Primary Care Guidelines for the Management of HIV/AIDS in British Columbia

On behalf of the Primary Care Guidelines Panel
BC Centre for Excellence in HIV/AIDS

August 2015
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ACKNOWLEDGEMENTS

We would like to acknowledge the following external medical experts who were consulted during the revising of the Guidelines:

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We would also like to acknowledge the External Review Panel of community physicians, pharmacist, nurse, and nurse practitioners from across B.C.

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INTRODUCTION

There has been a significant decrease in the morbidity and mortality of HIV-positive individuals in the province of British Columbia since the introduction of potent antiretroviral treatment in 1996. According to the Public Health Agency of Canada’s most recent estimates using data from 2011, there are approximately 11,700 (ranging from 9,400-14,000) HIV-positive individuals living in British Columbia. Among them, approximately only 6,750 were receiving antiretroviral treatment in 2015.

In response to the need to expand HIV treatment and requests from the larger community of primary care providers for HIV-specific guidelines, the British Columbia Centre for Excellence in HIV/AIDS (BC-CfE) has developed these guidelines to support care and treatment programs for people living with HIV.

OBJECTIVES

1. To provide consensus guidelines for the management of HIV-positive individuals in the primary care setting.
2. To provide flow-care sheets based on the guidelines that can be used as an electronic or paper-based template.

METHODS

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 these guidelines.

Process Overview

In 2014/15, the committee collectively undertook a review of the 2011 guidelines. Where applicable, committee members added new evidence up to December 2014 and revised or added new recommendations. Changes to the guidelines are highlighted in yellow throughout the document and summarized in the “Summary of Changes in the 2015 Update.”

Consensus Development on the Basis of Evidence

The committee met a total of seven 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 report manuscript was reviewed by all committee members as well as by external review panel of primary care providers to ensure applicability prior to dissemination.
Table 1. Strength of Recommendation Taxonomy (SORT) [adapted from Ebell 2004]³

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Type of Evidence</th>
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<tbody>
<tr>
<td>Grade A</td>
<td>Consistent, good quality patient-oriented evidence</td>
</tr>
<tr>
<td>Grade B</td>
<td>Inconsistent or limited quality patient-oriented evidence</td>
</tr>
<tr>
<td>Grade C</td>
<td>Consensus, disease-oriented evidence, usual practice, expert opinion, or case series for studies of diagnosis, treatment, prevention, or screening</td>
</tr>
</tbody>
</table>

Quality of evidence

<table>
<thead>
<tr>
<th>Level</th>
<th>Evidence from at least 1 properly designed randomized, controlled trial</th>
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<tbody>
<tr>
<td>Level II</td>
<td>Evidence from at least 1 well designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from &gt;1 centre); from multiple time series; or from dramatic results of uncontrolled experiments</td>
</tr>
<tr>
<td>Level III</td>
<td>Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees</td>
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</tbody>
</table>

Conflicts of Interest

Panel members were asked to report any conflicts of interest. Aida Sadr, Martin Payne, Jonathan Postnikoff, and Linda Akagi have no conflicts to disclose.

Disclosures: Rolando Barrios has received speaking honoraria from Gilead Sciences, Inc. Marianne Harris has received grants for research support, honoraria for advisory board participation and/or speaking engagements, and/or other honoraria from AbbVie, Bristol-Myers Squibb Canada, Gilead Canada Inc., GlaxoSmithKline, Janssen Inc., Merck Canada Inc., Vertex Pharmaceuticals, and ViiV Healthcare. Neora Pick has participated in advisory boards for Janssen, Abbvie, Merck, and Gilead, and received research funding from CIHR. Peter Phillips has received honoraria or participated in advisory boards for the following companies: Pfizer Inc., Janssen Pharmaceutical Schering-Plough, Fujisawa, Merck, and Astellas. Silvia Guillemi has received honoraria for advisory board participation, other honoraria, and/or consultancies including speaking engagements for Bristol-Myers Squibb, Gilead, Merck, Janssen and ViiV.

References

### Glossary of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>AFB</td>
<td>Acid-Fast Bacilli</td>
</tr>
<tr>
<td>AIDS</td>
<td>Acquired Immunodeficiency Syndrome</td>
</tr>
<tr>
<td>anti-HBs</td>
<td>Anti-hepatitis B surface antibody</td>
</tr>
<tr>
<td>anti-HBc</td>
<td>Anti-hepatitis B core antibody</td>
</tr>
<tr>
<td>Anti-ART</td>
<td>Antiretroviral Therapy</td>
</tr>
<tr>
<td>ARV</td>
<td>Antiretroviral(s)</td>
</tr>
<tr>
<td>ASO</td>
<td>AIDS Service Organization</td>
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<tr>
<td>BCCDC</td>
<td>British Columbia Centre for Disease Control</td>
</tr>
<tr>
<td>BC-CfE</td>
<td>British Columbia Centre for Excellence in HIV/AIDS</td>
</tr>
<tr>
<td>BC-PHMRL</td>
<td>British Columbia Public Health Microbiology Reference Laboratory</td>
</tr>
<tr>
<td>BMD</td>
<td>Bone Mineral Density</td>
</tr>
<tr>
<td>BMI</td>
<td>Body Mass Index</td>
</tr>
<tr>
<td>CCR5</td>
<td>C-C chemokine receptor type 5</td>
</tr>
<tr>
<td>CD4</td>
<td>Cell counts (absolute and fraction) are clinical indicators of immunocompetence in patients with HIV infection</td>
</tr>
<tr>
<td>CDC</td>
<td>United States Centers for Disease Control</td>
</tr>
<tr>
<td>CNS</td>
<td>Central Nervous System</td>
</tr>
<tr>
<td>COPD</td>
<td>Chronic Obstructive Pulmonary Disease</td>
</tr>
<tr>
<td>CSF</td>
<td>Cerebrospinal Fluid</td>
</tr>
<tr>
<td>CT</td>
<td>Computed Tomography</td>
</tr>
<tr>
<td>CVD</td>
<td>Cardiovascular Disease</td>
</tr>
<tr>
<td>DF</td>
<td>Tenofovir disoproxil fumarate</td>
</tr>
<tr>
<td>DM</td>
<td>Diabetes Mellitus</td>
</tr>
<tr>
<td>DS</td>
<td>Double Strength</td>
</tr>
<tr>
<td>DXA</td>
<td>Dual Energy X-Ray Absorptiometry</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>eGFR</td>
<td>Estimated Glomerular Filtration Rate</td>
</tr>
<tr>
<td>EIA</td>
<td>Enzyme Immunoassay</td>
</tr>
<tr>
<td>FBG</td>
<td>Fasting Blood Glucose</td>
</tr>
<tr>
<td>FIT</td>
<td>Fecal Immuno-chemical test</td>
</tr>
<tr>
<td>GC</td>
<td>Gonorrhoea and Chlamydia</td>
</tr>
<tr>
<td>GLP-1</td>
<td>Glucagon-like Peptide-1</td>
</tr>
<tr>
<td>HAART</td>
<td>Highly Active Antiretroviral Therapy</td>
</tr>
<tr>
<td>HAV</td>
<td>Hepatitis A Virus</td>
</tr>
<tr>
<td>HbA1C</td>
<td>Glycated Haemoglobin</td>
</tr>
<tr>
<td>HBsAg</td>
<td>Hepatitis B virus surface antigen</td>
</tr>
<tr>
<td>HBV</td>
<td>Hepatitis B Virus</td>
</tr>
<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
</tr>
<tr>
<td>HCV</td>
<td>Hepatitis C Virus</td>
</tr>
<tr>
<td>HDL</td>
<td>High-Density Lipoprotein</td>
</tr>
<tr>
<td>HIV RNA</td>
<td>Quantitative HIV ribonucleic acid (RNA) measures plasma viral load.</td>
</tr>
<tr>
<td>HLA-</td>
<td>Human Leukocyte Antigen B*5701 allele; genetic test to identify persons</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
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</tr>
<tr>
<td>B*5701</td>
<td>at a high risk for hypersensitivity reaction to the antiretroviral agent abacavir.</td>
</tr>
<tr>
<td>HPV</td>
<td>Human Papillomavirus</td>
</tr>
<tr>
<td>HSCRP</td>
<td>High-Sensitivity C-Reactive Protein</td>
</tr>
<tr>
<td>HSR</td>
<td>Hypersensitivity Reaction</td>
</tr>
<tr>
<td>IGRA</td>
<td>Interferon Gamma Release Assay, used to screen for tuberculosis infection.</td>
</tr>
<tr>
<td>IM</td>
<td>Intramuscularly</td>
</tr>
<tr>
<td>IgA</td>
<td>Immunoglobulin A</td>
</tr>
<tr>
<td>IgG</td>
<td>Immunoglobulin G</td>
</tr>
<tr>
<td>IPD</td>
<td>Invasive Pneumococcal Disease</td>
</tr>
<tr>
<td>IR</td>
<td>Insulin Resistance</td>
</tr>
<tr>
<td>IU</td>
<td>International Units</td>
</tr>
<tr>
<td>IUD</td>
<td>Interuterine Device</td>
</tr>
<tr>
<td>LDL</td>
<td>Low-Density Lipoprotein</td>
</tr>
<tr>
<td>LTBI</td>
<td>Latent Tuberculosis Infection</td>
</tr>
<tr>
<td>MAC</td>
<td>Mycobacterium Avium Complex</td>
</tr>
<tr>
<td>MSM</td>
<td>Men who have sex with men</td>
</tr>
<tr>
<td>MMR</td>
<td>Mumps, Measles, Rubella</td>
</tr>
<tr>
<td>MMT</td>
<td>Methadone Maintenance Therapy</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>MSP</td>
<td>Medical Services Plan</td>
</tr>
<tr>
<td>NAAT</td>
<td>Nucleic Acid Amplification Test</td>
</tr>
<tr>
<td>NACI</td>
<td>National Advisory Committee on Immunization</td>
</tr>
<tr>
<td>NNRTI</td>
<td>Non-nucleoside Reverse Transcriptase Inhibitor</td>
</tr>
<tr>
<td>NRTI</td>
<td>Nucleoside Reverse Transcriptase Inhibitor</td>
</tr>
<tr>
<td>NSAIDS</td>
<td>Non-Steroidal Anti-Inflammatory Drugs</td>
</tr>
<tr>
<td>OI</td>
<td>Opportunistic infection</td>
</tr>
<tr>
<td>PCR</td>
<td>Polymerase Chain Reaction</td>
</tr>
<tr>
<td>PI</td>
<td>Protease Inhibitor</td>
</tr>
<tr>
<td>PO</td>
<td>per os (by mouth)</td>
</tr>
<tr>
<td>PPD</td>
<td>Purified Protein Derivative</td>
</tr>
<tr>
<td>PWID</td>
<td>People Who Inject Drugs</td>
</tr>
<tr>
<td>pVL</td>
<td>HIV plasma viral load (copies/mL)</td>
</tr>
<tr>
<td>RPR</td>
<td>Rapid Plasma Reagin</td>
</tr>
<tr>
<td>STI</td>
<td>Sexually Transmitted Infections</td>
</tr>
<tr>
<td>SC</td>
<td>Subcutaneously</td>
</tr>
<tr>
<td>TB</td>
<td>Tuberculosis or Mycobacterium tuberculosis</td>
</tr>
<tr>
<td>TD</td>
<td>Tetanus and Diphtheria</td>
</tr>
<tr>
<td>TMP-SMX</td>
<td>Trimethoprim-Sulphamethoxazole</td>
</tr>
<tr>
<td>TRT</td>
<td>Testosterone Replacement Therapy</td>
</tr>
<tr>
<td>TST</td>
<td>Tuberculin Skin Test</td>
</tr>
<tr>
<td>UACR</td>
<td>Urine Albumin to Creatnine Ratio</td>
</tr>
<tr>
<td>VZV</td>
<td>Varicella Zoster Virus</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>
SUMMARY OF PRIMARY CARE RECOMMENDATIONS FOR THE MANAGEMENT OF HIV/AIDS

Section II: Medical History and Physical Examination

1. All HIV-positive individuals should be evaluated by a primary care clinician with knowledge and experience in the management of HIV infection. (BII) Primary care clinicians without expertise in HIV care should consult with a physician with this expertise. (CIII)
2. Clinicians should obtain a comprehensive present and past medical history, as well as a medication/social/family history, review of systems, and conduct a complete physical examination upon the patient’s entry into care. (AI)
3. Clinicians should schedule routine monitoring visits at least every 3-6 months for all HIV-positive individuals whose clinical status is stable and on antiretroviral therapy. More frequent visits should be scheduled for those whose clinical status is unstable or not on antiretroviral therapy. (CI)
4. Clinicians should assess vital signs, weight, and body mass index (BMI) at each visit, and also note abnormalities and changes in general appearance, body habitus, physical well-being, frailty, and mobility. (CIII)

Section III: HIV Disease Specific Testing

1. 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. (AI)
2. Clinicians should obtain baseline CD4 cell counts (absolute and fraction) and quantitative HIV RNA (plasma viral load) for all patients upon entry into care. (AII)
3. All patients should be assessed for transmitted HIV drug resistance using genotypic drug resistance testing, regardless of the estimated duration of the infection. Ideally, the drug resistance testing should be conducted on the first available sample of HIV plasma viral load (AI). Note that in British Columbia, genotypic resistance testing can be performed on archived plasma samples (all samples are archived at the BC-CfE in perpetuity).
4. If antiretroviral therapy is deferred, a repeat genotypic drug resistance testing close to the time of initiation of therapy is recommended because of the potential for superinfection (CII).
5. Genotypic drug resistance testing should be conducted for patients experiencing treatment failure or incomplete viral suppression (HIV plasma viral load >250 copies/mL) while receiving antiretroviral therapy. (AI)

HLA-B*5701

1. HLA-B*5701 testing is recommended once at baseline for all patients. (CIII) HLA-B*5701-positive patients must not be given abacavir-containing regimens. (AII)
2. All patients taking an abacavir-containing regimen should be screened for HLA-B*5701, if not previously screened, regardless of how well they have tolerated abacavir in the past. (CIII). If patients stop abacavir therapy and are HLA-B*5701 positive, they should not restart abacavir-containing therapy, as they are at a high risk of hypersensitivity reaction (HSR). (CIII)
Section IV: Screening and Immunization for Selected Co-morbid Infections

Part 1: Screening for Co-morbidities

Tuberculosis Screening
1. All HIV-positive individuals should be screened at baseline for *Mycobacterium tuberculosis* (TB) infection. (AI) Screening involves reviewing history of TB exposure and/or treatment history, a recent chest X-ray (within 3 months), and previous tuberculin skin test (TST) and/or interferon gamma release assay (IGRA) results. (AIII)

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

3. IGRA.s are currently recommended as an adjunct test to TST and may be valuable in the following two situations: a) HIV-positive individuals with CD4 cell count <200 cells/mm³ who are TST-negative (if possible, T-spot is preferred); and b) HIV-positive individuals with a history of contact with active TB and who are TST-negative. (BIII)

Chest X-Rays
1. All HIV-positive individuals should have a chest X-ray at baseline. (CIII)

Toxoplasmosis Screening
1. All HIV-positive individuals should be screened at baseline for Toxoplasma IgG antibodies to determine prior exposure to *Toxoplasma (T.) gondii*. (BIII)

Hepatitis Screening
1. HIV-positive individuals should be screened at baseline for hepatitis A virus (HAV) using total anti-HAV antibodies. (CIII)

2. HIV-positive individuals should be screened at baseline for hepatitis B virus (HBV) using HBsAg, anti-HBs and anti-HBc. (AIII) Individuals testing negative for HBsAg and anti-HBs but testing positive for anti-HBc should have HBV DNA testing to rule out occult HBV infection. (CIII)

3. HIV-positive individuals should be screened at baseline for hepatitis C virus (HCV) using a test for HCV antibodies. (BIII) Positive HCV antibody test results should be confirmed by measuring HCV RNA PCR. (AII)

Screening for Syphilis and other Sexually Transmitted Infections (STIs)
1. All HIV-positive individuals should be screened for syphilis at baseline. (AIII) Syphilis screening should be repeated annually or every 3-6 months in the presence of ongoing risk behaviours, or in the presence of symptoms. (BII)

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. (AI)

3. All HIV-positive individuals should be screened for gonorrhoea and chlamydia. (AII)

4. STI assessments should be done at baseline and repeated if there is ongoing risk. (AIII)
Part 2: Immunizations and HIV

RECOMMENDED VACCINES

**Hepatitis A**
1. All HIV-positive individuals who are susceptible (anti-hepatitis A [HAV] negative) should be vaccinated against HAV, ideally when CD4 >200 cells/mm³. (BII)
2. The HAV vaccine should be administered intramuscularly at the standard dose (AI), at 0, 1 and 6 months. (AII)

**Hepatitis B**
1. All HIV-positive individuals who are susceptible to hepatitis B virus (HBV) infection (HBsAg negative and anti-HBs less than 10 IU) should be vaccinated against HBV, ideally when CD4 >200 cells/mm³. (BII)
2. HBV vaccination should also be offered to those who have positive hepatitis B total core antibody (anti-HBc) with negative HBsAg and anti-HBs results and undetectable HBV DNA. (AIII)
3. In the situations described above, HBV vaccine should be administered intramuscularly (IM) to adults 20 years of age and older at a higher dose (40 mcg). (BII)
   - Recombivax (10 mcg/mL): give 4.0 mL IM at 0, 1, and 6 months
   - Recombivax Adult Dialysis formulation (40 mcg/mL) give 1.0 mL IM at 0, 1, and 6 months
   - Engerix Adult (20 mcg/mL): give 2.0 mL IM at 0, 1, 2 and 6 months
4. Post-serologic testing (using anti-HBs) within 1 to 6 months of completion of the vaccine series is recommended to monitor success of immune response to vaccine. (CIII)

**Pneumococcal Disease**
1. All HIV-positive individuals should be vaccinated against pneumococcal disease using standard vaccine doses (AI), 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 eight weeks later by one dose of polysaccharide pneumococcal vaccine (Pneu-P-23). (AI)
   (ii) Individuals who have received a pneumococcal polysaccharide vaccine (Pneumo-P-23) previously: The Pneu-C-13 dose should be administered at least one year after any previous dose of Pneu-P-23. (CIII)
   (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. (CIII)

**Influenza**
1. All HIV-positive individuals should be vaccinated annually against influenza using standard doses of the inactivated vaccine, regardless of CD4 cell counts or HIV plasma viral load. (AII)

**Tetanus and diphtheria**
1. All HIV-positive individuals should be offered a tetanus and diphtheria (Td) toxoid booster every 10 years, ideally when CD4 >200 cells/mm³. (AII)
VACCINES INDICATED UNDER SPECIAL CIRCUMSTANCES

**Measles, Mumps and Rubella (New subsection added March 2015)**
1. All HIV-positive individuals without evidence of immunity and with CD4 cell counts >200 cells/mm³ should be considered for measles and/or mumps and/or rubella vaccination (given as a two dose series of MMR vaccine). (BII)
2. All HIV-positive individuals born before 1970 or who have previously received two doses of measles- and mumps-containing vaccine, have serologic proof of immunity against measles or rubella, or have had lab diagnosed disease, are considered to have immunity against one or more of these diseases. If they are susceptible to one of these diseases, the only vaccine available for use is measles, mumps and rubella vaccine. MMR vaccine is safe for use in those with prior immunity. (BII)
3. All HIV-positive individuals 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. (AII)

**Varicella (New subsection added July 2015)**
1. All HIV-positive individuals without evidence of immunity and with CD4 cell counts >200 cells/mm³ may be considered for varicella vaccination (given as a two dose series of varicella vaccine). (CIII)

