV%20Guideline%20FINAL%20April_2021.pdf	BC Centre for Disease Control
The management of chronic hepatitis C: 2018 guideline update from the Canadian Association for the Study of the Liver	https://www.cmaj.ca/content/190/22/e677	Canadian Association for the Study of the Liver
An update on the management of chronic hepatitis C: 2015 consensus guidelines from the Canadian Association for the Study of the Liver	https://www.liver.ca/wp-content/uploads/2017/09/CASL_Hep_C_Consensus_Guidelines_Update_-_Jan_2015.pdf	Canadian Association for the Study of the Liver
CIHR Canadian HIV Trials Network Coinfection and Concurrent Diseases Core Research Group: 2016 Updated Canadian HIV/Hepatitis C Adult Guidelines for Management and Treatment	https://pubmed.ncbi.nlm.nih.gov/27471521/	Canadian HIV Trials Network HIV/Hepatitis C Management and Treatment Guidelines Working Group Non-Infectious Co-Morbid Conditions
Non-Infectious Co-Morbid Conditions		
Cancer		
Breast cancer screening	http://www.bccancer.bc.ca/screening/health-professionals/breast	BC Cancer (PHSA)
Breast Screening for Transgender, Gender-Diverse and Non-Binary People	http://www.bccancer.bc.ca/screening/Documents/Breast-Screening-Transgender-Patients-Provider-Guide.pdf	BC Cancer (PHSA)
Cervical Cancer screening	http://www.bccancer.bc.ca/screening/health-professionals/cervix	BC Cancer (PHSA)
Cancer screening in LGBTQ communities	http://convio.cancer.ca/site/PageServer?pagename=SSL_ON_T_Home#.VaBZE-t9SXv	Canadian Cancer Society
Colon Cancer screening	http://www.bccancer.bc.ca/screening/health-professionals/colon	BC Cancer (PHSA)
Recommendations on screening for prostate cancer with the prostate-specific antigen test	http://www.cmaj.ca/content/186/16/1225 or https://canadiantaskforce.ca/guidelines/published-guidelines/prostate-cancer/	Canadian Task Force on Preventive Health Care
Cardiovascular		
Guideline Resources: Calculators and Forms	https://ccs.ca/calculators-and-forms/	Canadian Cardiovascular Society

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2021 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult	https://www.onlinecjc.ca/action/showPdf?pii=S0828-282X%2821%2900165-3	Canadian Journal of Cardiology
2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk	https://www.ahajournals.org/doi/full/10.1161/01.cir.0000437741.48606.98	American College of Cardiology/American Heart Association
QT Drugs Resources	https://www.crediblemeds.org/index.php	CredibleMeds
Cardiovascular Risk Assessment (10-year, ACC/AHA 2013)	https://www.merckmanuals.com/medical-calculators/ACCAHA2013.htm	Merck Manuals
Do you know your cardiovascular age?	https://myhealthcheckup.com/cvd/?lang=en)8	MyHealthCheckUp
Canadian Hypertension Education Program Recommendations for Blood Pressure Measurement, Diagnosis, Assessment of Risk, Prevention, and Treatment of Hypertension (2014)	http://www.onlinecjc.ca/article/S0828-282X%2814%2900070-1/pdf	Canadian Hypertension Education Program
Diabetes		
Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada	https://guidelines.diabetes.ca/cpg	Diabetes Canada Clinical Practice Guidelines Expert Committee
Osteoporosis		
Recommendations for evaluation and management of bone disease in HIV	https://pubmed.ncbi.nlm.nih.gov/25609682/	Brown TT, Hoy J, Borderi M, et al.
Fracture Risk Assessment Tool (FRAX)	https://www.sheffield.ac.uk/FRAX/tool.aspx?country=19	Centre for Metabolic Bone Diseases, University of Sheffield, UK
Osteoporosis: Diagnosis, Treatment and Fracture Prevention	https://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/bc-guidelines/osteoporosis	Guidelines and Protocols Advisory Committee, Medical Services Commission
Clinical Practice Guidelines and Recommendations	https://osteoporosis.ca/health-care-professionals/clinical-practice-guidelines/	Osteoporosis Canada
Clinical practice guidelines for the diagnosis and management of osteoporosis in Canada (2010)	https://www.cmaj.ca/content/cmaj/182/17/1864.full.pdf	The Scientific Advisory Council of Osteoporosis Canada
General Prevention and Screening: Musculoskeletal Health	http://transhealth.ucsf.edu/trans?page=protocol-screening#S6X	Centre of Excellence for Transgender Health, University of California San Francisco
Renal		
Clinical Practice Guideline for the Management of Chronic Kidney Disease in Patients Infected With HIV: 2014 Update	http://cid.oxfordjournals.org/content/early/2014/09/12/cid.ciu617.full.pdf+html	HIV Medicine Association of the Infectious Diseases Society of America

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Respiratory		
COPD guidelines	https://cts-sct.ca/guideline-library/	Canadian Thoracic Society
Contraception		
Interactions between Antiretrovirals (ARVs) and Hormonal Contraceptives	http://www.hivclinic.ca/main/drugs_interact_files/Oral%20Contraceptive-int.pdf	Toronto General Hospital, Immunodeficiency Clinic
Contraceptive Eligibility for Women at High Risk of HIV (2019)	https://apps.who.int/iris/bitstream/handle/10665/326653/9789241550574-eng.pdf?ua=1	World Health Organization
Best Practices to Minimize Risk of Infection with Intrauterine Device Insertion	http://sogc.org/guidelines/best-practices-minimize-risk-infection-intrauterine-device-insertion/	Society of Obstetricians and Gynaecologists of Canada
Immunization		
Communicable Disease Control Manual	http://www.bccdc.ca/dis-cond/comm-manual/CDManualChap2.htm	BC Centre for Disease Control
Communicable Disease Control Manual. Chapter 2: Immunization Manual, Part 4: Biological Products (Vaccines and Immune Globulins)	http://www.bccdc.ca/health-professionals/clinical-resources/communicable-disease-control-manual/immunization/biological-products	BC Centre for Disease Control
Canadian Immunization Guide (2015)	http://www.phac-aspc.gc.ca/publicat/cig-gci/index-eng.php	Public Health Agency of Canada, National Advisory Committee on Immunization
Update the Recommended Human Papillomavirus (HPV) Vaccine Immunization Schedule	http://www.phac-aspc.gc.ca/naci-ccni/acs-dcc/2015/hpv-vph_0215-eng.php	Public Health Agency of Canada, National Advisory Committee on Immunization
Interim Statement on HPV Vaccination of Men Who Have Sex with Men (2014)	https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/373531/JCVI_interim_statement_HPV_vacc.pdf	Joint Committee on Vaccination and Immunisation
Opportunistic Infection		
Therapeutic Guidelines for Opportunistic Infections (2009)	http://bccfe.ca/therapeutic-guidelines/opportunistic-infection-therapeutic-guidelines	BC Centre for Excellence in HIV/AIDS
Pregnancy		
British Columbia Guidelines for the Care of HIV-positive Pregnant Women and Interventions to Reduce Perinatal Transmission	http://www.bcwomens.ca/Professional-Resources-site/Documents/Oak%20Tree/BCHIVinpregnancyguidelinesFINALAug72014.pdf	BC Women's Hospital + Health Centre
Canadian consensus guidelines for the management of pregnant HIV-positive women and their offspring	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC161612	Canadian HIV Trials Network Working Group on Vertical HIV Transmission
Guidelines for the Care of Pregnant Women Living With HIV and Interventions to Reduce Perinatal Transmission	https://www.jogc.com/article/S1701-2163(15)30515-6/fulltext	Society of Obstetricians and Gynaecologists of Canada

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HIV/AIDS Resources	http://www.bcwomens.ca/health-professionals/professional-resources/hiv-aids-resources	BC Women's Hospital + Health Centre
Referral Form – Oak Tree Clinic (Preconception counselling, Specialized obstetrical services)	http://www.bcwomens.ca/health-professionals/refer-a-patient/oak-tree-clinic-hiv-care	BC Women's Hospital + Health Centre
Primary Care Guidelines		
Primary Care Guidance for Persons With Human Immunodeficiency Virus: 2020 Update by the HIV Medicine Association of the Infectious Diseases Society of America	https://pubmed.ncbi.nlm.nih.gov/33225349/	HIV Medicine Association of the Infectious Diseases Society of America
Transgender Primary Medical Care: Suggested Guidelines for Clinicians in British Columbia (2014)	http://lgbtqpn.ca/wp-content/uploads/woocommerce_uploads/2014/08/Guidelines-primarycare.pdf	Transcend Transgender Support & Education Society and Vancouver Coastal Health
Transgender and Gender Diverse Care		
Breast Screening for Transgender, Gender-Diverse and Non-Binary People	http://www.bccancer.bc.ca/screening/Documents/Breast-Screening-Transgender-Patients-Provider-Guide.pdf	BC Cancer (PHSA)
Clinical Resources	http://www.phsa.ca/transcarebc/health-professionals/clinical-resources	Trans Care BC (PHSA)
Endocrine Therapy for Transgender Adults in British Columbia: Suggested Guidelines	http://www.phsa.ca/transcarebc/Documents/HealthProf/BC-Trans-Adult-Endocrine-Guidelines-2015.pdf	Trans Care BC (PHSA)
Gender-affirming Care for Trans, Two-Spirit, and Gender Diverse Patients in BC: A Primary Care Toolkit	http://www.phsa.ca/transcarebc/Documents/HealthProf/Primary-Care-Toolkit.pdf	Trans Care BC (PHSA)
Sexual Health Screening and Pelvic Examination	http://www.phsa.ca/transcarebc/Documents/HealthProf/Sexual_Health_Screening_and_Pelvic_Exam.pdf	Trans Care BC (PHSA)
Women and HIV		
BC Women's Hospital + Health Centre HIV/AIDS Resources	http://www.bcwomens.ca/health-professionals/professional-resources/hiv-aids-resources	BC Women's Hospital + Health Centre
Pocket guide: menopause management	https://www.sigmamenopause.com/sites/default/files/pdf/publications/Final-Pocket%20Guide.pdf	Canadian Menopause Society
Menopause Therapies	https://www.menopauseandu.ca/therapies/	The Society of Obstetricians and Gynaecologists of Canada
Caring for Women Living with HIV: Women-Centred HIV Care Toolkit	https://whai.ca/resource/caring-for-women-living-with-hiv-women-centred-hiv-care-toolkit/	Women & HIV/AIDS Initiative
Other		
Trauma-Informed Care	https://www.traumainformedcare.chcs.org/what-is-trauma-informed-care/	Center for Health Care Strategies; Robert Wood Johnson Foundation