**Herpes Zoster (New subsection added March 2015)**
1. Herpes zoster vaccine is contraindicated in HIV-positive individuals with CD4 <200 cells/mm³. (BII)
2. The use of herpes zoster vaccine for prevention of shingles in HIV-positive adults with CD4 >200 cells/mm³ is not routinely recommended. (BIII)

**Human Papillomavirus (HPV) (New subsection added March 2015)**
1. HPV4 vaccine is recommended for HIV-positive girls and women (AII) and HIV-positive boys and men (BII) between 9-26 years of age, regardless of their CD4 counts, to prevent infection caused by HPV types 6, 11, 16 and 18 and related diseases. A 3-dose series is recommended, regardless of age. (AII)

Section V: Schedule of Care for HIV-positive Individuals

1. All HIV-positive individuals who are not on antiretroviral therapy should have CD4 cell counts and plasma viral loads (pVL) measured every 3-4 months. (BII)
2. All individuals initiating antiretroviral therapy should have CD4 cell counts and pVL measured on a monthly basis until pVL is <40 copies/mL, and thereafter monitoring can occur every 3-4 months. (BII)
3. In clinically stable patients with dependable antiretroviral adherence, once pVL is consistently <40 copies/mL for two years and CD4 counts are consistently ≥350 cells/mm³, pVL monitoring can occur at intervals of up to six months and CD4 monitoring is optional. (CIII)
4. Safety laboratory parameters (complete blood count, renal and liver function, fasting lipids, and glucose) should be monitored approximately one month after initiation of antiretroviral therapy (with the first pVL and CD4 count) and every 3-6 months thereafter (see Table 6 on p. 57).
Monitoring should be undertaken more frequently in the presence of relevant underlying co-morbid conditions, known potential toxicities of specific antiretroviral drugs, and/or concomitant medications. (CIII)

Section VI: Special Considerations for Women and Transgender Individuals with HIV

Special Considerations Related to Care before, during, and after Pregnancy
1. Contraception and pregnancy plans should be discussed with all individuals of childbearing potential upon initiation of HIV care and routinely thereafter, as pregnancy may affect the choice and timing of antiretrovirals. (AIII) Contraceptive counselling should also be included as a critical aspect of postpartum care. (AIII)
2. Preconception counselling in HIV-positive individuals is recommended for anyone contemplating pregnancy, especially in the setting of HIV-serodiscordant couples. (BII)
3. Pregnancy in HIV-positive individuals is considered a high risk and complex; therefore, consultation with or referral to an obstetrician experienced in HIV is highly recommended. (BIII)
4. All HIV-positive pregnant individuals should be treated with ART for HIV infection, regardless of their immunologic or virologic status, to prevent infection of their fetus. (AI) Antiretroviral therapy should be continued after delivery and reassessed by providers of adult HIV care. (AII)
5. Breastfeeding is not recommended, regardless of HIV viral load and use of ART, for HIV-positive individuals in Canada. (AI)
6. Clinicians should avoid prescribing efavirenz, or any new under-studied drug, during the first trimester of pregnancy, to anyone who wishes to become pregnant, and to individuals of childbearing potential who are not using effective and consistent contraception. A pregnancy test should be done before initiation of efavirenz in individuals of childbearing potential and counselling should be provided on the potential risk to the fetus while the mother is receiving efavirenz. (AIII)
7. Clinicians should not prescribe nevirapine to antiretroviral-naïve women or trans-masculine individuals who have CD4 cell counts >250 cells/mm³, nor start nevirapine during pregnancy (AI)

Contraception in the Context of HIV
1. Health care 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. (AII)
2. Intrauterine devices (IUDs) can be considered as a safe and effective contraception option for HIV-positive women and adolescents. (BII)

Screening for Cervical and Breast Cancer in HIV-positive Individuals
1. Cervical Pap smear should be done for any individual with a cervix starting at age 21 or 3 years after first sexual contact, whichever occurs first. For those eligible HIV-positive individuals cervical screening should be done upon initiation of care, and should be repeated 6 months later. If results are normal in both tests, cervical Pap smear should be done annually thereafter. (AI) If Pap smear results are abnormal, the individual should be referred for colposcopy and directed biopsy, as recommended by the BC Cancer Agency, with further treatment as indicated by results. (AII)
2. Breast cancer screening for HIV-positive people should follow provincial guidelines for the general population. (AII) Consider screening in transgender women on long-term hormone replacement >5 years, and in transgender men and others who may have had mastectomy for non-cancer related reasons.

**Menopause**

1. Hormone replacement therapy may be considered in patients who experience severe menopausal symptoms (i.e. vasomotor symptoms and vaginal dryness) but should generally be used only for a limited period of time and at the lowest effective doses. (BII)
2. Hormone replacement for HIV-positive transgender individuals should be provided in consultation with an endocrinologist or other clinician who has experience providing endocrine care to transgender individuals.

**Section VII: Common Non-infectious Comorbidities**

**Cardiovascular Disease**

1. All HIV-positive individuals should be screened for risk of cardiovascular disease at least annually, and modifiable cardiovascular risk factors should be addressed where possible. (AI)
2. Assess fasting lipids (total, HDL, LDL cholesterol, and triglycerides) or apolipoprotein B at baseline and every six months once patient begins antiretroviral therapy. (AIII)
3. An ECG should be performed at baseline and monitored periodically (at intervals determined by the degree of risk) in patients taking protease inhibitors and/or rilpivirine with other PR- or QTc-prolonging drugs. (CIII)

**Insulin Resistance (IR) and Diabetes Mellitus (DM)**

1. Fasting blood glucose (FBG) and/or glycated hemoglobin (HbA1c) should be performed in all HIV-positive individuals at baseline and at six-month intervals during antiretroviral therapy. Abnormalities in fasting glucose and/or HbA1c should be evaluated and managed according to the Canadian Diabetes Society guidelines ([http://guidelines.diabetes.ca/](http://guidelines.diabetes.ca/)). (AIII)
2. Initial management of blood glucose abnormalities in HIV-positive individuals involves lifestyle changes (weight loss, diet, exercise). (AIII)
3. Oral anti-glycemic agents and injectable anti-glycemic agents (insulin, glucagon-like peptide-1 [GLP-1] receptor agonists) should be used as required, keeping in mind drug interactions with some antiretrovirals. (AIII)

**Bone Disease**

1. Clinicians should undertake preventive measures for bone loss in all HIV-positive individuals, including 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). (AIII)
2. Vitamin D supplementation should be considered for all HIV-positive individuals (e.g. 1000-2000 IU/day). (BIII)
3. Clinicians should consider performing a baseline dual energy X-ray absorptiometry (DXA) scan to assess bone mineral density for HIV-positive women who are post-menopausal and in all HIV positive men aged 50 years and older, and in patients of any age with a history of fragility
fractures or significant risk factors for osteoporosis (http://www.osteoporosis.ca/health-care-professionals/guidelines/) (BIII).

4. DXA scan should be repeated at intervals according to local provincial guidelines. (BIII)

5. For HIV-positive transgender people who have undergone gender-affirming interventions, such as hormone therapy or gonadectomy, clinicians should refer to appropriate resources for guidance on osteoporosis screening. (CIII)

6. If decreased bone density is diagnosed, secondary causes such as hypogonadism, alcoholism, glucocorticoid exposure, and vitamin D deficiency should be investigated and treated appropriately, including referral to a specialist if necessary. (AIII)

Renal Disease

1. Due to the risk of renal disease related to HIV and antiretroviral medications, it is recommended that blood pressure and laboratory assessment of renal function (serum creatinine and phosphate, estimated glomerular filtration rate [eGFR], urinalysis for protein and sediment, and spot urine for albumin to creatinine ratio [UACR]) should be performed in all HIV-positive individuals at baseline and every 3-4 months after starting antiretrovirals, increasing to six-month intervals when stable (depending on degree of risk). (AIII)

2. In case of renal dysfunction, clinicians should adjust doses of medications, including antiretrovirals that are cleared by the kidney. 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. (AII)

Hypogonadism (New subsection added March 2015)

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

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

3. Hormone replacement for HIV-positive transgender individuals should be provided in consultation with an endocrinologist or other clinician who has experience providing endocrine care to transgender individuals. (CIII)

Neurocognitive Impairment (New subsection added March 2015)

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

2. HIV-positive individuals presenting with cognitive complaints that affect their daily functioning should be investigated to rule out relevant underlying conditions. (AII)

Lung Disease (New subsection added March 2015)

1. Smoking cessation should be strongly encouraged in all HIV-positive patients, because they are at a higher risk for chronic obstructive pulmonary disease (COPD) and lung cancer than smokers who do not have HIV. (AII)
2. A chest X-ray should be performed at baseline in all HIV-positive patients. 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. (AI)

3. A diagnosis of COPD should be considered, and spirometry performed as a screening test, among HIV-positive patients of any age presenting with persistent respiratory complaints, especially those with additional risk factors such as smoking. COPD should be managed according to current Canadian Thoracic Society guidelines (http://www.respiratoryguidelines.ca/); however, concomitant use of inhaled steroids with ritonavir or cobicistat should be avoided if possible. (AII)

Liver Disease/Cirrhosis (New subsection added March 2015)
1. Liver enzymes and liver function should be assessed in all HIV-positive individuals at baseline and every 3-4 months after starting antiretrovirals, increasing to six-month intervals when stable. (AIII)
2. All HIV-positive individuals with cirrhosis who are co-infected with Hepatitis B and/or C should be screened for hepatocellular carcinoma every six months using ultrasound. (AII)
3. All HIV-positive individuals with cirrhosis should be referred for a baseline gastroscopy to screen for esophageal varices. (AII)

Cancer (New subsection added March 2015)
1. In HIV-positive patients, screening for breast, colorectal, ovary, and prostate cancers should follow current provincial recommendations for the general population. (BII)
2. HIV-positive patients may be at increased risk for lung cancer, HPV-related cancers (oropharyngeal, cervical, anal), and hepatocellular cancer as compared to the general population. Increased surveillance for these cancers is recommended. (AII)

Section VIII: Optimizing Adherence to Antiretroviral Therapy
1. All HIV-positive individuals should have timely access to routine and urgent care that is linguistically and culturally appropriate to patient needs. (BII)
2. An interprofessional team model, with a primary provider for each patient, should be utilized to promote trusting relationships between the patient and their health care team members. (BII)
3. Clinicians should involve patients in antiretroviral regimen selection. Clinicians should ensure that patients understand treatment goals and are motivated to initiate and maintain adherence to antiretroviral therapy. (BII)
4. Clinicians should educate and support patients to help maintain adherence to antiretroviral therapy by positively reinforcing treatment success. (BII)
5. Potential behavioural, structural, and psycho-social barriers to adherence and engagement in care, such as mental illness or substance abuse, should be identified and addressed in collaboration with appropriate providers. These barriers may change with time and should be re-evaluated on an ongoing basis by all health care team members. (BIII)
Section IX: Special Consideration for HIV-positive Individuals with Addictions

1. All HIV-positive individuals should be asked about substance use at baseline and at least annually thereafter. Those with a history of substance use should be re-evaluated for drug and alcohol use at least quarterly. (CIII)

2. Clinicians should offer and support a variety of substance use treatment options for HIV-positive substance users, including abstinence, a reduction in use, and safer use strategies. (CIII)

3. HIV-positive substance users receiving methadone or buprenorphine while on antiretroviral therapy should be monitored for potential drug-drug interactions. (AII)

4. Substance users are at a high risk for multiple co-morbid medical and mental health conditions, such as hepatitis B and C virus infection, tuberculosis, skin and soft tissue infections, recurrent bacterial pneumonia, endocarditis, and depression. Primary care providers of HIV-positive substance users should be familiar with the prevention, diagnosis, and treatment of these co-morbidities. (BII)

Section X: Special Consideration for Individuals with Advanced HIV – Opportunistic Infection & Prophylaxis

See Table 9 (p. 92).

Section XI: Psycho-social Implications of HIV Infection

Model of care

1. HIV care and patient education should be provided in a socially, culturally and gender appropriate manner using a patient-centred, collaborative, and interdisciplinary chronic disease care model which fosters trusting patient-provider relationships and improves retention in care. (CIII)

Linkage to and retention in care

1. All HIV-positive individuals should have timely access to routine primary care and treatment. (BII)

2. Case management for individuals with a new HIV diagnosis is recommended. (BII)

3. Intensive outreach for individuals not engaged in medical care within 6 months of a new HIV diagnosis may be considered. (CIII)

4. Clinical and non-clinical providers are strongly encouraged to incorporate quality improvement strategies that focus on improving delivery and quality of HIV care to HIV-positive individuals. (CIII)

Peer and social support

1. Clinicians should perform thorough assessments of the social circumstances of HIV-positive individuals at baseline and re-evaluate annually. (CIII)

2. All individuals living with HIV should be offered a referral to an AIDS service organization (ASO) for counselling, social, and peer support. (CIII)

3. Peer support workers should be identified and utilized to help improve patient outcomes. (CIII)
I. Background

A. Introduction

The advent of potent antiretroviral therapy (ART) significantly improved the management of HIV infection and led to substantial reductions in HIV- and AIDS-related morbidity and mortality. ART has transformed HIV disease into a chronic, manageable condition. In addition, new cohort data provide evidence for the effectiveness of ART treatment to prevent transmission of HIV to sexual and needle-sharing (injection drug use) partners.1-4

In order for ART to be effective, individuals must be fully engaged in care, from the initial assessment following diagnosis to long-term retention, and receive timely initiation of antiretroviral therapy and, if necessary, effective psycho-social support systems.

B. Modes of HIV Transmission

The key modes of HIV transmission – sexual contact, perinatal transmission, and exposure to infected blood through sharing of injection drug use paraphernalia or receipt of contaminated blood products – were clarified early in the AIDS epidemic. In untreated HIV-positive individuals, HIV is present in significant concentrations in blood, semen, pre-seminal fluids (pre-cum), vaginal and rectal fluids, breast milk and any other body fluids contaminated with blood. The likelihood of HIV transmission by different routes varies, as shown in Table 2 (adapted from Garcia-Tejedor and Lewthwaite).5,6 (For further information on rates of HIV transmission, refer to Appendix 2A of the BC-CfE Accidental Exposure Guidelines http://www.cfenet.ubc.ca/sites/default/files/uploads/docs/Accidental_Exposure_Therapeutic_Guidelines_Nov82010.pdf)

Table 2. Methods of HIV Transmission

<table>
<thead>
<tr>
<th>Method</th>
<th>Risk of acquisition per 100 exposures (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occupational injury</td>
<td>0.2</td>
</tr>
<tr>
<td>Sexual</td>
<td>0.2-0.5</td>
</tr>
<tr>
<td>Intravenous drug use</td>
<td>0.5-1.0</td>
</tr>
<tr>
<td>Mother-to-child</td>
<td>18-25</td>
</tr>
<tr>
<td>Parental (blood or blood product recipient)</td>
<td>90</td>
</tr>
</tbody>
</table>

* In the absence of antiretroviral therapy in the source patient

Studies suggest that as many as 50% of HIV transmission events may occur from index patients who are in the acute and very early stages of illness.7-11 Thus, early detection of HIV infection
may also be a critical component of preventing further transmission. Several factors contribute to the increased risk of transmission during acute infection, including:

- Very high levels of viremia during acute infection.
- Likelihood that high-risk behaviours are ongoing during this period because the individual is unaware of their HIV status.
- The non-specific “influenza-” or “mononucleosis-like” symptoms of acute HIV infection may be either absent or unrecognized as an indication of HIV infection.

C. 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, although only an estimated 34% of HIV-positive individuals will experience symptomatic seroconversion illness. After the initial drop in CD4 cell counts and peak of viremia during seroconversion, CD4 cell counts will increase, although to levels typically below pre-infection levels, and viral load will decrease and stabilize at a set point for several years (Figure 1). There is considerable variability in the time of onset of further symptoms and late-stage disease. Patients whose CD4 cell counts stabilize above 500 cells/mm$^3$ may remain healthy for several years before CD4 cell counts begin to decline. For some patients, CD4 cell counts will drop rapidly after infection; however, the usual scenario is one in which CD4 cell counts decline over approximately five to eight years until symptoms begin to appear. A small proportion of HIV-infected individuals (5-10%), called “long-term non-progressors,” will maintain low viral load and stable CD4 cell counts for decades without specific treatment.

Figure 1. Natural History of HIV/AIDS (Adapted from Lewthwaite, 2005)
Some HIV-positive individuals may not exhibit any symptoms initially, while others may have minor symptoms and/or persistent generalized lymphadenopathy, which usually affects cervical, axillary and inguinal nodes, but often goes unnoticed by the patient. 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. As CD4 cell counts begin to decrease, HIV-positive individuals become 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 1 on p. 106). In addition, uncontrolled HIV replication and immune activation lead to a chronic inflammatory state, resulting in end-organ damage and co-morbid conditions.\textsuperscript{15}

D. HIV Disease Staging

Introduced in 1982, surveillance definitions for AIDS cases were initially developed to track and monitor a disease that later was attributed to infection with the HIV virus. The definition of AIDS has been revised over the years for increased utility for national and international surveillance reporting systems and for public health purposes.\textsuperscript{16}

There are currently two main HIV disease classification systems, developed by the US Centers for Disease Control (CDC) and by the World Health Organization (WHO).\textsuperscript{16,17} In British Columbia, AIDS and HIV are reportable conditions (consult the HIV testing guidelines: [http://www2.gov.bc.ca/assets/gov/health/about-bc-s-health-care-system/office-of-the-provincial-health-officer/hiv-testing-guidelines-bc.pdf](http://www2.gov.bc.ca/assets/gov/health/about-bc-s-health-care-system/office-of-the-provincial-health-officer/hiv-testing-guidelines-bc.pdf)). See Appendix 1 (p. 106) for a list of AIDS-defining illnesses.

E. Acute HIV Infection

Other terms for acute HIV infection are acute retroviral syndrome, acute HIV seroconversion, and primary HIV infection. The following indicators should alert primary care providers to the possibility of an acute HIV infection when certain patients present with influenza- or mononucleosis-like symptoms: those who request HIV testing; those who have had recent sexual or parenteral exposure to a known HIV-positive partner or a partner of unknown HIV sero-status in the past 2-6 weeks; men who report having condomless sexual practices with men; transgender people, in particular transgender women who have sex with men; those working in sex trade; those who report needle use; those who present with a recent or newly diagnosed sexually transmitted infection (STI); and those who present with aseptic meningitis. Unexplained skin rash and mucocutaneous ulcers should also alert providers to the possibility of an acute HIV infection. Appendix 2 on p. 107 further describes common symptoms and the frequency of their occurrence in individuals who are symptomatic.

F. Diagnosis (Subsection revised March 2015)

For HIV testing, the window (or eclipse) period refers to the interval between the time when a person is infected and when the test can first detect HIV infection. For serological tests, the
window or eclipse period is approximately 22 days for the third generation enzyme immunoassay (EIA), otherwise known as enzyme-linked immunosorbent assay (ELISA), and about 17 to 18 days for the fourth generation EIA or ELISA. By 6 weeks to 3 months after infection, almost everyone who is infected will develop detectable HIV antigen or antibody. See Figure 2 for a timeline.

**Figure 2.** Sequence of appearance of laboratory markers for HIV-1 infection

![Figure 2](image)

At the British Columbia Provincial Public Health Reference Laboratory, as of May 27th, 2015, all samples submitted for HIV serology are screened by the fourth generation EIA or ELISA. The sensitivity of the fourth generation EIA or ELISA is about 99.9% and the specificity is about 99.7%. Any reactivity on the screening HIV EIA or ELISA 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 (Figure 3 on the next page):

- All EIA or ELISA positive samples are retested using a different manufacturer’s fourth generation EIA. Samples which are concordantly positive on two manufacturers’ assays are more likely to be true positive. The secondary EIA or ELISA is often referred to as a supplemental test.
- In the past, the Western blot, which detects an array of HIV specific proteins, has been the gold standard for the diagnosis of established HIV infection. However, the Western blot can be negative or indeterminate during acute infection.
To help identify acute HIV infections, which are known to be correlated with a higher risk of onward transmission, the EIA or ELISA signals from the screening assay and the supplemental assay are reviewed. If weak EIA or ELISA signals or an indeterminate or negative Western blot are identified, the sample will automatically undergo an individual HIV RNA nucleic acid amplification test (NAAT). If HIV RNA is detected, the specimen will be reported as being suggestive of acute HIV infection, and a follow up ethylenediamine tetraacetic acid (EDTA) blood sample will be requested to confirm HIV infection.

If the EIA or ELISA signals are weak and the individual NAAT is negative, the specimen will be reported as not being consistent with HIV infection, and a follow up EDTA sample will be requested to confirm if the initial EIA or ELISA result was true or false positive.

To help identify acute pre-seroconversion infections in high-risk individuals, a limited number of pooled HIV RNA NAATs are performed on patients attending clinics that serve high-risk populations to improve diagnosis of acute HIV infection.\textsuperscript{21}

**Figure 3.** Current algorithm for EIA or ELISA screening in British Columbia\textsuperscript{22}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{algorithm.png}
\caption{Current algorithm for EIA or ELISA screening in British Columbia}
\end{figure}

\* Screening by 3\textsuperscript{rd} generation EIA.  
4\textsuperscript{th} generation EIA is used as a supplemental test, if 3\textsuperscript{rd} generation EIA is positive.

\textbf{G. Management of Acute HIV Infection}

Providers should offer assistance to patients in notifying sexual partners and should counsel patients about the increased risk of HIV transmission during an acute HIV infection. HIV is a reportable infection, and the BCCDC provides assistance in contact tracing. Baseline HIV genotypic testing should be undertaken (to request this test, complete and fax this form: [http://www.cfenet.ubc.ca/publications/centre-documents/laboratory-requisition-form-british-columbia](http://www.cfenet.ubc.ca/publications/centre-documents/laboratory-requisition-form-british-columbia)).

Providers should also consult with a physician with experience in treating HIV-positive individuals to determine whether to initiate treatment during the acute phase and to discuss possible antiretroviral regimens.\textsuperscript{23} Treatment for individuals with acute infection is supported under current provincial and international guidelines.
H. Treatment as Prevention (New subsection added March 2015)

Evidence of the effect of antiretroviral treatment on the prevention of HIV transmission can be derived from several models, including mother-to-child transmission, serodiscordant couples, and clinical trial evidence. Hence, on the basis of these data, antiretroviral treatment, which was already deemed cost-effective on a patient-centred basis, can generate an additional substantial cost saving once its effect on HIV transmission is considered. Furthermore, Montaner et al. have shown a strong population-level association between increasing antiretroviral treatment coverage, decreased viral load, and decreased number of new HIV diagnoses per year. 

References


II. Medical History and Physical Examination of HIV-Positive Individuals

Recommendations:

1. All HIV-positive individuals should be evaluated by a primary care clinician with knowledge and experience in the management of HIV infection. (BII) Primary care clinicians without expertise in HIV care should consult with a physician with this expertise. (CIII)

2. Clinicians should obtain a comprehensive present and past medical history, as well as a medication/social/family history, review of systems, and conduct a complete physical examination upon the patient’s entry into care. (AIII)

3. Clinicians should schedule routine monitoring visits at least every 3-6 months for all HIV-positive individuals whose clinical status is stable and on antiretroviral therapy. More frequent visits should be scheduled for those whose clinical status is unstable or not on antiretroviral therapy. (CIII)

4. Clinicians should assess vital signs, weight, and body mass index (BMI) at each visit, and also note abnormalities and changes in general appearance, body habitus, physical well-being, frailty, and mobility. (CIII)

Evidence (adapted from New York State Department of Health AIDS Institute, 2014 & Aberg et al., 2014)¹,²:

Many studies have demonstrated that better outcomes are achieved in HIV-positive outpatients cared for by a clinician with HIV expertise,³-⁸ which reflects the complexity of HIV infection and its treatment. Thus, appropriate training and experience, as well as ongoing continuing medical education, are important components for the provision of optimal care. Primary care providers with limited HIV experience should be encouraged to link with an experienced mentor who will provide advice and consultation support when needed, or consider accessing some of the training programs provided by the BC-CfE. For more information, visit: [http://education.cfenet.ubc.ca](http://education.cfenet.ubc.ca).

A comprehensive current and past medical history should be obtained, with an emphasis on HIV specific issues (Appendix 3 on pp. 108-109). Important elements include HIV exposure history (date and place of diagnosis, route of exposure), history of symptoms related to acute HIV infection, and history of prior opportunistic infections or AIDS-related events. It is critical to obtain a history of prior antiretroviral regimens including date of initiation, prior resistance testing, and adverse antiretroviral drug reactions. Particular emphasis should also be placed on a review of systems, eliciting a comprehensive listing of symptoms, including those that patients may not deem important to mention. In the course of taking a medical history, health care providers should also assess a patient’s understanding of HIV disease, including risk for HIV transmission, explore potential barriers to treatment adherence, and identify the patient’s psycho-social needs.
Providers should inquire about chronic medical conditions such as neurological conditions, gastrointestinal disease, chronic viral hepatitis, dyslipidemia, diabetes mellitus, cardiovascular disease (or risk), kidney disease, and psychiatric disorders that might affect the choice of antiretroviral therapy. Other past medical conditions that may have implications for HIV-infected patients include a history of chickenpox or shingles; tuberculosis or tuberculosis exposure, including results of prior testing for latent *Mycobacterium tuberculosis* infection; sexually transmitted infections (STIs); abnormal cervical or anal cytology; and gynecologic problems. The status of adult immunizations as detailed in Table 4 (p. 44) should be elicited.

Patients should be asked about all medications they take, including non-prescription, herbal and over-the-counter products, since some may interact with antiretroviral therapies. A history of medication intolerance or allergies should be obtained, with an emphasis on prior antiretroviral exposure.

Clinicians should perform a comprehensive physical examination at baseline and annually, with particular attention to systems potentially affected by HIV. Please refer to Appendix 4 (p. 110-111). Since weight fluctuations are common in HIV-positive patients, 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](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.

**References**

III. HIV Disease Specific Testing

Recommendations:

1. 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. (AIII)

2. Clinicians should obtain baseline CD4 cell counts (absolute and fraction) and quantitative HIV RNA (plasma viral load) for all patients upon entry into care. (AI)

3. All patients should be assessed for transmitted HIV drug resistance using genotypic drug resistance testing, regardless of the estimated duration of the infection. Ideally, the drug resistance testing should be conducted on the first available sample of HIV plasma viral load (AII). Note that in British Columbia, genotypic resistance testing can be performed on archived plasma samples (all samples are archived at the BC-CfE in perpetuity).

4. If antiretroviral therapy is deferred, a repeat genotypic drug resistance testing close to the time of initiation of therapy is recommended because of the potential for superinfection (CIII).

5. Genotypic drug resistance testing should be conducted for patients experiencing treatment failure or incomplete viral suppression (HIV plasma viral load >250 copies/mL) while receiving antiretroviral therapy. (AII)

A. CD4 cell counts, HIV viral load, and HIV resistance testing

Evidence:

Documented HIV antibody testing is necessary for a number of reasons. Patients may have tested non-nominally or 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) among individuals identified as HIV-positive for the first time. Patients may also be unclear about whether an HIV test has been performed, or they may present with misinformation regarding previous test results. The absolute CD4 cell count is a significant clinical indicator of immunocompetence in patients with HIV infection. The fraction of CD4 cells, expressed as a percentage of the total number of lymphocytes, has also been used to predict mortality. These markers are used to stage HIV disease initially and are subsequently used as predictors of disease progression and survival. CD4 cell counts are also used to determine the need for prophylaxis for opportunistic infections (OIs) or other AIDS-defining illnesses, the risk of OIs, and when to stop prophylaxis. Caution should be used when interpreting CD4 cell counts. In British Columbia, two distinct reporting measures are in place. The more widely available measure uses absolute cells/µL (or cells/mm³) and fraction of lymphocytes expressed as a percentage (e.g. absolute CD4 cell count: 500
cells/µL [or cells/mm³], and fraction: 25%). The less common measure uses numbers of cells x 10⁹/L (e.g. absolute CD4 cell count: 0.500 cells x 10⁹/L and fraction: 0.25), requiring some calculations to convert to the more explicit method of absolute cell count.

Plasma viral load testing is another way to assess patient prognosis and to determine a patient’s need for antiretroviral therapy. The association between a decrease in plasma viremia and improved outcomes has been well-established; thus, HIV plasma viral load is an essential indicator of therapeutic response and for identifying patients who are experiencing treatment failure. HIV plasma viral load is also useful in predicting clinical progression.

After the introduction of the Roche TaqMan test for measuring HIV plasma viral load (range from 40-10,000,000 copies/mL) in British Columbia, a significant number of specimens with low-level viremia have been reported. Current laboratory assays in use for quantifying HIV plasma viral load have a good correlation across their linear range, but concordance at the lower level of quantification is generally poor. Hence, it can be challenging to interpret low-level viremia results and to assess the relevance of these results to the clinical management of HIV-positive individuals receiving antiretroviral therapy. In this setting, a review of the patient’s treatment adherence and close monitoring (i.e. repeat viral load testing) may be warranted. However, plasma viral load testing should not be undertaken more frequently than once a month. In addition, if viremia reaches levels greater than 250 copies/mL, genotypic drug resistance testing is strongly recommended (complete and submit the BC-CfE Laboratory Requisition Form to receive HIV genotype drug resistance testing: [http://www.cfenet.ubc.ca/publications/centre-documents/laboratory-requisition-form-british-columbia]). Genotypic resistance testing may also be requested for patients with consistently detectable plasma viral load between 200-250 copies/mL; these levels of viremia have been shown in some studies to be predictive of later virologic failure. However, the success of genotypic testing decreases at lower viral loads. For management of antiretroviral treatment failure, clinicians should refer to the BC-CfE Therapeutic Guidelines for Antiretroviral (ARV) Treatment of Adult HIV Infection ([http://www.cfenet.ubc.ca/therapeutic-guidelines/adult]).

In addition to the development of drug-resistant virus after being exposed to antiretroviral therapy (secondary resistance), drug-resistant virus can be transmitted from one person to another in the absence of previous exposure to antiretroviral therapy (primary resistance). Resistant viral strains lead to suboptimal virological response to initial antiretroviral therapy. Results of drug resistance testing are useful in guiding initial antiretroviral therapy and assessing failing therapy and have also been shown to improve the outcomes of people taking antiretrovirals. In British Columbia, genotypic drug resistance testing can be done retrospectively from the first HIV plasma viral load test sample (or any other stored plasma viral load sample).

B. Tropism testing

Tropism testing is not recommended at baseline as it can change over time. However, it is a test that has relevance when considering the use of CCR5 receptor antagonist drug, maraviroc. For more information about indications and type of tropism testing, see: [http://www.cfenet.ubc.ca/clinical-activities/lab-tests/ccr5-tropism];

C. HLA-B*5701

**Recommendations:**

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

2. **All patients taking an abacavir-containing regimen should be screened for HLA-B*5701, if not previously screened, regardless of how well they have tolerated abacavir in the past. (CIII).** If patients stop abacavir therapy and are HLA-B*5701 positive, they should **not** restart abacavir-containing therapy, as they are at a high risk of hypersensitivity reaction (HSR). (CIII)

**Evidence:**

HLA-B*5701 is not a specific HIV viral 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 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. Therefore, all patients taking an abacavir-containing regimen and who have not previously undergone screening should be screened once for HLA-B*5701, regardless of how well they have tolerated abacavir in the past. Patients in these circumstances are at a higher risk of developing abacavir-related HSR if treatment is interrupted and re-introduced. For more information about indications for abacavir and screening for HLA-B*5701, see: http://www.cfenet.ubc.ca/clinical-activities/lab-tests/hla-b5701; to order the test in BC, requisition form available at: http://www.cfenet.ubc.ca/publications/centre-documents/laboratory-requisition-form-british-columbia.
Table 3. HIV Disease Specific Tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Baseline</th>
<th>Follow-up before ART initiation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV Infection Status</td>
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<tr>
<td>HIV diagnostic test</td>
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<tr>
<td>Immunologic Assessment</td>
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<tr>
<td>CD4 absolute count and percentage</td>
<td>√</td>
<td>Every 3-4 months</td>
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<tr>
<td>HIV Plasma Viral Load (HIV pVL)</td>
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<tr>
<td>Quantitative RNA testing</td>
<td>√</td>
<td>Every 3-4 months</td>
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<tr>
<td>Drug Resistance Testing</td>
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<tr>
<td>HIV genotypic drug resistance</td>
<td>√  (At the time of first HIV pVL)</td>
<td>At the time of initiation of ART</td>
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<tr>
<td>Other</td>
<td></td>
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<tr>
<td>HLA-B*5701</td>
<td>√</td>
<td>At baseline or before initiating or restarting therapy with abacavir, if not previously done.</td>
</tr>
<tr>
<td>Other</td>
<td>Tropism testing</td>
<td>When considering CCR5 antagonist</td>
</tr>
</tbody>
</table>

*For frequency of follow-up after antiretroviral initiation, see Section V: Schedule of Care, Table 6 (p. 57)

References


IV. Screening And Immunization For Selected Co-Morbid Infections

PART 1: SCREENING FOR CO-MORBID INFECTIONS

A. Tuberculosis Screening

**Recommendations:**

1. All HIV-positive individuals should be screened at baseline for Mycobacterium tuberculosis (TB) infection. (AI) Screening involves reviewing history of TB exposure and/or treatment history, a recent chest X-ray (within three months), and previous tuberculin skin test (TST) and/or interferon gamma release assay (IGRA) results. (AIII)

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

3. IGRA s are currently recommended as an adjunct test to TST and may be valuable in the following two situations: a) HIV-positive individuals with CD4 cell count <200 cells/mm3 who are TST-negative (if possible, T-spot is preferred); and b) HIV-positive individuals with a history of contact with active TB and who are TST-negative. (BIII)

**Evidence:**

Among HIV-positive individuals, the annual risk of reactivating latent TB 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 in individuals receiving effective antiretroviral therapy.\(^3,4\) Thus, the identification of latent TB infection (LTBI) and the implementation of measures to prevent the development of active disease are of high priority in the care of HIV-positive individuals.

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 for an HIV-positive individual.\(^1\) 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 also not uncommon in those who have received Bacille Calmette-Guerin (BCG) vaccination.$^5$

Interferon gamma release assay (IGRA) is an immunologic in vitro 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) and T-SPOT®.TB (T-spot) assays. Overall superiority of either IGRA test has yet to be clearly demonstrated,$^6$ despite some studies suggesting IGRA may be less affected by low CD4 count (especially T-spot) or prior BCG vaccination.$^7$–$^9$ Therefore, IGRA is currently recommended as an adjunct test to TST and may be valuable in the following two situations:$^9$,$^{10}$ a) HIV-positive individuals with CD4 count <200 cells/mm$^3$ who are TST-negative (if possible, T-spot is preferred); and b) HIV-positive individuals with a history of contact with active TB and who are TST-negative.

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 patients 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 HIV-positive individuals.$^{11}$ However, HIV-positive individuals 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.$^{12}$ A systematic review including eleven clinical trials concluded that treatment of latent TB infection (LTBI) significantly reduces the risk of active TB in HIV-positive individuals with a positive TST.$^{13}$ TB screening (including TST, exposure history, symptom screening, and chest X-ray) should be repeated annually for individuals with negative baseline TST results who are at ongoing risk for exposure. Testing may be repeated more frequently if there is evidence of new exposure to TB.

Positive TST results should be followed by treatment for LTBI once active TB disease is ruled out. All TST- or IGRA-positive individuals should have sputum acid-fast bacilli (AFB) microscopy and culture for $M.~tuberculosis$ performed, regardless of symptoms and chest X-ray results.
B. Chest X-Rays

**Recommendation:**

1. All HIV-positive individuals should have a chest X-ray at baseline. (CIII)

**Evidence:**

Chest X-rays are used in conjunction with sputum acid-fast bacilli (AFB) and culture to rule out active tuberculosis, particularly among those who test positive during TB screening.

Certain populations, such as the homeless, individuals abusing alcohol and drugs, and chronic smokers, are at an increased risk of having radiographic abnormalities. Because of the potentially high prevalence of these risk factors in the HIV-positive population in British Columbia, it is important to perform a chest X-ray at baseline in all HIV-positive individuals, not only to rule out abnormalities but also to use as a comparison for future evaluation of respiratory complaints.

C. Toxoplasmosis Screening

**Recommendation:**

1. All HIV-positive individuals should be screened at baseline for Toxoplasma IgG antibodies to determine prior exposure to *Toxoplasma (T.) gondii*. (BIII)

**Evidence:**

Seroprevalence of *T. gondii* in North American adults is approximately 10-20%. The serologic test for *Toxoplasma* cannot be used to diagnose or exclude toxoplasmosis in HIV-positive individuals. Toxoplasma encephalitis is the most frequent clinical manifestation of central nervous system (CNS) disease in HIV-positive individuals. While positive serology identifies individuals at a greater risk, up to 16% of those presenting with CNS toxoplasmosis will have negative serology. Among HIV-positive/*T. gondii*-infected (i.e. *Toxoplasma* IgG antibody positive) adults not receiving prophylaxis and with CD4 cell counts of <100 cells/mm³, the probability of developing clinical toxoplasmosis is approximately 38%.

D. Hepatitis Screening

**Recommendations:**

1. HIV-positive individuals should be screened at baseline for hepatitis A virus (HAV) using total anti-HAV antibodies. (CIII)
2. HIV-positive individuals should be screened at baseline for hepatitis B virus (HBV) using HBsAg, anti-HBs and anti-HBc. (AIII) Individuals testing negative for HBsAg and anti-HBs but testing positive for anti-HBc should have HBV DNA testing to rule out occult HBV infection. (CIII)

3. HIV-positive individuals should be screened at baseline for hepatitis C virus (HCV) using a test for HCV antibodies. (BIII) Positive HCV antibody test results should be confirmed by measuring HCV RNA PCR. (AII)

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. Rarely, HAV is transmitted through exposure to HAV-contaminated blood or blood products. Transmission through sexual activities that involve direct or indirect oral-anal contact can also occur. In Canada, the number of cases of HAV has steadily declined since 2003. 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. Pre-immunization serologic testing is only cost-effective in populations that have a seroprevalence of >30%. Older people, people coming from endemic areas, and people with a history of jaundice or hepatitis should be considered for assessment of immunity before immunization is undertaken. Because these risk factors and populations are highly prevalent among HIV-positive individuals, all HIV-positive individuals 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. The reported prevalence of HIV-HBV co-infection is between 6-10%, with higher rates observed in PWID, in MSM, and in individuals from endemic areas. HIV-HBV co-infection is associated with an eight-fold increase in risk of mortality compared to HBV mono-infection. 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). Management of chronic HBV infection should follow standard international guidelines (see Table 10 on p. 100).

In Canada, the prevalence of HIV-hepatitis C (HCV) co-infection ranges from 20% to almost 90% in certain subgroups. HCV is highly prevalent among PWID; a review of international studies suggests that between 50-95% of PWID are infected with HCV. Canadian studies report HCV rates as high as 82% among PWID. If left untreated, HCV infection becomes chronic in 50-85% of co-infected individuals, potentially leading to death. 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, antiretroviral therapy did not appear to fully reverse the adverse effect of HIV infection on HCV disease prognosis.\textsuperscript{26} The probability of survival is also reduced among HIV-HCV co-infected individuals compared to those who are HIV mono-infected.\textsuperscript{27} Anti-HCV antibody is the standard screening test; however, approximately 6\% of HIV-HCV co-infected patients do not develop HCV antibodies.\textsuperscript{14} 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 be managed according to current guidelines.\textsuperscript{28}

E. Screening for Syphilis and other Sexually Transmitted Infections (STIs)

\begin{tcolorbox}
**Recommendations:**

1. All HIV-positive individuals should be screened for syphilis at baseline. (AIII) Syphilis screening should be repeated annually or every 3-6 months in the presence of ongoing risk behaviours, or in the presence of symptoms. (BII)

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. (AI)

3. All HIV-positive individuals should be screened for gonorrhoea and chlamydia. (AII)

4. STI assessments should be done at baseline and repeated if there is ongoing risk. (AIII)

**Evidence:**

In North America, sexual transmission is the predominant route for acquiring HIV. This has prompted the recommendation to screen all HIV-positive individuals for asymptomatic STIs. A cohort study reported a baseline STI prevalence of 14\% among HIV-positive individuals (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).\textsuperscript{29}

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 to 8.1 per 100,000 population as of 2012.\textsuperscript{30} Similarly, the overall provincial trend for genital gonorrhoea has increased steadily since 1998, with a slight decrease in 2012 to 28.1 per 100,000 population (1,291 cases). In 2012, the rate of genital chlamydia was 267.9 per 100,000 population (12,364 cases), continuing an overall increase since 1998. MSM continue to be the most affected, representing 84\% of new syphilis cases in the same period. Among MSM whose HIV status was known, over 65\% were syphilis and HIV co-infected.\textsuperscript{29}
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 rapid plasma reagin (RPR) antibody test to an Enzyme Immunoassay (EIA), a Treponema pallidum-specific antibody test. Because Treponema pallidum antibodies persist for the life of an individual, the EIA test will detect a greater number of old syphilis cases. Confirmatory tests do not need to be ordered by clinicians as they are automatically done by the BC-PHMRL.  

For gonorrhoea and chlamydia (GC), Nucleic Acid Amplification Test (NAAT) should be conducted in all HIV-positive patients using first-catch urine specimen for urethral samples. In women and transgender individuals who have a cervix, a cervical swab also should be taken. Although not validated, vaginal swabs can be used for screening in transgender women who are post-operative (i.e. after gender reassignment surgery). MSM who are symptomatic should be screened for GC using pharyngeal (throat) and anal swabs using a standard culture and sensitivity transport media. Pharyngeal and anal swabs should be considered for other patients who are at risk (e.g. individuals engaging in anal or oral sex practices, regardless of sexual orientation). In cases of possible sexual assault, pharyngeal, anal, and/or vaginal swabs should be taken. In patients who wish to avoid pelvic and/or anal examinations, the clinician should rely on the NAAT of a urine specimen.

STI screening for HIV-positive individuals has generally been recommended to be performed at baseline and repeated at least annually. However, limiting screening to annually likely leaves patients infectious for long periods and there are reports that as many as 24% of asymptomatic STIs would have been missed by risk-based screening. Increasing screening frequency has minimal effect on the cost of identifying asymptomatic STIs.

Prevalent and incident asymptomatic STIs are common among HIV-positive MSM, and thus increasing the frequency of screening to every 3-6 months is warranted for those with ongoing risk factors such as unprotected intercourse, multiple partners, anonymous sex, illicit drug use in association with sex, recreational drug use, methamphetamine use, attendance at sex-on-premises venues, and seeking sexual partners through the Internet.

F. Papanicolaou (Pap) Smear Screening

Regarding screening for cervical cancer, please see Section VI: Special Considerations for Women and Transgender Individuals in HIV (pp. 64-65).

Anal cytological screening (anal Pap smear) in HIV-positive individuals is not considered standard of care at this time but is being performed in some health care centres in Canada. A few US guidelines have recommended routine anal Pap tests for some populations. The rationale behind screening for anal cancer is based on the similarities between anal dysplasia and cervical dysplasia, and the success of the cervical Pap screening program. However, there are currently no randomized clinical trials to corroborate the benefits of anal Pap smear in decreasing incidence of anal cancer and related mortality. Additional studies of screening and treatment protocols, diagnostic approaches, natural history of the condition, and cost-effectiveness analysis are in progress and will inform the decision whether to include anal Pap smears as a standard of care in the future.
PART 2: IMMUNIZATIONS AND HIV

Prevention of inter-current illness is a crucial aspect of HIV care.\textsuperscript{14,35} The use of vaccines provides an opportunity to prevent infectious diseases in HIV-positive individuals, who are more susceptible to these diseases.\textsuperscript{17} Immunosuppression can reduce the effectiveness of vaccines and increase the risks associated with live vaccines.\textsuperscript{17,19,39} CD4 cell counts are an important measure that can be used to help optimize the timing of immunizations and predict patient response to vaccines.

General principles that primary care physicians can follow for HIV-positive individuals are shown below (adapted from the Canadian Immunization Guide)\textsuperscript{17}:

- Tailor immunizations to the needs of each patient.
- 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 $\geq 200$ cells/mm$^3$.
- The magnitude and duration of vaccine-induced immunity are often reduced in immunocompromised individuals.
- Use caution in the use of live vaccines based on CD4 cell counts and recommendations for use.
- There is no contraindication to the use of inactivated or component vaccines at any CD4 level.

RECOMMENDED VACCINES

A. Hepatitis A

\begin{table}[h!]
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\begin{tabular}{|c|}
\hline
\textbf{Recommendations:} \\
\hline
1. All HIV-positive individuals who are susceptible (anti-hepatitis A [HAV] negative) should be vaccinated against HAV, ideally when CD4 $>200$ cells/mm$^3$. (BII) \\
2. The HAV vaccine should be administered intramuscularly at the standard dose (AI), at 0, 1 and 6 months. (AII) \\
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Evidence:

Serologic response rates of all HAV vaccines are between 95-100% amongst HIV negative individuals.\textsuperscript{17} Seroconversion rates are lower among HIV-positive individuals for many vaccines and HAV seroconversion is no exception, with rates ranging from 48-64\% (depending on the timing of measurement of serological response).\textsuperscript{40,41} A meta-analysis reported an overall response rate of 64\% for HIV-positive individuals.\textsuperscript{42} A three dose regimen (0, 1, 6 months) has been shown to have better results than a two dose regimen (0, 6 months) among HIV-positive individuals, with reported seroconversion rates in one study of 78\% and 61\%, respectively.\textsuperscript{43} The standard HAV vaccination doses are 1.0 mL intramuscularly (IM).\textsuperscript{39}
B. Hepatitis B

**Recommendations:**

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

2. HBV vaccination should also be offered to those who have positive hepatitis B total core antibody (anti-HBc) with negative HBsAg and anti-HBs results and undetectable HBV DNA. (AIII)

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

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

**Evidence:**

The overall seroconversion rate (defined as HBsAb >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%.\textsuperscript{17,44-46} The etiology of poor seroconversion rates in individuals who are HIV-positive 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.\textsuperscript{44,47,48} In particular, higher HBV seroconversion rates are reported in HIV-positive individuals on antiretroviral therapy 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 one month and 6 months after the completion of the initial vaccination series.\textsuperscript{49}

Patients with isolated antibody to hepatitis B core antigen (HBsAg and anti-HBsAg antibody negative and no detectable HBV DNA) also benefit from HBV vaccination.\textsuperscript{50}

Vaccine non-responders following the first series should receive a complete second series of 3 doses. If they fail to respond to a second series, they should be recorded as susceptible and receive Hepatitis B immune globulin (HBIG) following an exposure.\textsuperscript{51}
C. Pneumococcal Disease

Evidence:

HIV-positive individuals are at a higher risk of developing invasive pneumococcal disease than HIV-negative individuals.\textsuperscript{52-56} \textit{Streptococcus pneumoniae} is the most common agent causing pneumonia in HIV-positive individuals, followed by gram negative bacteria, including \textit{Haemophilus influenzae}, \textit{Pseudomonas aeruginosa} and \textit{Legionella pneumophila}.\textsuperscript{57,58} Low CD4 cell count is a predictor of the occurrence of bacterial infections, but these 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 antiretroviral treatment.\textsuperscript{59-61}

Two forms of pneumococcal vaccine are currently available in BC: conjugated vaccine (Pneu-C-13) and polysaccharide vaccine (Pneu-P-23). The efficacy of any form of the pneumococcal vaccine is unclear for HIV-positive individuals with CD4 cell counts <200 cells/mm\textsuperscript{3}. A study of individuals on antiretroviral therapy showed a failure to induce serotype specific antibodies when administering Pneu-P-23 to patients with CD4 cell counts <100 cells/mm\textsuperscript{3}.\textsuperscript{62} However, another study demonstrated that, although Pneu-P-23 failed to prevent the occurrence of invasive pneumococcal disease (IPD), it decreased the severity and mortality of illness related to IPD.\textsuperscript{63} Research on the efficacy of the pneumococcal conjugate 7-valent vaccine (Pneu-C-7) in HIV-positive individuals has demonstrated improved health outcomes,\textsuperscript{64,65} yet also showed the emergence of non-vaccine type pneumococci, which may highlight the need for greater breadth of \textit{Streptococcus pneumoniae} serotype coverage in regard to conjugated vaccines.\textsuperscript{66,67} Research is ongoing to develop an optimal vaccine regime against IPD in the HIV-positive population.

Recommendations:

1. All HIV-positive individuals should be vaccinated against pneumococcal disease using standard vaccine doses (AI), 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 eight weeks later by one dose of polysaccharide pneumococcal vaccine (Pneu-P-23). (AI)

   (ii) Individuals who have received a pneumococcal polysaccharide vaccine (Pneumo-P-23) previously: The Pneu-C-13 dose should be administered at least one year after any previous dose of Pneu-P-23. (CIII)

   (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 five years after the initial Pneu-P-23 dose. (CIII)
While one study comparing Pneu-C-7 to Pneu-P-23 found that the conjugated vaccine elicited better serologic response,68 other studies have looked into possible synergistic effect of a dual vaccination regimen that incorporates both the conjugate and the polysaccharide vaccines.69-71 Although there are no data on the efficacy and effectiveness of Pneu-C-13 in the HIV-positive population, it is logical to extrapolate such data from previous research on the use of Pneu-7 in this population, since the components of the two vaccines are so similar (Pneu-C-13 is equivalent to Pneu-C-7 plus six other serotypes). Based on this extrapolation, a recent cost-effectiveness vaccine study supports adding Pneu-C-13 to the existing Pneu-P-23 regimen in HIV-positive individuals.72 The National Advisory Committee on Immunization (NACI) concluded that there is good evidence to recommend the use of Pneu-C-13 for HIV-positive patients, given the efficacy and immunogenicity of Pneu-C-7.73 Nevertheless, further research will need to be done on Pneu-C-13 alone or in combination with Pneu-P-23 in the HIV-positive population to validate this assumption.71 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.79

D. Influenza

**Recommendation:**

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

**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 HIV-positive individuals form part of the group at the greatest risk of serious infections, complications, hospitalizations, and/or death from influenza.17,74 In the HIV-positive population, 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 HIV-positive individuals. One study estimated that vaccine efficacy decreased from 65% in patients with CD4 cell counts >100 cells/mm3 to 11% in those with lower CD4 cell counts.76 The same study also showed that efficacy was 52% in patients with plasma HIV RNA levels below 30,000 copies/mL and 40% in those with higher viral loads.75 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 HIV-positive individuals, regardless of CD4 cell counts or HIV plasma viral load.77 A single annual intramuscular dose of 0.5 mL is currently recommended.17,39 There is no indication for pre- or post-immunization
serology testing. Inactivated influenza vaccine is recommended and live attenuated intranasal vaccine should not be used in this population.

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 BC Communicable Disease Control’s Immunization Manual (http://www.bccdc.ca/dis-cond/comm-manual/CDManualChap2.htm).

E. Tetanus and diphtheria

**Recommendation:**

1. All HIV-positive individuals should be offered a tetanus and diphtheria (Td) toxoid booster every 10 years, ideally when CD4 >200 cells/mm$^3$. (AII)

**Evidence:**

The recommendation above assumes that the diphtheria vaccination 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. 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.

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. After the primary vaccination series in immunocompetent individuals, over 99% develop antibody levels that are considered protective against disease. The antitoxin is believed to persist at protective levels for ten years or more. Titres decline slowly with time but are boosted by additional vaccine doses.

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. The antibody response to tetanus boosters given to adults with HIV or other humoral immune deficiencies is suboptimal.
<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Recommendation</th>
</tr>
</thead>
</table>
| **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 susceptible individuals.  
**Dosage**: 2 mL (20 mcg of Recombivax HB® or 40 mcg of Engerix®-B)  
**Route of administration**: IM |
| **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 eight weeks later by **Pneu-P-23**. Then, a single **Pneu-P-23** booster five 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 five years after the initial **Pneu-P-23** dose, and at least eight 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/CDManualChap2.htm](http://www.bccdc.ca/dis-cond/comm-manual/CDManualChap2.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 |

* All publicly funded in B.C.
VACCINES INDICATED UNDER SPECIAL CIRCUMSTANCES (New subsection added March 2015)

A. **Measles, Mumps and Rubella** (New subsection added March 2015)

**Recommendation:**

1. All HIV-positive individuals 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) (BII).

2. All HIV-positive individuals born before 1970 or who have previously received two doses of measles- and mumps-containing vaccine, have serologic proof of immunity against measles or rubella, or have had lab diagnosed disease, are considered to have immunity against one or more of these diseases. If they are susceptible to one of these diseases, the only vaccine available for use is measles, mumps and rubella vaccine. MMR vaccine is safe for use in those with prior immunity (BII).

3. All HIV-positive individuals 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 (AII).

**Evidence:**

In general, live-virus vaccines should not be used among HIV-positive individuals. In severely immunocompromised populations, measles can present critically and in a prolonged fashion, with a high risk for severe complications.\(^{82-85}\) Measles, Mumps, Rubella (MMR) vaccination in HIV-positive individuals with CD4 cell counts >200 cells/mm$^3$ appears to be safe with no serious adverse events reported.\(^{86-88}\) Thus, all HIV-positive individuals 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.\(^{14,89}\) Evidence of immunity includes being born before 1970 or having previously received two doses of measles- or mumps-containing vaccine. All HIV-positive individuals 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.\(^{90}\)
B. Varicella (New subsection added July 2015)

**Recommendation:**

1. All HIV-positive individuals without evidence of immunity and with CD4 cell counts >200 cells/mm³ may be considered for varicella vaccination (given as a 2-dose series of varicella vaccine) (CIII).

**Evidence:**

At the time of publication of these guidelines, there were no published data on varicella vaccination among susceptible HIV-positive individuals. However, based on expert opinion, varicella vaccine may be safe to offer to susceptible individuals with CD4 counts >200 cells/mm³. Live attenuated varicella vaccine remains contraindicated in HIV-infected individuals with CD4 counts <200 cells/mm³.

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 not having 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.91

C. Herpes Zoster (New subsection added March 2015)

**Recommendation:**

1. Herpes zoster vaccine is contraindicated in HIV-positive individuals with CD4 <200 cells/mm³. (BII)

2. The use of herpes zoster vaccine for prevention of shingles in HIV-positive adults with CD4 >200 cells/mm³ is not routinely recommended. (BIII)

**Evidence:**

Herpes zoster, commonly known as shingles, is a cutaneous manifestation of the reactivation of the varicella zoster virus (VZV), which causes chickenpox. The use of Zostavax II ® (a live attenuated herpes zoster vaccine) in healthy HIV-negative adults aged 60 and older for prevention of shingles is currently recommended by National Advisory Committee on Immunization (NACI) in Canada.92 A study in immunocompetent older adults demonstrated that vaccination with high potency live attenuated VZV vaccine reduces the frequency of herpes zoster by half and its morbidity by two-thirds.93 Unfortunately, the same level of confidence in
the safety, efficacy, and effectiveness in the ability of this vaccine to prevent shingles could not be replicated directly in HIV-positive persons without rigorous research. It is also recognized that shingles is common in HIV-positive individuals, in whom impaired cell-mediated immunity may lead to increased incidence, severity, and complications of shingles.\textsuperscript{94-98} However, while there are currently limited data to show the safety of vaccinating HIV-positive adults with CD4 >200 cells/mm\textsuperscript{3} against herpes zoster, some small cohorts have shown that two doses of VZV vaccine were safe in HIV-infected subjects with CD4 ≥400 cells/mm\textsuperscript{3}, but were only modestly immunogenic.\textsuperscript{99,100} Thus, the vaccine’s efficacy in shingles prevention is yet to be clearly demonstrated in HIV-positive persons. An evidence-based recommendation for the VZV vaccine in all immunocompetent HIV-positive adults (i.e. with CD4 >200 cells/mm\textsuperscript{3}) cannot be made at this time. Since the VZV vaccine is a live vaccine, it is contraindicated in HIV-positive individuals with CD4 <200 cells/mm\textsuperscript{3}.

As in the general population, one’s risk of developing shingles increases with increasing age. It will be prudent to revisit this topic as more research becomes available, since the life expectancy of HIV-positive individuals is continuously improving in the era of antiretroviral therapy, with many patients expected to live well into old age.

D. \textbf{Human Papillomavirus (HPV)} (New subsection added March 2015)

| Recommendation:
1. HPV4 vaccine is recommended for HIV-positive girls and women (AII) and HIV-positive boys and men (BII) between 9-26 years of age, regardless of their CD4 counts, to prevent infection caused by HPV types 6, 11, 16 and 18 and related diseases. A 3-dose series is recommended, regardless of age. (AII) |

Evidence:

Human Papillomavirus (HPV) is a sexually transmitted pathogen that causes ano-genital disease in males and females. 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.\textsuperscript{101} 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, and probably high risk are: 51, 56, 39, and 59.\textsuperscript{102} 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).\textsuperscript{103} The same HPV genotypes that cause cancer of the cervix also cause most cases of anal cancer,\textsuperscript{104} 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.\textsuperscript{105}
In an international study, 77% of HIV-positive women had HPV detected at least once (incident infection). HPV 16 was the most frequent genotype, with mixed infection seen in 26%. Persistent infection was seen in 41.5% of women. Canadian Women’s HIV study group found high-risk HPV genotypes, as detected by genital tract sampling in HIV-infected women, 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 highly active antiretroviral therapy (HAART).

HIV-positive men who have sex with men (MSM) are at an increased risk for anal cancer, of which 80% is caused by vaccine-preventable HPV. External genital warts can also be challenging to treat in HIV-positive MSM, and are mostly due to vaccine-preventable HPV. The quadrivalent human papillomavirus (HPV4) vaccine decreases risk of developing anal cancer precursors (75%) and external genital warts (90%). Canada’s National Advisory Committee of Immunization (NACI) recommends HPV4 vaccine for boys and men between 9-26 years of age. Although the randomized controlled trial demonstrating these clinical outcomes excluded HIV-positive men, HPV4 vaccine has been shown to be safe and immunogenic in HIV-positive men. However, clinical efficacy data in HIV-positive individuals are lacking.

The prevalence of anal HPV is high among HIV-positive women. The clinical significance of these findings is unclear, since anal cancer remains extremely rare in this population and the clinical utility of anal Pap screening in HIV-positive women has not yet been determined at this time.

Safety and efficacy data of the HPV vaccine in the context of HIV infection are sparse. There are a few studies evaluating the immunogenicity of the HPV vaccine in HIV-positive men and women. HPV4 vaccine appears safe, and immunogenic in the short term among young women with HIV, including those with CD4 <200 cells/mm³. The long-term protection level of these vaccines in HIV-positive women needs to be further studied, as there is some preliminary evidence that HPV antibody levels in HIV-positive girls and women will decline more rapidly compared to those in HIV-negative women.

It may not be cost-effective to give HPV4 vaccine to boys if uptake in girls is high and provides herd immunity. However, MSM may not benefit from herd immunity provided by vaccinated girls and women. A recent British model suggested that at the current price of the HPV4 vaccine, it would be cost effective to vaccinate HIV-positive MSM 16-40 years old (although certain operational and delivery issues would need to be addressed). The CDC also reports cost-effectiveness for vaccination of MSM through 26 years, referencing an analysis showing <$50,000 per quality-adjusted life year.

The quadrivalent HPV vaccine, Gardasil®, consisting of the L1 capsid protein of each of four HPV strains (types 6, 11, 16 and 18), and the bivalent HPV vaccine, Cervarix™, consisting of L1 capsid proteins of two HPV genotypes (HPV type 16 and HPV type 18), are available in Canada. The 9-valent HPV vaccine (HPV9), which will cover additional strains (types 6, 11, 16, 18, 31, 33, 45, 52, 58), is expected to become available in the next couple of years.

HPV testing as an adjunct to Pap testing is not currently available in BC outside of research settings.
### Table 5. Vaccines provided free of charge to HIV-positive adults in British Columbia (New table added August 2015)*

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Publicly Funded</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hepatitis A Vaccine</strong> (Inactivated virus vaccine)</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Hepatitis B Vaccine</strong> (Monovalent recombinant DNA vaccine)</td>
<td>Yes</td>
</tr>
</tbody>
</table>
| **Pneumococcal Vaccine**
  PNEU-P-23 (23-valent pneumococcal polysaccharide vaccine), and
  PNEU-C-13 (13-valent conjugate pneumococcal vaccine) | Yes             |
| **Influenza Vaccine** (Inactivated virus vaccine) | Yes             |
| **Td (Tetanus, diphtheria) - adsorbed**      | Yes             |
| **Measles, Mumps, Rubella (MMR) Vaccine**    | Yes             |
| **Varicella Vaccine**                        | Yes             |
| **Herpes Zoster Vaccine**                    | No              |
| **HPV Vaccine**                              | Yes, but limited. [HPV4 vaccine (Gardasil®) is free to females aged 9-14 as part of routine immunization in grade 6, girls and young women born in 1994 or later, and at-risk boys and young men between 9 to 26 years of age. HPV2 vaccine (Cervarix®) is ONLY free to young women who are 26 years old and younger and born before 1994 through a one-time and time limited program.] |

*Note: Based on HealthLink BC’s Immunization Schedule for BC Adults, Seniors and Individuals at High Risk[^20]*

**CONTRAINDICATED VACCINES** (New subsection added March 2015)

For HIV-positive individuals, live vaccines 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 their HIV-positive patients.

**References**


V. Schedule of Care for HIV-positive Individuals

**Recommendations:**

1. All HIV-positive individuals who are not on antiretroviral therapy should have CD4 cell counts and plasma viral loads (pVL) measured every 3-4 months. (BII)

2. All individuals initiating antiretroviral therapy should have CD4 cell counts and pVL measured on a monthly basis until pVL is <40 copies/mL, and thereafter monitoring can occur every 3-4 months. (BII)

3. In clinically stable patients with dependable antiretroviral adherence, once pVL is consistently <40 copies/mL for two years and CD4 counts are consistently ≥350 cells/mm³, pVL monitoring can occur at intervals of up to six months and CD4 monitoring is optional. (CIII)

4. Safety laboratory parameters (complete blood count, renal and liver function, fasting lipids, and glucose) should be monitored approximately one month after initiation of antiretroviral therapy (with the first pVL and CD4 count) and every 3-6 months thereafter (see Table 6 on p. 57). Monitoring should be undertaken more frequently in the presence of relevant underlying co-morbid conditions, known potential toxicities of specific antiretroviral drugs, and/or concomitant medications. (CIII)

**Evidence:**

The frequency of clinical and laboratory follow-up of HIV-positive individuals is dependent on stage of HIV disease, rate of disease progression, overall clinical stability, the presence of co-morbidities, and the need for other services offered in the clinic. Regular monitoring is important because individuals engaged in care are more likely to be adherent to their medications and have improved health outcomes.1 Moreover, risk of virologic failure decreases with duration of viral suppression.2-4 Recent evidence indicates that, for patients receiving stable antiretroviral therapy with consistently undetectable plasma viral loads and adequate CD4 cell counts, routine CD4 cell count monitoring is not medically necessary5; CD4 monitoring in this setting is now optional according to recent international guidelines.6,7 Since CD4 cell counts have been a cornerstone of HIV management in the past, patient education around this issue may be necessary to alleviate stress and confusion, particularly in long-term survivors of HIV. CD4 monitoring should be resumed if the plasma viral load becomes consistently detectable or if there is any significant change in the patient’s clinical condition related to HIV or co-morbid conditions.

All antiretroviral agents are associated with potential adverse effects, which can lead patients to switch or cease therapy.8 Certain factors may increase the risk of adverse effects for some individuals, such as gender, age, baseline CD4 count, concomitant medical conditions, genetics, and interactions with other medications. Individuals at a higher risk of developing adverse effects are often under-represented in clinical trials, resulting in uncertainty around the frequency and
severity of adverse events in real-life clinical settings. Clearly, the presence of co-morbid conditions and/or concomitant medications, as well as the known toxicities of certain antiretroviral medications, need to be taken into consideration when determining the appropriate frequency of laboratory safety monitoring during antiretroviral therapy.

Age, in particular, is a key factor in determining frequency of follow-up. There has been an increase in the proportion of HIV-positive individuals who are over the age of 50 years; this population is more likely to experience a faster progression of HIV disease and is less likely to be routinely evaluated for antiretroviral therapy. In addition, higher rates of co-morbid conditions and antiretroviral toxicities have been observed in older HIV-positive individuals. This requires a shift from focusing solely on CD4 cell counts, plasma viral loads, and AIDS-defining illnesses to a more comprehensive care model that is focused on managing a complex, chronic disease.

Table 6. Laboratory Monitoring* (Table revised March 2015)

<table>
<thead>
<tr>
<th>Test</th>
<th>Baseline</th>
<th>First 2 years after ART initiation*</th>
<th>After 2 years on stable suppressive ART*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic Assessment</td>
<td>Complete blood count (CBC) with differential and platelet count</td>
<td>√</td>
<td>With first pVL (after 1 month), then every 3-4 months</td>
</tr>
<tr>
<td>HIV plasma viral load (pVL)</td>
<td>HIV RNA</td>
<td>√</td>
<td>Monthly until &lt;40 copies/mL, then every 3-4 months</td>
</tr>
<tr>
<td>CD4 cell count, absolute and percentage</td>
<td>√</td>
<td>Monthly until pVL &lt;40 copies/mL, then every 3-6 months</td>
<td>Every 6 months</td>
</tr>
<tr>
<td>Renal Function</td>
<td>Creatinine, estimated glomerular filtration rate (eGFR), phosphate, urinalysis, spot urine for albumin to creatinine ratio (UACR)</td>
<td>√</td>
<td>With first pVL (after 1 month), then every 3-4 months</td>
</tr>
<tr>
<td>Liver Tests</td>
<td>Spot urine for albumin to creatinine ratio (UACR), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, international normalized ratio (INR)</td>
<td>√</td>
<td>With first pVL (after 1 month), then every 3-4 months</td>
</tr>
</tbody>
</table>

Table continued on next page…
**Fasting Lipid Profile**

<table>
<thead>
<tr>
<th>Test</th>
<th>Baseline</th>
<th>First 2 years after ART initiation*</th>
<th>After 2 years on stable suppressive ART*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (TC), high density cholesterol (HDL), low-density lipoprotein (LDL), triglycerides (TG), and/or apolipoprotein B</td>
<td>√</td>
<td>With first pVL (after 1 month), then every 6 months</td>
<td>Every 6 months</td>
</tr>
</tbody>
</table>

**Blood Glucose**

<table>
<thead>
<tr>
<th>Test</th>
<th>Baseline</th>
<th>First 2 years after ART initiation*</th>
<th>After 2 years on stable suppressive ART*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting glucose and/or HbA1C</td>
<td>√</td>
<td>With first pVL (after 1 month), then every 6 months</td>
<td>Every 6 months</td>
</tr>
</tbody>
</table>

*Frequency of laboratory monitoring may be adjusted according to medical history of relevant co-morbid conditions, potential toxicities of specific antiretroviral drugs and concomitant medications, previous or ongoing laboratory abnormalities, and clinical status. In most cases the timing of safety laboratory monitoring can be coordinated with monitoring of HIV RNA and CD4 cell counts.

**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 (AIII).**

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

**References**

VI. Special Consideration for Women and Transgender† Individuals with HIV

A. Introduction

In Canada in 2012, 23.3% of the 71,300 HIV-positive known cases were among women.¹ An estimate of 1,682 HIV-positive women are known to currently live in British Columbia.² Women may inherit social roles and responsibilities as caretakers for extended family members and friends, and may not give sufficient priority to their own medical care. Furthermore, heterosexual women frequently face unequal power and socioeconomic relationships with their male partners. These social factors may increase women’s isolation and depression, and compromise their adherence.

Transgender populations are disproportionately affected by HIV. A worldwide meta-analysis shows rates of HIV infections of up to 27% among transgender women (excluding those involved in sex work).³

The indications for and goals of antiretroviral therapy (ART) are the same for people of any gender, unless pregnancy is desired.⁶ Various studies have suggested that sex may influence the frequency, presentation, and severity of some ART-related adverse events.⁷ Although data are limited, evidence also suggests that pharmacokinetics for some ARV drugs may differ between men and women,⁸ possibly due to differences between men and women in 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.⁹⁻¹¹

Several studies indicate that women experience metabolic complications associated with ART use differently than men. These metabolic differences have not been studied in transgender people, but presumably hormonal therapy could shift metabolic responses into a more male or female pattern for those using masculinizing or feminizing therapies, respectively. HIV-positive women are more likely to experience increases in central fat and are at a higher risk of developing particular patterns of lipodystrophy than their male counterparts.¹² However, women are less likely to have triglyceride elevations on treatment.¹³ In addition, women have an increased risk of osteopenia/osteoporosis, particularly after menopause, and this risk may be exacerbated by HIV and ART.¹⁴,¹⁵ (See also F. Menopause on p. 64, as well as Section VII: Non-Infectious Co-morbidities on p. 69).

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† In this section, the term women refers to self-identified women, whose biological sex, external genitalia, or sex assigned at birth match their gender identity. Transgender women refers to self-identified women, whose biological sex, external genitalia, or sex assigned at birth does not match the gender by which they identify. Transgender men refers to self-identified men, whose biological sex, external genitalia, or sex assigned at birth does not match the gender by which they identify (adapted from United States Centers for Disease Control and Prevention and Bauer et al.⁵). For more information on the care of transgender individuals, see Transgender Primary Medical Care: Suggested Guidelines for Clinicians in British Columbia (http://lgbtqpn.ca/wp-content/uploads/woocommerce_upl@ads/2014/08/Guidelines-primarycare.pdf).
B. Special Considerations Related to Care before, during, and after Pregnancy

Recommendations:

1. Contraception and pregnancy plans should be discussed with all individuals of childbearing potential upon initiation of HIV care and routinely thereafter, as pregnancy may affect the choice and timing of antiretrovirals. (AIII) Contraceptive counselling should also be included as a critical aspect of postpartum care. (AIII)

2. Preconception counselling in HIV-positive individuals is recommended for anyone contemplating pregnancy, especially in the setting of HIV-serodiscordant couples. (BII)

3. Pregnancy in HIV-positive individuals is considered a high risk and complex; therefore, consultation with or referral to an obstetrician experienced in HIV is highly recommended. (BIII)

4. All HIV-positive pregnant individuals should be treated with ART for HIV infection, regardless of their immunologic or virologic status, to prevent infection of their fetus. (AI) ART should be continued after delivery and reassessed by providers of adult HIV care. (AII)

5. Breastfeeding is not recommended, regardless of HIV viral load and use of ART, for HIV-positive individuals in Canada. (AI)

6. Clinicians should avoid prescribing efavirenz, or any new under-studied drug, during the first trimester of pregnancy, to anyone who wishes to become pregnant, and to individuals of childbearing potential who are not using effective and consistent contraception. A pregnancy test should be done before initiation of efavirenz in individuals of childbearing potential and counselling should be provided on the potential risk to the fetus while the mother is receiving on efavirenz. (AIII)

7. Clinicians should not prescribe nevirapine to antiretroviral-naïve women or transmasculine individuals who have CD4 cell counts >250 cells/mm³, nor start nevirapine during pregnancy (AI)

Evidence:

Preconception

Approximately 80% of HIV-positive women are of childbearing age. Since perinatal HIV transmission can be prevented by the appropriate use of antiretroviral therapy, health care providers should discuss menstrual history, safe sexual practices, pregnancy desires, and contraceptive practices with their female patients at each visit. The goal of these discussions is to ensure that patients make informed decisions about pregnancy, contraception, and reproductive health, and to prevent unintended pregnancies. HIV status of the sexual partner should be
discussed. Pregnancy history should include the number of pregnancies and outcomes (miscarriage, ectopic, preterm, term), significant obstetrical complications, number of living children, and the individual’s general state of health.

In anyone at risk for pregnancy (not using effective and consistent contraception), providers should carefully review all medications and avoid drugs with potential reproductive toxicity. The time of greatest risk to the fetus is the first trimester, often before pregnancy is even recognized. Efavirenz (in Sustiva® and Atripla® as well as generic forms) has been associated with teratogenic effects in non-human primates, and there are reports of central nervous system abnormalities in human infants exposed to efavirenz during the first trimester.16 If pregnancy is desired, preconception counselling with a specialized infectious disease obstetrician is recommended, especially for HIV serodiscordant couples who can be counselled about ways to reduce transmission to the uninfected partner while trying to conceive. In British Columbia, such services can be obtained from the Oak Tree Clinic in Vancouver: www.oaktreeclinic.bc.ca or 604-875-2212.

During pregnancy

Pregnancy in HIV-positive individuals is considered a high risk and complex. Therefore, consultation with an obstetrician specialising in the management of HIV is recommended. The use of ART and the resultant reduction of maternal HIV viral load decrease perinatal transmission of HIV. The goal of ART in pregnancy is to achieve maximal and sustained suppression of the HIV RNA levels during pregnancy and delivery.17-19

The risk of teratogenic events of efavirenz was recently estimated using data from the Women’s Interagency HIV Study. The study found that the rate of teratogenic events was 77.26/100,000 in women exposed to efavirenz, compared with 72.46/100,000 in unexposed women.16 If a pregnant individual presents after week 12 on efavirenz, it is not recommended to change the regimen, but rather to refer to an obstetrician who is experienced in managing high risk pregnancies as early as possible, for neural tube follow-up and further management of HIV in pregnancy.

Nevirapine has been associated with an increased risk of symptomatic, potentially fatal, and often rash-associated liver toxicity among antiretroviral-naïve individuals. Those with higher CD4 cell counts appear to be at greatest risk: a meta-analysis of nevirapine-related clinical trials found that, in women, a CD4 cell count of >250 cells/mm³ at the time of nevirapine initiation was associated with a 9.8-fold increase in symptomatic hepatic events compared with lower CD4 cell counts.16 Introducing nevirapine during pregnancy resulted in higher rates of toxicity and is not recommended.20,21

Due to limited data on the use of tenofovir disoproxil fumarate (DF) in human pregnancy and concerns about potential fetal bone effects, tenofovir DF should be used in pregnancy only after careful consideration and consultation with an HIV specialist. Potential long-term effects of newer ART agents on the fetus or newborn are not known.

Post partum (New subsection added August 2015)

Following delivery, clinical, immunologic, and virologic follow-up should continue as recommended for non-pregnant adults and adolescents. Because use of ART during lactation
reduces but does not eliminate the risk of transmission of HIV in breast milk, and because postnatal transmission can occur despite parental ART, HIV-positive women should also be counselled to avoid breastfeeding.\textsuperscript{22} HIV-infected adults should avoid pre-mastication of food fed to their infants because the practice has been associated with transmission of HIV from parent to child.\textsuperscript{23} Considerations regarding continuation of ART for therapeutic indications during pregnancy are the same as those for ART use in non-pregnant individuals.\textsuperscript{22,23} Discontinuation of ART postpartum is no longer recommended.\textsuperscript{6}

Several studies have demonstrated that adherence to ART may worsen in the postpartum period.\textsuperscript{24,25} Clinicians caring for postpartum individuals who receive ART should specifically address adherence, including an evaluation of specific facilitators and barriers to adherence.

C. Contraception in the Context of HIV

<table>
<thead>
<tr>
<th>Recommendations:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Health care 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. (AII)</td>
</tr>
<tr>
<td>2. Intrauterine devices (IUDs) can be considered as a safe and effective contraception option for HIV-positive women and adolescents. (BII)</td>
</tr>
</tbody>
</table>

Evidence:

The incidence and prevalence of gynaecological problems are high among HIV-positive individuals throughout the course of their HIV disease.\textsuperscript{26} At the initial patient assessment, a comprehensive gynaecologic history should be obtained, including menstrual history, sexual practices, contraceptive history, current status and consistency of contraceptive use, sexually transmitted infections (STIs) and treatments, and prior abnormal Pap results, including subsequent tests and treatments. History of gynaecological conditions such as uterine fibroids, endometriosis, infertility, and surgeries should be obtained. Current gynaecological symptoms such as vaginal discharge, bleeding, amenorrhea, odour, dysuria, itchiness, dyspareunia, and pelvic pain should also be assessed. Mid-cycle bleeding and recurrent urinary tract infections should prompt an evaluation for STIs if appropriate. Most women and transmasculine individuals with gonorrhoea and chlamydia (GC) infections will be asymptomatic. For recommendations regarding GC screening, see pp. 35-36 of Section IV: Screening and Immunization for Selected Co-morbid Infections.

Several protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) have significant drug interactions with combined oral contraceptives. 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 (see Table 7 on p. 65). Several ritonavir-boosted protease inhibitors (PIs) decrease oral contraceptive estradiol levels. Although there is minimal information about drug interactions with the use of newer combined
hormonal contraceptive methods (e.g. transdermal patch, vaginal ring), an additional or alternative contraceptive method should also be considered on the basis of established drug interactions between antiretroviral agents and oral contraceptives. There is limited data on drug interactions between antiretroviral agents and progestin-only contraceptive methods; however, recent studies have found no significant changes in antiretroviral drug concentrations of nelfinavir, nevirapine, or efavirenz when used with depot medroxyprogesterone acetate (DMPA), and there is no evidence of reduced DMPA effectiveness. Contraindications to combined hormonal methods, such as diabetes mellitus, hyperlipidemia, and chronic liver disease, are more common in HIV-positive individuals. In general, those who are on PIs or NNRTIs should use an alternative or additional method of contraception (e.g. barrier methods). For a summary of drug-drug interactions between ARVs and hormonal contraceptives, see Table 7 on p. 65. For recommendations on the use of hormonal contraceptives among women who are HIV-positive or at a high risk of acquiring HIV, see the World Health Organization’s 2014 guidance statement (http://apps.who.int/iris/bitstream/10665/128537/1/WHO_RHR_14.24_eng.pdf). For a list of interactions between ARVs and hormonal contraceptives, see the tables in the Toronto General Hospital’s Immunodeficiency Clinic’s guide (http://www.hivclinic.ca/main/drugs_interact_files/Oral%20Contraceptive-int.pdf).

Regardless of contraception use, condom or other barrier use should be recommended with each sexual act. Condoms reduce the risk of pregnancy, STIs, and superinfection with different HIV strains. Barrier methods may reduce risk of HIV infection by approximately 69%, 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. Internal condoms offer an option for individuals and couples who cannot or will not use the traditional condom. Patients should be counselled about the greater effectiveness of condoms when used with a second method of protection.

In the past, intrauterine devices (IUDs) were not considered as an option for contraception due to fears of pelvic inflammatory disease and infections among immunocompromised women. However, with improved ARVs and earlier initiation of ART, current evidence supports the safety and efficacy of IUDs in HIV-positive women, and this option should be considered, especially for women with CD4 >200 cells/mm³. Cervical infections should be treated prior to the insertion of the IUD. The data are still sparse. Most studies have focused on non-hormonal IUDs (copper IUDs); several small studies have found the levonorgestrel-releasing IUDs to be safe and not associated with increased genital shedding of HIV. For a more detailed discussion of recommendations for the use of IUDs among women who are HIV-positive or at a high risk of acquiring HIV, 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/) or the WHO’s guidance statement (http://apps.who.int/iris/bitstream/10665/128537/1/WHO_RHR_14.24_eng.pdf).
Table 7. Hormonal Contraceptives and ARV Interactions *(New table added August 2015, adapted from University of Liverpool).*

<table>
<thead>
<tr>
<th>Protagide Inhibitors</th>
<th>NNRTIs</th>
<th>Integrase Inhibitors</th>
<th>NRTIs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ATV/r</td>
<td>DRV/r</td>
<td>FPV/r</td>
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<tr>
<td>Estrogen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethinylestradiol</td>
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<td>↓</td>
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<tr>
<td>Estradiol</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
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<tr>
<td>Progestins</td>
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<tr>
<td>Desogestrel</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
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<tr>
<td>Drospirenone</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
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<tr>
<td>Dydrogestrone</td>
<td>↑</td>
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<td>↑</td>
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<tr>
<td>Etonogestrel</td>
<td>↑</td>
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<tr>
<td>Gestodene</td>
<td>↑</td>
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<tr>
<td>Levonorgestrel</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
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<tr>
<td>Medroxyprogesterone (IM)</td>
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<tr>
<td>Medroxyprogesterone (oral)</td>
<td></td>
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<tr>
<td>Norelgestromin</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Norethisterone (Norethindrone)</td>
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<td></td>
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</tr>
<tr>
<td>Norgestimate</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Norgestrel</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levonogestrel (EC)</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Mifepristone</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Ulipristal</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
</tbody>
</table>

**Text Legend**

↑ Potential increased exposure to the hormone
↓ Potential decreased exposure to the hormone
☒ No significant effect
☒ Potential interaction predicted to be of weak intensity. No dosage adjustment required.

**Colour Legend**

- No clinically significant interaction expected
- Potential interaction which may require a dose adjustment or close monitoring
- Potential interaction predicted to be of weak intensity. No dosage adjustment required.
D. Screening for Cervical and Breast Cancer in HIV-positive Individuals

**Recommendations:**

1. Cervical Pap smear should be done for any individual with a cervix starting at age 21 or 3 years after first sexual contact, whichever occurs first. For those eligible HIV-positive individuals cervical screening should be done upon initiation of care, and should be repeated 6 months later. If results are normal in both tests, cervical Pap smear should be done annually thereafter. (AI) If Pap smear results are abnormal, the individual should be referred for colposcopy and directed biopsy, as recommended by the BC Cancer Agency, with further treatment as indicated by results. (AII)

2. Breast cancer screening for HIV-positive people should follow provincial guidelines for the general population. (AII) Consider screening in transgender women on long-term hormone replacement >5 years, and in transgender men and others who may have had mastectomy for non-cancer related reasons.

**Evidence:**

Abnormal cervical cytology is ten times more prevalent in HIV-positive individuals compared with the general population, and is associated with the presence of Human Papilloma Virus (HPV) infection and the degree of immune dysfunction. More frequent Pap smears should be considered in the following circumstances:

- If there is a previous history of an abnormal Pap smear (atypical squamous cells, either of unknown significance [ASC-US] or low grade intraepithelial lesion [LSIL], or high grade [ASC-H, or HSIL], or squamous carcinoma)
- In those with known HPV infection
- In those with CD4 <200 cells/mm³
- In HIV-positive individuals who have had a hysterectomy, and history of abnormal cervical cytology before or at the time of the procedure. These individuals are at an increased risk for pathological lesion and should undergo screening with vault Pap smears. Although the appropriate interval for screening has not been established, it is reasonable to follow guidelines similar to those for those who have not undergone a hysterectomy, or once yearly.

For transgender patients on testosterone, make sure to mark this on the cytology requisition for accurate results. Screening for STIs (including gonorrhea, chlamydia, trichomonas, bacterial vaginosis, syphilis, and herpes) should be performed at routine gynaecological visits and when symptomatic or considered at risk. For more details about BC cervical screening recommendations for women and transgender people in the general population, see the BC Cancer Agency’s website (http://www.screeningbc.ca/Cervix/default.htm).

E. Human Papillomavirus (HPV)

See Section IV: Screening and Immunization for Selected Co-morbid Infections, Part 2: Immunization, H. Human Papillomavirus (HPV) (pp. 45-46).

F. Menopause

**Recommendations:**

1. Hormone replacement therapy may be considered in patients who experience severe menopausal symptoms (i.e. vasomotor symptoms and vaginal dryness) but should generally be used only for a limited period of time and at the lowest effective doses. (BII)

2. Hormone replacement for HIV-positive transgender individuals should be provided in consultation with an endocrinologist or other clinician who has experience providing endocrine care to transgender individuals.

**Evidence:**

An increasing number of HIV-positive women are living past menopausal age or are becoming infected when they are over 50. In Canada, women over 50 years of age constitute 8.5% of the HIV-positive population. Menopause may be diagnosed clinically as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. There are currently no randomized controlled trials delineating the use of hormonal replacement therapy in HIV-positive women. There are conflicting data on the effect of HIV on menopausal age and symptoms. Factors that can influence menopausal symptoms, including smoking, stress, drug use, low body mass index, and race/ethnicity, are also relatively more prevalent among HIV-positive populations. A review of age at menopause in HIV-positive women did not find conclusive data to affirm early menopause in HIV-positive women. However, sample size was limited in these studies and larger studies are required to determine if there is early ovarian failure in HIV-positive women, and whether it is related to the virus, to antiretrovirals, to lifestyle, or to genetic factors.

There is an increased risk of premature bone loss (osteopenia and osteoporosis) during and after menopause. The prevalence of osteoporosis in HIV-positive women is three times greater...
compared with HIV-uninfected women in the same age group in the United States. The pathogenesis of the reduced bone mineral density noted in HIV-positive individuals is most likely multi-factorial, with risk increased by some ART (tenofovir DF, efavirenz, protease inhibitors), as well as by HIV itself. Traditional risk factors for osteoporosis, including smoking, menstrual irregularities (oligomenorrhea and amenorrhea), substance abuse, and low body weight, are more common in HIV-positive individuals. As per provincial guidelines, periodic bone density screening every 3-5 years starting at age 50 (or at any age if there is a fragility fracture) should be offered to postmenopausal women (in BC, the Medical Services Plan [MSP] covers every 3 years), especially if they are receiving tenofovir DF. For additional information on management of bone loss please refer to the discussion on bone health in Section VII: Non-infectious Co-morbidities (pp. 72-73).

Sexual practices in menopausal women are not well described. In a study from the British Columbia Centre for Disease Control (BCCDC), 53% of 48 women who self-identified as menopausal reported being sexually active in the previous 6 months, and 30% of them reported having unprotected sex. Thus, it is important for physicians to discuss safer sex practices with individuals of all ages and to consider HIV diagnosis in women above the age of 45 years and those who are menopausal.

References


41. Pick NOG. Sexual lifestyle behaviour of menopausal HIV+ women compared to reproductive age group peers. Canadian Association for HIV Research. 2007.
VII. Common Non-Infectious Co-Morbidities (New Subsections March 2015)

A. Introduction

A number of conditions not traditionally associated with AIDS, including cardiovascular and renal disease, are exacerbated in the presence of uncontrolled HIV replication. Therefore, despite the potential for long-term complications due to chronic antiretroviral therapy, the benefits outweigh the potential risks in HIV-positive individuals who are appropriately treated and monitored. To this end, clinical and laboratory assessment of relevant co-morbid conditions should be performed at baseline before initiation of antiretroviral therapy and during follow-up. Screening for long-term complications of antiretroviral therapy is described in Appendix 5 (pp. 112-113).

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 four weeks after initiation of therapy, decreasing to up to every six months after stabilization of the patient on their antiretroviral regimen. In most cases the timing of safety laboratory monitoring can be coordinated with monitoring of HIV RNA and CD4 cell counts.

B. Cardiovascular disease

Recommendations:

1. All HIV-positive individuals should be screened for risk of cardiovascular disease at least annually, and modifiable cardiovascular risk factors should be addressed where possible. (A1)

2. Assess fasting lipids (total, HDL, LDL cholesterol, and triglycerides) or apolipoprotein B at baseline and every six months once patient begins antiretroviral therapy. (AIII)

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

Evidence:

As in the general population, cardiovascular disease (CVD) is a common cause of morbidity and mortality in HIV-positive individuals. It was the second most common cause of death in the HIV-positive participants of the SMART trial (after non-AIDS defining cancers). Uncontrolled HIV infection, including during antiretroviral therapy interruption, is associated with an unfavourable lipid profile and increased risk of cardiovascular events. However, antiretrovirals are also associated with increased CVD risk, with the rate of cardiovascular events increasing by 16% per year of exposure to antiretroviral therapy, particularly protease inhibitors.
Antiretroviral-induced risk is not entirely explained by drug-induced dyslipidemia. The antiretroviral-associated risk of CVD has decreased with the use of newer antiretroviral regimens but can still be significant in patients with HIV, especially in the presence of other cardiovascular risk factors, such as age and smoking.\textsuperscript{6,7} The Canadian Cardiovascular Society Guidelines (http://www.onlinecjc.ca/article/S0828-282X%2812%2901510-3/pdf) recognizes HIV as a significant risk factor for premature CVD and an indication for screening for cardiovascular risk factors, including lipids.\textsuperscript{8} Antiretroviral therapy should not be stopped due to concern over perceived high cardiovascular risk, e.g. to correct dyslipidemia.\textsuperscript{2,5}

Apolipoprotein B (apoB) measurement is subject to less laboratory error than LDL cholesterol, particularly in patients with hypertriglyceridemia (as often seen in HIV); therefore, this parameter should be monitored where available and used as a treatment target (as an alternative to LDL) per the Canadian Cardiovascular Society Guidelines.\textsuperscript{8} In the absence of a history of severe hypertriglyceridemia, an apoB measurement can be used instead of fasting LDL cholesterol for the assessment of cardiovascular risk and monitoring of patients on treatment.

Elevated levels of some inflammatory biomarkers, notably high-sensitivity C-reactive protein (hsCRP), are independently associated with a higher risk of myocardial infarction in the HIV-positive population, as in the general population.\textsuperscript{9,10} However, the interpretation of hsCRP can be complicated in the setting of the chronic inflammatory state associated with HIV infection. Although antiretroviral therapy 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 the setting of HIV is unknown.

Despite the impact of antiretroviral therapy and HIV infection itself, traditional CVD risk factors (including age, smoking, and gender) remain the most important contributors to CVD in this population. The Framingham Risk Score, which has been validated in Canada, is the recommended tool for assessing total CVD risk, but may underestimate cardiovascular risk in the setting of HIV infection.\textsuperscript{8,11} The Reynolds Risk Score (www.reynoldsriskscore.org), which incorporates family history and hsCRP as well as traditional cardiovascular risk factors, may be a more accurate alternative, but has not yet been validated in a Canadian population nor in HIV.\textsuperscript{8}

Regardless of underlying cardiovascular risk, modifiable risk factors should be aggressively addressed in all HIV-positive individuals as in the general population, including smoking, sedentary lifestyle, and excess weight.\textsuperscript{8} Smoking cessation is particularly critical and has been demonstrated to reduce clinical CV events in a large HIV-positive population.\textsuperscript{2,12} Dyslipidemia, where present, should be managed according to current general population guidelines, taking into account potentially significant drug-drug interactions between lipid-lowering agents and antiretrovirals (e.g. statins and protease inhibitors) (www.hiv-druginteractions.org).\textsuperscript{8} Of note, HIV-positive individuals may not reach desirable lipid targets with conventional statin therapy and combination therapy may be necessary.\textsuperscript{13}

Some older HIV protease inhibitors (specifically saquinavir and lopinavir/ritonavir) were associated with PR interval prolongation or QTc interval prolongation.\textsuperscript{14-16} Cardiac conduction abnormalities may become clinically significant when a ritonavir-boosted protease inhibitor 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 (e.g. digitalis, calcium channel blockers, anti-arrhythmics, and beta-blockers). Also, the non-nucleoside reverse transcriptase inhibitor 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.17-19 An electrocardiogram (ECG) should be performed at baseline before starting a ritonavir-boosted protease inhibitor 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 two days after starting atazanavir/ritonavir, three days after starting darunavir/ritonavir, or ten 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).20

C. Insulin resistance (IR) and diabetes mellitus (DM)

Recommendations:

1. Fasting blood glucose (FBG) and/or glycated hemoglobin (HbA1c) should be performed in all HIV-positive individuals at baseline and at six-month intervals during antiretroviral therapy. Abnormalities in fasting glucose and/or HbA1c should be evaluated and managed according to the Canadian Diabetes Society guidelines (http://guidelines.diabetes.ca/). (AIII)

2. Initial management of blood glucose abnormalities in HIV-positive individuals involves lifestyle changes (weight loss, diet, exercise). (AIII)

3. Oral anti-glycemic agents and injectable anti-glycemic agents (insulin, glucagon-like peptide-1[GLP-1] receptor agonists) should be used as required, keeping in mind drug interactions with some antiretrovirals. (AIII)

Evidence:

Diabetes mellitus (DM) is more prevalent in the HIV-positive population than in the general population, particularly in those who are co-infected with hepatitis C.2,21,22 Insulin resistance (IR) is associated with use of some nucleoside reverse transcriptase inhibitors and protease inhibitors, but may be transient; clinical hyperglycemia is less common than dyslipidemia in this setting, occurring in less than 5% of protease inhibitor-treated individuals. The evidence is inconclusive that switching antiretrovirals will improve glucose tolerance.2 Traditional risk factors for DM remain relevant in HIV-positive individuals. HbA1c may be monitored as an alternative to fasting blood glucose, particularly if fasting status is difficult to ascertain; however, HbA1c can be misleading in certain anemic conditions (e.g. iron deficiency) and in situations where erythrocyte half-life is reduced (e.g. recent transfusion, hemolysis, or blood loss) or increased (e.g. asplenia).2,23
D. Bone disease

**Recommendations:**

1. Clinicians should undertake preventive measures for bone loss in all HIV-positive individuals, including 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). (AIII)

2. Vitamin D supplementation should be considered for all HIV-positive individuals (e.g. 1000-2000 IU/day). (BIII)

3. Clinicians should consider performing a baseline dual energy X-ray absorptiometry (DXA) scan to assess bone mineral density for HIV-positive women who are post-menopausal and in all HIV positive men aged 50 years and older, and in patients of any age with a history of fragility fractures or significant risk factors for osteoporosis (http://www.osteoporosis.ca/health-care-professionals/guidelines/) (BIII).

4. DXA scan should be repeated at intervals according to local provincial guidelines. (BIII)

5. For HIV-positive transgender people who have undergone gender-affirming interventions, such as hormone therapy or gonadectomy, clinicians should refer to appropriate resources for guidance on osteoporosis screening. (CIII)

6. If decreased bone density is diagnosed, secondary causes such as hypogonadism, alcoholism, glucocorticoid exposure, and vitamin D deficiency should be investigated and treated appropriately, including referral to a specialist if necessary. (AIII)

**Evidence:**

HIV-positive individuals are at a greater risk of fractures than non-infected individuals.\(^{24}\) The loss of bone density associated with normal aging is accelerated by HIV infection and by exposure to antiretrovirals.\(^{25}\) The role of specific antiretrovirals in causing bone loss is controversial and inconsistent; however, most recent evidence points to tenofovir DF and possibly ritonavir-boosted protease inhibitors as the leading culprits.\(^{26,27}\) Efavirenz has also been implicated as a contributor to low bone mass, mediated through its effect on vitamin D metabolism.\(^{28}\)

There are currently no validated or widely accepted North American guidelines for screening, assessing, monitoring, or treating low bone mineral density (BMD) in HIV-positive individuals. When using dual energy X-ray absorptiometry (DXA) scan data to assess BMD in HIV-positive individuals, clinicians should use caution in the interpretation of T-scores, and the Z-score is probably preferable in this population.\(^{29}\) Osteoporosis cannot be diagnosed using DXA alone in
men aged less than 50 years or in premenopausal women; in fact, many experts feel that a DXA scan is generally not indicated in this population unless patients have a fragility fracture or another risk factor – although in this context, HIV may be considered a sufficient risk factor.²⁶,³⁰,³¹

With or without DXA results, a patient’s ten-year risk of fracture can be assessed using the WHO Fracture Risk Assessment tool (http://www.sheffield.ac.uk/FRAX/); however, this instrument has not been validated for use in patients with HIV.

For HIV-positive transgender people, different methods of prevention and screening for osteoporosis are needed, depending on the type and duration of gender-affirming interventions, such as hormone therapy or gonadectomy. Clinicians should refer to appropriate resources for guidance (http://transhealth.ucsf.edu/trans?page=protocol-screening#S6X). For HIV-positive transgender people who have not undergone any medical or surgical transition, clinicians should follow guidelines based on birth sex.

Most HIV patients 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 HIV-positive individuals.³²,³³ While there is no consensus regarding the optimal dose in the setting of HIV, supplementation with vitamin D at doses of 1000 to 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.

E. Renal disease

Recommendations:

1. Due to the risk of renal disease related to HIV and antiretroviral medications, it is recommended that blood pressure and laboratory assessment of renal function (serum creatinine and phosphate, estimated glomerular filtration rate [eGFR], urinalysis for protein and sediment, and spot urine for albumin to creatinine ratio [UACR]) should be performed in all HIV-positive individuals at baseline and every 3-4 months after starting antiretrovirals, increasing to six-month intervals when stable (depending on degree of risk). (AIII)

2. In case of renal dysfunction, clinicians should adjust doses of medications, including antiretrovirals that are cleared by the kidney. 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. (AII)

Evidence:

Renal dysfunction is frequently seen in HIV-positive individuals, 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, and certain co-morbidities (including diabetes mellitus, hypertension, hepatitis B or C, and other liver disease).\textsuperscript{34} 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 blacks of West African or Haitian descent in association with advanced HIV disease; as such, it is an indication for starting antiretroviral therapy regardless of CD4 count.\textsuperscript{3} Despite a small potential for nephrotoxicity, overall large studies show that current antiretroviral therapy is beneficial for renal function.\textsuperscript{1,35}

Numerous forms of acute and chronic renal disease are seen in the setting of HIV:
- 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 protease inhibitors\textsuperscript{53-56}
- Drug interactions, e.g. ritonavir-boosted protease inhibitors/statins (rhabdomyolysis and myoglobinuria)

Certain etiologies of renal disease may also be related to antiretrovirals, specifically:
- Risk of tubular dysfunction and renal phosphate wasting with tenofovir DF, especially in patients with other risk factors or eGFR <90 mL/min at baseline\textsuperscript{34,40}
- Other NRTIs (didanosine, stavudine, and lamivudine) rarely associated with tubular disorders
- Nephrolithiasis risk with indinavir and, less commonly, with atazanavir.\textsuperscript{41,42} 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\textsuperscript{3}).
- Rarely, acute interstitial nephropathy with reversible acute renal failure has been described in association with hypersensitivity reactions to abacavir, efavirenz, and atazanavir\textsuperscript{43}

Establishing the etiology of renal dysfunction in HIV-positive individuals 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 antiretrovirals (specifically all NRTIs except abacavir) are renally cleared and may require dosage adjustment if renal function is abnormal. 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 antiretroviral therapy, tenofovir DF should be discontinued if possible and replaced with another agent (e.g. abacavir if HLA-B*5701 negative) rather than dose-reduced.

Certain antiretroviral agents (dolutegravir, rilpivirine, raltegravir) and pharmacokinetic enhancers (ritonavir, cobicistat) affect renal tubular creatinine transporters resulting in decreased tubular creatinine secretion and increased serum creatinine levels.\textsuperscript{18,19,44-48} This is manifested as a factitious increase in serum creatinine during the initial 2-4 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. The mean increase in creatinine to be expected on starting any of these agents is around 10-12 μmol/L for dolutegravir, rilpivirine, or cobicistat, and approximately 5 μmol/L for raltegravir or ritonavir. If the serum creatinine increase is much greater than expected (e.g. 20-30 μmol/L), is accompanied by any other signs of renal dysfunction (e.g. proteinuria), or continues to increase after the first four weeks of a new therapy, further renal investigations should be undertaken and nephrology referral should be considered.

F. **Hypogonadism** (New subsection added March 2015)

<table>
<thead>
<tr>
<th>Recommendations:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. HIV-positive men presenting with symptoms of hypogonadism (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) may be assessed with a morning serum total testosterone level; an abnormal testosterone level should be confirmed with repeat testing. An estimated bioavailable testosterone measurement may be helpful to assess certain individuals, including obese men with borderline low total testosterone levels. (AII)</td>
</tr>
<tr>
<td>2. Testosterone replacement is indicated only for symptomatic men with total testosterone levels less than 10 mmol/L, and should be prescribed in consultation with a specialist. (AII)</td>
</tr>
<tr>
<td>3. Hormone replacement for HIV-positive transgender individuals should be provided in consultation with an endocrinologist or other clinician who has experience providing endocrine care to transgender individuals. (CIII)</td>
</tr>
</tbody>
</table>

**Evidence**

In the pre-highly active antiretroviral therapy (pre-HAART) 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. While less prevalent in the HAART era, low testosterone levels are still present in a significant minority of HIV-positive men.

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. HIV-positive men 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. An estimated bioavailable testosterone measurement may be helpful to assess certain individuals, specifically obese men with borderline low total testosterone levels. Normal serum testosterone levels in women are unknown.

Testosterone replacement therapy (TRT) is indicated only for men with symptomatic low testosterone levels, and should be prescribed according to current guidelines, preferably in consultation with an endocrinologist or other specialist. In HIV-positive men 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.\textsuperscript{49} 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 men with HIV.\textsuperscript{52}

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 six months.\textsuperscript{51}

\textbf{G. Neurocognitive Impairment} (New subsection added March 2015)

\begin{center}
\textit{Recommendations:}
\end{center}

\begin{itemize}
\item 1. Antiretroviral therapy to suppress plasma viral load should be started early and administered continuously, to prevent or minimize HIV-related neurocognitive impairment. (AII)
\item 2. HIV-positive individuals presenting with cognitive complaints that affect their daily functioning should be investigated to rule out relevant underlying conditions. (AII)
\end{itemize}

\textbf{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 antiretroviral therapy. 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.\textsuperscript{53}

HIV-positive individuals 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.\textsuperscript{54} Potential underlying conditions that need to be ruled out include (see \url{https://online.epocrates.com/u/2911900})\textsuperscript{55}:

\begin{itemize}
\item Psychiatric conditions, e.g. depression
\item Alcohol and other substance use
\item CNS infections, e.g. encephalitis, meningitis, neurosyphilis
\item CNS lymphoma
\item Cerebrovascular disease
\item History of head trauma
\item Endocrine disorders e.g. thyroid disease, hypogonadism
\end{itemize}
Nutritional deficiencies
Side effects of antiretrovirals or other medications

HIV-positive individuals presenting with significant cognitive complaints (affecting their work performance, housekeeping, and/or social functioning) should have their plasma HIV viral load assessed, and antiretroviral therapy started or adjusted as necessary to ensure good adherence and consistent viral suppression. Those already receiving suppressive antiretroviral therapy 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. 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 antiretroviral therapy regimen to include agents with better CSF penetration can stabilize or improve neurocognitive function in this setting. 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.

H. Lung Disease (New subsection added March 2015)

**Recommendations:**

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

2. A chest X-ray should be performed at baseline in all HIV-positive patients. 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. (AI)

3. A diagnosis of COPD should be considered, and spirometry performed as a screening test, among HIV-positive patients of any age presenting with persistent respiratory complaints, especially those with additional risk factors such as smoking. COPD should be managed according to current Canadian Thoracic Society guidelines (http://www.respiratoryguidelines.ca/); however, concomitant use of inhaled steroids with ritonavir or cobicistat should be avoided if possible. (AII)

**Evidence:**

Compared to the general population, HIV-positive patients 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. COPD should be managed according to current Canadian Thoracic Society guidelines (available at...
http://www.respiratoryguidelines.ca/), 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 antiretroviral therapy regimen, due to the risk of adrenal suppression and iatrogenic Cushing’s syndrome.\textsuperscript{60,61} Beclometasone cannot be recommended as a “safer” alternative in this setting; a recent systematic review showed this agent has no clinical effect in COPD.\textsuperscript{62} 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 regimens containing ritonavir or cobicistat. Salmeterol is not recommended with concomitant ritonavir or cobicistat in HIV-positive patients with COPD because of elevated salmeterol levels that may increase the risk of cardiovascular adverse events;\textsuperscript{63} however, other single-agent LABAs (e.g. indacaterol, formoterol) can be used safely in this setting.

A chest X-ray should be performed at baseline in all HIV-positive patients. As HIV confers an increased risk of lung cancer, HIV care providers should have a low threshold for performing a chest X-ray or chest computerized tomography (CT) in the presence of significant respiratory symptoms, particularly in smokers.\textsuperscript{64-66} After appropriate management of infectious etiologies, consultation with a respiratory specialist is advisable to investigate persistent symptoms or abnormal imaging findings.

I. Liver Disease/Cirrhosis (New subsection added March 2015)

**Recommendations:**

1. Liver enzymes and liver function should be assessed in all HIV-positive individuals at baseline and every 3-4 months after starting antiretrovirals, increasing to six-month intervals when stable (AIII).

2. All HIV-positive individuals with cirrhosis who are co-infected with Hepatitis B and/or C should be screened for hepatocellular carcinoma every six months using ultrasound (AII).

3. All HIV-positive individuals with cirrhosis should be referred for a baseline gastroscopy to screen for esophageal varices (AII).

**Evidence:**

Chronic liver disease is a leading cause of morbidity and mortality among HIV-positive individuals.\textsuperscript{67,68} Due to shared routes of transmission, a significant proportion of HIV-positive individuals are co-infected with Hepatitis B and/or C virus.\textsuperscript{68-70} See also Section IV, Part I (pp. 33-35) Other important etiologies of liver disease in HIV-positive individuals include alcoholic hepatitis, non-alcoholic steatohepatitis (NASH), and drug-induced hepatotoxicity.\textsuperscript{68,71-73} Due to HIV being well-controlled with antiretroviral therapy, opportunistic infections of the liver are now uncommon.
HIV-positive individuals who are co-infected with HBV and/or HCV have a relatively rapid rate of progression to cirrhosis compared to HIV-negative individuals with viral hepatitis.\textsuperscript{74,75} Once cirrhotic, this population also has a higher rate of hepatic decompensation and hepatocellular carcinoma.\textsuperscript{85,76} HCV and HBV in HIV-positive individuals should be managed according to current guidelines to prevent cirrhosis (http://www.hcvguidelines.org/full-report/unique-patient-populations-hivhcv-coinfection-box-summary-recommendations-hivhcv; http://aidsinfo.nih.gov/contentfiles/lvguidelines/glchunk/glchunk_25.pdf). HIV-positive individuals with confirmed cirrhosis should undergo routine hepatocellular carcinoma surveillance with ultrasound every six months (see Table 6 on p. 57).\textsuperscript{77,78} These individuals should also undergo a baseline gastroscopy to screen for varices.\textsuperscript{77,79} Serum alpha-fetoprotein (AFP) monitoring lacks adequate sensitivity and specificity for hepatocellular carcinoma surveillance and is no longer recommended.\textsuperscript{78} Cirrhosis in HIV-positive individuals should be managed in collaboration with experts in liver diseases.

\textbf{J. Cancer} (New subsection added March 2015)

\begin{table}[h]
\centering
\begin{tabular}{|l|}
\hline
\textbf{Recommendations:} \\
\hline
1. In HIV-positive patients, screening for breast, colorectal, ovary, and prostate cancers should follow current provincial recommendations for the general population. (BII) \\
2. HIV-positive patients may be at increased risk for lung cancer, HPV-related cancers (oropharyngeal, cervical, anal), and hepatocellular cancer as compared to the general population. Increased surveillance for these cancers is recommended. (AII) \\
\hline
\end{tabular}
\end{table}

\textbf{Evidence:}

The incidence of AIDS-defining cancers, Kaposi’s sarcoma, and non-Hodgkin’s lymphoma, has markedly decreased in the highly active antiretroviral therapy era (with the exception of invasive cervical cancer which has remained relatively unchanged), while non-AIDS-defining cancers have become more common.\textsuperscript{80-82} This is attributable at least in part to the increasing risk of malignancy as the HIV-positive population ages.

In general, people living with HIV are not at a greater risk of common cancers (breast, colorectal, ovary, prostate) than their age-matched HIV-negative counterparts.\textsuperscript{83} Screening for these cancers in HIV-positive patients should follow current provincial recommendations for the general population.

However, even after controlling for relevant risk factors such as smoking, HIV-positive individuals are at a higher risk for lung cancer (see Section VII, H. Lung Disease, p. 77) and cancers attributable to infectious etiologies, specifically\textsuperscript{83,84}:

- Anogenital and oropharyngeal cancers, secondary to Human Papilloma Virus (HPV)\textsuperscript{82} – see Section IV (pp. 45-46)
- Lymphoma, secondary to Epstein-Barr Virus (EBV)\textsuperscript{85}
- Hepatocellular cancer, related to hepatitis B and C viruses (HBV and HCV)\(^8\) – see Section VII, I. Liver disease (pp. 78-79)

Recommendations for cancer screening in HIV-positive individuals are summarized in Table 8 below.

**Table 8. Recommendations for cancer screening in HIV-positive individuals (adapted from 2014 EACS Guidelines)**

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Population</th>
<th>Screening test</th>
<th>Baseline</th>
<th>Screening interval</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anal</td>
<td>Men who have sex with men (MSM)</td>
<td>Digital rectal exam</td>
<td>√</td>
<td>1-3 years</td>
<td>Anal Pap test may be considered where available, but not standard of care (see Section IV[F] (p. 36)</td>
</tr>
<tr>
<td>Breast</td>
<td>Women</td>
<td>Mammography</td>
<td></td>
<td>Follow standard BC guidelines*</td>
<td>Follow standard BC guidelines*; See Section VI (pp. 64-65)</td>
</tr>
<tr>
<td>Cervical(†)</td>
<td>Women</td>
<td>Pap test</td>
<td>√</td>
<td>Repeat at 6 months; if both tests normal, repeat annually</td>
<td>Patients with abnormal Pap test should be referred for colposcopy; see Section VI (pp. 63-65)</td>
</tr>
<tr>
<td>Colorectal</td>
<td>Men and women 50-74 years</td>
<td>Fecal immunochemical test (FIT)</td>
<td>Follow standard BC guidelines</td>
<td>2 years(‡)</td>
<td>Patients with abnormal FIT test should be referred for colonoscopy(‡)</td>
</tr>
<tr>
<td>Hepatocellular</td>
<td>HCV+</td>
<td>Abdominal ultrasound</td>
<td>√(§)</td>
<td>- (unless cirrhosis present)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HCV+ with cirrhosis; or HBV+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>regardless of fibrosis stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Non-cirrhotic, HBV- and HCV-</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>All</td>
<td>Chest X-ray</td>
<td>√</td>
<td>-</td>
<td>Consider chest CT specially in smokers</td>
</tr>
<tr>
<td>Prostate</td>
<td>Men &gt;50 years</td>
<td>Digital rectal exam</td>
<td>√</td>
<td>1-3 years</td>
<td>Use of the prostate-specific antigen (PSA) test for screening is controversial(¶,**)</td>
</tr>
</tbody>
</table>

* [http://www.screeningbc.ca/Breast/ForHealthProfessionals/Eligibility.htm](http://www.screeningbc.ca/Breast/ForHealthProfessionals/Eligibility.htm)
† [http://www.screeningbc.ca/Cervix/ForHealthProfessionals/Default.htm](http://www.screeningbc.ca/Cervix/ForHealthProfessionals/Default.htm)
‡ [http://www.screeningbc.ca/Colon/ForHealthProfessionals/ProgramDetails.htm](http://www.screeningbc.ca/Colon/ForHealthProfessionals/ProgramDetails.htm)
References


VIII. Optimizing Adherence to Antiretroviral Therapy

**Recommendations:**

1. All HIV-positive individuals should have timely access to routine and urgent care that is linguistically and culturally appropriate to patient needs. (BII)

2. An interprofessional team model, with a primary provider for each patient, should be utilized to promote trusting relationships between the patient and their health care team members. (BII)

3. Clinicians should involve patients in antiretroviral regimen selection. Clinicians should ensure that patients understand treatment goals and are motivated to initiate and maintain adherence to antiretroviral therapy. (BII)

4. Clinicians should educate and support patients to help maintain adherence to antiretroviral therapy by positively reinforcing treatment success. (BII)

5. Potential behavioural, structural, and psycho-social barriers to adherence and engagement in care, such as mental illness or substance abuse, should be identified and addressed in collaboration with appropriate providers. These barriers may change with time and should be re-evaluated on an ongoing basis by all health care team members. (BIII)

**Evidence:**

High levels of adherence to antiretroviral therapy (≥95%) are necessary to ensure the optimum effect of treatment on HIV disease progression.\(^1\) Sub-optimal adherence leads to a high probability of the development of drug resistance. Early engagement and retention in care is critical to helping patients achieve high levels of adherence and treatment success.\(^2\)

Patients should be educated on the importance of maintaining adherence to HIV treatment and they should be encouraged to inform all their care providers of their HIV treatment when they are transferring care. HIV medications are not routinely entered onto Pharmanet when medications are dispensed in B.C.

There is a dearth of information on how to effectively assess patient readiness for HIV treatment in terms of patient ability to adhere to antiretroviral therapy.\(^3\) Adherence counselling training for clinic team members has been proposed as a method to improve understanding about the challenges associated with adherence and strategies to reduce adherence-related barriers.\(^4\)

Depression and substance abuse are common co-morbidities in persons living with HIV infection and are important barriers to HIV treatment adherence and care. It is important to identify patients with depression because treating depression can improve adherence to antiretroviral therapy.\(^5\)
Adherence to therapy is a dynamic process and should be evaluated at each clinic visit to facilitate early intervention and support to patients where necessary. Mixed results have been observed regarding the effects of directly observed therapy on adherence and clinical outcomes in hard-to-treat populations. A comprehensive model of HIV care that addresses medical and social issues is essential for providing care to marginalized populations. If appropriate, simplification of therapy (e.g. decreased number of daily doses, fixed-dose combinations) may enhance adherence to antiretroviral therapy. Patients who consent may also benefit from the use of adherence tools (e.g. pill boxes, reminder devices) and the involvement of community partners (e.g. HIV service organizations, community health representatives).

References

IX. Special Consideration for HIV-positive Individuals with Addictions

**Recommendations:**

1. All HIV-positive individuals should be asked about substance use at baseline and at least annually thereafter. Those with a history of substance use should be re-evaluated for drug and alcohol use at least quarterly. (CIII)

2. Clinicians should offer and support a variety of substance use treatment options for HIV-positive substance users, including abstinence, a reduction in use, and safer use strategies. (CIII)

3. HIV-positive substance users receiving methadone or buprenorphine while on antiretroviral therapy should be monitored for potential drug-drug interactions. (AII)

4. Substance users are at a high risk for multiple co-morbid medical and mental health conditions, such as hepatitis B and C virus infection, tuberculosis, skin and soft tissue infections, recurrent bacterial pneumonia, endocarditis, and depression. Primary care providers of HIV-positive substance users should be familiar with the prevention, diagnosis, and treatment of these co-morbidities. (BII)

**Evidence:**

There is a significant prevalence of illicit substance use among HIV-positive individuals.\(^1\) Substance abuse is associated with decreased access to and use of health care, reduced likelihood of being prescribed antiretrovirals, and reduced adherence to antiretrovirals.\(^2\) **HIV-positive individuals should be asked about substance use annually, even if their baseline screen result is negative.** Commonly used substances include tobacco, alcohol, marijuana, heroin, cocaine, and methamphetamines. Asking about the use and abuse of prescription opiates and benzodiazepines is also important.

Individuals with a known history of substance dependence are at a high risk for relapse, particularly when stressed by a new diagnosis of HIV or by its complications. Interventions to improve the medical care of HIV-positive individuals who are substance-dependent should include integration of drug abuse treatment with HIV primary care.\(^3\) Clinicians should be familiar with the range of substance use treatment programs and services in their area. There is some evidence that integrating harm reduction interventions within HIV care settings is beneficial, and that a supervised injection facility can positively influence access to care for HIV-positive people who inject drugs (PWID).\(^4\)

Methadone maintenance therapy (MMT) is another intervention that has been shown to increase access and adherence to antiretroviral drug treatment among PWID.\(^5,6\) Clinicians should closely monitor HIV-positive individuals who are concurrently receiving antiretroviral therapy and MMT. There are a number of drug-drug interactions between most antiretrovirals and methadone.\(^7\) **Buprenorphine (co-formulated with naloxone in Suboxone®) is also increasingly**
being used for opioid use disorder but information regarding its interaction with antiretrovirals is currently limited.\(^8,9\) However, based on the available studies, buprenorphine has a more favourable drug interaction profile compared to methadone. For a complete list of interactions between antiretrovirals and other medications, please refer to Table 19 (a,b,c,d) in the DHHS 2015 guidelines (http://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf) or seek advice from a pharmacist with antiretroviral expertise if you practice in BC (call the St. Paul’s HIV Pharmacy at 1-888-511-6222).

There are a number of common co-morbidities among HIV-positive substance users. Serologic evidence of past hepatitis B virus (HBV) and hepatitis C virus (HCV) infection has been found in more than two thirds of long-term users of injection drugs.\(^10,11\) HIV-related tuberculosis has been closely associated with injection drug use, partly due to the high endemic levels of latent *Mycobacterium tuberculosis* infection in the population groups in which substance users are concentrated, such as the urban poor.\(^12\) Several studies have documented an elevated risk of bacterial pneumonia in HIV-positive individuals who use drugs.\(^13-15\) The most common injection drug use related infectious disease complications are skin and soft tissue infections, which include cellulitis and abscesses.\(^16-18\) Endocarditis is independently associated with HIV infection among PWID.\(^17\) High rates of depressive disorders have also been reported among those with a substance use disorder.\(^19,20\) Familiarity with the prevention, diagnosis and treatment of these co-morbidities in HIV-positive substance users is an essential component of their comprehensive HIV care.

**References**


X. Special Consideration for Individuals with Advanced HIV – Opportunistic Infection & Prophylaxis

Despite efforts to expand HIV testing and the accessibility of effective antiretroviral therapy in British Columbia, a number of individuals still present to medical care at an advanced stage of HIV disease. Others may not access medical care including antiretroviral therapy, or be unable to adhere to it consistently. Such individuals may have a low CD4 cell count, 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 antiretroviral therapy, primary prophylaxis can often be discontinued once the patient is clinically stable and has established consistent adherence. For more information on Immune Reconstitution Inflammatory Syndrome (IRIS) in HIV-infected patients, refer to the BC-CfE Therapeutic Guidelines (http://www.cfenet.ubc.ca/therapeutic-guidelines/adult). 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 9 on p. 93.

References

Table 9: Prophylaxis to prevent first episode of opportunistic disease, and criteria for when to discontinue or restart primary prophylaxis for adults and adolescents with HIV infection (Table updated March 2015, adapted from [http://aidsinfo.nih.gov/guidelines](http://aidsinfo.nih.gov/guidelines) 2013)1

<table>
<thead>
<tr>
<th>Pathogen*</th>
<th>Indication</th>
<th>First choice</th>
<th>Alternative</th>
<th>Criteria for discontinuing primary prophylaxis</th>
<th>Criteria for restarting primary prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Pneumocystis Jeroveci Pneumonia (PJP) (previously PCP)</em></td>
<td>CD4 cell count &lt;200 cells/mm³ or oropharyngeal candidiasis or CD4 cell count &lt;14% or history of AIDS-defining illness or CD4 cell count &gt;200 but &lt;250 cells/mm³ if monitoring CD4 cell count every 1-3 months is not possible</td>
<td>Trimethoprim-sulfamethoxazole (TMP-SMX)*, 1 double strength (DS) per os (by mouth) (PO) daily; or 1 single strength (SS) PO daily</td>
<td>• 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 Respigrard® II nebulizer every month</td>
<td>CD4 cell count &gt;200 cells/mm³ for &gt;3 months in response to antiretroviral therapy (ART) or CD4 cell count 100-200 cells/mm³ for &gt;3 months in response to ART, and HIV RNA &lt;40 copies/mL.230</td>
<td>CD4 cell count &lt;200 cells/mm³, if HIV RNA &gt;40 copies/mL; or CD4 &lt;100 cells/mm³ if HIV RNA &lt;40 copies/mL.</td>
</tr>
<tr>
<td><em>Toxoplasma gondii encephalitis</em></td>
<td>Toxoplasma IgG positive patients with CD4 cell count &lt;100 cells/mm³</td>
<td>Trimethoprim-sulfamethoxazole (TMP-SMX)*, 1 DS PO daily</td>
<td>• 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</td>
<td>CD4 cell count &gt;200 cells/mm³ for &gt;3 months in response to ART</td>
<td>CD4 cell count &lt;100-200 cells/mm³</td>
</tr>
</tbody>
</table>
**Mycobacterium tuberculosis** infection (TB)  
[Treatment of latent TB infection (LTBI)]

<table>
<thead>
<tr>
<th>Condition</th>
<th>Diagnostic Criteria</th>
<th>Treatment</th>
<th>CD4 Count</th>
</tr>
</thead>
</table>
| 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 a 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 Rifabutin 300 mg po daily (dose adjusted based on concomitant ART) x 4 months (For persons exposed to drug-resistant TB, selection of drugs after consultation with public health authorities) | Not applicable |
| Disseminated Mycobacterium avium complex (MAC) disease | CD4 cell count <50 cells/mm³ 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/mm³ for ≥3 months in response to ART |

* 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.
XI. Psycho-Social Implications of HIV Infection

A coordinated interdisciplinary care approach is an important aspect of primary care for HIV-positive individuals. Best practices for delivering this care, including testing and treatment, must be informed by an array of psycho-social considerations that stem from the reality of the lives of HIV-positive individuals. The impact of these considerations depends on individual circumstances and on an individual’s stage within the HIV disease trajectory.

From a clinical perspective, the continuum of HIV care has been summarized as: (1) HIV diagnosis; (2) linked to HIV care; (3) retained in HIV care; (4) on antiretroviral therapy (ART); (5) adherent to ART; and (6) achieving a suppressed viral load. These stages have also been turned into indicators, collectively known as the cascade of care, that can serve as a tool for improving the delivery and quality of HIV care. In BC, these indicators reveal disparities and thus potential opportunities for improvement. Preventing losses at each step of the cascade will benefit the individual (decrease morbidity and mortality), the community (decrease HIV transmissions) and the system (save costs of new infections and cost of acute care utilization).

A. Model of care

**Recommendation:**

1. HIV care and patient education should be provided in a socially, culturally and gender appropriate manner using a patient-centred, collaborative, and interdisciplinary chronic disease care model which fosters trusting patient-provider relationships and improves retention in care. (CIII)

**Evidence:**

The collaborative and interdisciplinary chronic disease model of care should strengthen and support self-care while assuring effective medical care, prevention and health maintenance. The process should be dynamic and continuous, beginning with mutual respect, dialogue, and the establishment of mutually desired and obtainable goals, and progressing through stages to improve adherence, optimize health and increase survival. It is essential to this type of health care management that collaborative definitions of problems, goals, and planning are clearly established with the patient always at the centre to improve health outcomes.

In addition to having an interdisciplinary team approach, free HIV care should foster the development of a strong and trusting patient-provider relationship, preferably between the patient and a primary case manager. Trust and confidentiality are also essential on the part of care providers. Although confidentiality of all medical information is always mandatory, it is particularly important for HIV-positive individuals due to HIV-related stigma. Issues of trust and other barriers to care can impact an individual’s risk of acquiring HIV and can also impact the care of those who are HIV-positive.
B. **Linkage to and retention in care (New subsection May 2015)**

**Recommendations:**

1. All HIV-positive individuals should have timely access to routine primary care and treatment. (BII)

2. Case management for individuals with a new HIV diagnosis is recommended. (BII)

3. Intensive outreach for individuals not engaged in medical care within 6 months of a new HIV diagnosis may be considered. (CIII)

4. Clinical and non-clinical providers are strongly encouraged to incorporate quality improvement strategies that focus on improving delivery and quality of HIV care to HIV-positive individuals. (CIII)

**Evidence:**

Timely access to care is important for any health condition but especially important in the case of HIV, where delayed treatment can have serious consequences for the individual and others through unintended disease transmission.\(^2,14\) In British Columbia, all residents are eligible for care and treatment of HIV free of charge. Care providers who are faced with the ethical dilemma of caring for any person not eligible for treatment or care (visitors and/or persons residing in Canada illegally) should contact the BC Centre for Excellence in HIV/AIDS to advocate on the person’s behalf for coverage of the cost of medical treatment.

HIV-positive individuals who are not linked to and retained in care may face significant barriers to achieving optimal treatment outcomes.\(^15\) In some settings, interventions such as case management and intensive outreach that aim to improve linkage to care and sustained engagement can help support better treatment outcomes.\(^16\) As needs vary from one social and clinical context to another, more research evaluating what interventions work and where is needed.\(^16\)

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.\(^17\) 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://stophivaid.ca/hiv-continuum-collaborative/](http://stophivaid.ca/hiv-continuum-collaborative/)) or contact the BC Centre for Excellence in HIV/AIDS by phone at 604-806-8477.
C. Peer and social support

**Recommendations:**

1. Clinicians should perform thorough assessments of the social circumstances of HIV-positive individuals at baseline and re-evaluate annually. (CIII)

2. All individuals living with HIV should be offered a referral to an AIDS service organization (ASO) for counselling, social, and peer support. (CIII)

3. Peer support workers should be identified and utilized to help improve patient outcomes. (CIII)

**Evidence:**

Stigma, isolation, and marginalization are common realities in the lives of HIV-positive individuals. Ensuring access to social and emotional support for affected individuals is a crucial part of HIV primary care. Moreover, clinicians should ensure that the individual’s basic determinants of health, such as food security and access to adequate housing, are fulfilled. Patients should also be connected to peer support whenever possible. Peer support programs have proven successful in reducing harmful health behaviours, improving disease management, and improving depression outcomes. Peer support programs can also help improve linkages to and retention in care. AIDS service organizations (ASOs) are excellent starting points for many of these services. The Canadian AIDS Treatment and Information Exchange (http://catie.ca, 1-800-263-1638) is a national organization that provides useful support and information as well as a searchable listing of regional ASOs. Please refer to the Contact List (p. 105) for a list of provincial ASOs.

D. **Youth** (New subsection added March 2015)

**Recommendation:**

1. In view of the suboptimal rates of retention youth experience at each stage of the cascade of care, consideration should be given to the unique psycho-social issues that youth face when developing their care and treatment plan. (CIII)

**Evidence:**

Advances in antiretroviral therapy have resulted in the increasing survival of HIV-positive individuals, allowing those infected to live near normal life expectancies, yet those under 30 years of age continue to have suboptimal rates of retention at each stage across the cascade of care.
Clinicians providing care to both prenatally- and behaviourally-infected youth should be cognizant of the many psycho-social issues that affect retention in care and medication adherence rates, including stigma, discrimination, loss of family members, body dysmorphia, safer sex negotiation, and general feelings of youth invincibility. It is important that youth play an active role in their health care planning to increase autonomy and capacity. When possible, newer technologies, such as texting medication reminders, should be utilized to improve adherence. For more information on adherence to antiretroviral therapy, please refer to Section VIII. Optimizing Adherence to Antiretroviral Therapy on p. 85.

References

### Table 10: Other Guidelines related to the care of HIV-positive individuals

<table>
<thead>
<tr>
<th>Topic/Title</th>
<th>URL</th>
<th>Issuing Agency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antiretroviral Therapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug Interaction Tables, Immunodeficiency Clinic</td>
<td><a href="http://www.hivclinic.ca/main/drugs_interaction.html">http://www.hivclinic.ca/main/drugs_interaction.html</a></td>
<td>Toronto General Hospital, University Health Network</td>
</tr>
<tr>
<td><strong>Cancer</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cervical Cancer</td>
<td><a href="http://www.screeningbc.ca/Cervix/default.htm">http://www.screeningbc.ca/Cervix/default.htm</a></td>
<td>BC Cancer Agency</td>
</tr>
<tr>
<td></td>
<td><a href="http://www.screeningbc.ca/Cervix/ForHealthProfessionals/Default.htm">http://www.screeningbc.ca/Cervix/ForHealthProfessionals/Default.htm</a></td>
<td>BC Cancer Agency</td>
</tr>
<tr>
<td>Trans People</td>
<td><a href="http://convio.cancer.ca/site/PageServer?pageName=SSL_ON_T_Home#.VaBZEd9SXy">http://convio.cancer.ca/site/PageServer?pageName=SSL_ON_T_Home#.VaBZEd9SXy</a></td>
<td>Canadian Cancer Agency</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td><a href="http://www.screeningbc.ca/Breast/ForHealthProfessionals/Eligibility.htm">http://www.screeningbc.ca/Breast/ForHealthProfessionals/Eligibility.htm</a></td>
<td>BC Cancer Society</td>
</tr>
<tr>
<td>Colon Cancer</td>
<td><a href="http://www.screeningbc.ca/Colon/ForHealthProfessionals/ProgramDetails.htm">http://www.screeningbc.ca/Colon/ForHealthProfessionals/ProgramDetails.htm</a></td>
<td>BC Cancer Society</td>
</tr>
<tr>
<td><strong>Cardiovascular</strong></td>
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<td>Topic/Title</td>
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<tr>
<td><strong>Contraception</strong></td>
<td></td>
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<tr>
<td>Interactions between Antiretrovirals (ARVs) and Hormonal Contraceptives</td>
<td><a href="http://www.hivclinic.ca/main/drugs_interact_files/Oral%20Contraceptive-int.pdf">http://www.hivclinic.ca/main/drugs_interact_files/Oral%20Contraceptive-int.pdf</a></td>
<td>Toronto General Hospital, Immunodeficiency Clinic</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td></td>
<td></td>
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<tr>
<td><strong>Hepatitis B and Co-infection</strong></td>
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<tr>
<td><strong>Hepatitis C and Co-infection</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topic/Title</td>
<td>URL</td>
<td>Issuing Agency</td>
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</tbody>
</table>

**Immunization**

<table>
<thead>
<tr>
<th>Immunization Program</th>
<th>URL</th>
<th>Issuing Agency</th>
</tr>
</thead>
</table>

**Laboratory Testing**

| HIV testing, reporting, counselling and follow-up, and guidelines on point of care testing | [http://www.bccdc.ca/dis-cond/comm-manual/CDManualChap5.htm](http://www.bccdc.ca/dis-cond/comm-manual/CDManualChap5.htm) | BC Centre for Disease Control                                                   |

**Living with HIV**

<table>
<thead>
<tr>
<th>Topic/Title</th>
<th>URL</th>
<th>Issuing Agency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opportunistic Infections</td>
<td><a href="http://www.cfenet.ubc.ca/therapeutic-guidelines/opportunistic-infection">http://www.cfenet.ubc.ca/therapeutic-guidelines/opportunistic-infection</a></td>
<td>BC Centre for Excellence in HIV/AIDS</td>
</tr>
<tr>
<td>Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents</td>
<td><a href="http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oI.pdf">http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oI.pdf</a></td>
<td>Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America</td>
</tr>
<tr>
<td>1993 Revised Classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults.</td>
<td><a href="http://www.cdc.gov/mmwr/preview/mmwrhtml/00018871.htm">http://www.cdc.gov/mmwr/preview/mmwrhtml/00018871.htm</a></td>
<td>US Centers for Disease Control and Prevention</td>
</tr>
<tr>
<td>Fracture Risk Assessment tool</td>
<td><a href="http://www.sheffield.ac.uk/FRAX/">http://www.sheffield.ac.uk/FRAX/</a></td>
<td>World Health Organization</td>
</tr>
<tr>
<td>General Prevention and Screening: Musculoskeletal Health</td>
<td><a href="http://transhealth.ucsf.edu/trans?page=protocol-screening#S6X">http://transhealth.ucsf.edu/trans?page=protocol-screening#S6X</a></td>
<td>Centre of Excellence for Transgender Health, University of California San Francisco</td>
</tr>
<tr>
<td>Peer Support</td>
<td>How to support and facilitate peer engagement in service provision roles (2013)</td>
<td>Ontario HIV Treatment Network</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>British Columbia Guidelines for the Care of HIV-positive Pregnant Women and Interventions to Reduce Perinatal Transmission</td>
<td>BC Centre for Excellence in HIV/AIDS</td>
</tr>
<tr>
<td>Topic/Title</td>
<td>URL</td>
<td>Issuing Agency</td>
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<tr>
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<tr>
<td><strong>Nutrition</strong></td>
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<tr>
<td><strong>Renal</strong></td>
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<tr>
<td><strong>Respiratory</strong></td>
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</tr>
<tr>
<td>COPD guidelines</td>
<td><a href="http://www.respiratoryguidelines.ca/">http://www.respiratoryguidelines.ca/</a></td>
<td>Canadian Thoracic Society</td>
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<tr>
<td><strong>Sexually Transmitted Infections</strong></td>
<td></td>
<td></td>
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<tr>
<td>Sexually Transmitted Infections (Section I)</td>
<td><a href="http://www.bccdc.ca/dis-cond/comm-manual/CDManualChap5.htm">http://www.bccdc.ca/dis-cond/comm-manual/CDManualChap5.htm</a></td>
<td>BC Centre for Disease Control</td>
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<tr>
<td><strong>Tuberculosis</strong></td>
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</table>
## CONTACT LIST (Revised March 2015)

<table>
<thead>
<tr>
<th>Organization</th>
<th>Local Number</th>
<th>Other Number</th>
<th>Website</th>
</tr>
</thead>
</table>
| BC Centre for Excellence in HIV/AIDS  
For HIV treatment and management or guideline inquiries | 604-806-8477 | HIV/AIDS Treatment Program Information Line  
604-806-8515  
Drug Resistance Testing  
1-800-517-1119 | www.cfenet.ubc.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. | 604-806-8415 | N/A | www.education.cfenet.ubc.ca  
Email: sguillemi@cfenet.ubc.ca |
| BC-CfE HIV Preceptorship Training Program | 604-707-5600 | N/A | www.bccdc.ca |
| BC Centre for Disease Control  
For HIV testing and other STI inquiries | 604-875-2212 | 1-888-711-3030 | www.bcwcms.ca/Services/HealthServices/OakTreeClinic/ |

### Provincial HIV/AIDS Service Organizations

<table>
<thead>
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<th>Organization</th>
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<th>Website</th>
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<tr>
<td>Positive Living Society of BC</td>
<td>604-893-2200</td>
<td>1-800-994-AIDS</td>
<td><a href="http://www.positivelivingbc.org">www.positivelivingbc.org</a></td>
</tr>
<tr>
<td>Positive Women’s Network</td>
<td>604-692-3000</td>
<td>1-866-692-3001</td>
<td><a href="http://www.pwn.bc.ca">www.pwn.bc.ca</a></td>
</tr>
<tr>
<td>YouthCO HIV &amp; Hep C Society</td>
<td>604-688-1441</td>
<td>1-877-968-8426</td>
<td><a href="http://www.youthco.org">www.youthco.org</a></td>
</tr>
<tr>
<td>Western Canadian Paediatric AIDS Society</td>
<td>604-684-1701</td>
<td>N/A</td>
<td><a href="http://www.campmoomba.com">www.campmoomba.com</a></td>
</tr>
<tr>
<td>Pacific AIDS Network (PAN)</td>
<td>604-569-1998</td>
<td>N/A</td>
<td><a href="http://www.pacificaidssnetwork.org">www.pacificaidssnetwork.org</a></td>
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</tbody>
</table>
APPENDICES

Appendix 1: AIDS-defining conditions* (New Appendix added March 2015)
(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

Appendix 2: Signs and symptoms associated with HIV Seroconversion Syndrome/Acute Retroviral Syndrome and their frequency*

- 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%)

## Appendix 3: HIV-Related History (Appendix updated March 2015)

| General History | Review sources of past medical care; obtain medical records whenever possible  
| Past hospitalizations, past and current illnesses  
| Tuberculosis history  
| Possible recent exposure to tuberculosis  
| History of positive purified protein derivative (PPD), *Mycobacterium tuberculosis* (TB) disease, or treatment of latent TB infection  
| History of hepatitis A, B and C  
| Current prescription and non-prescription medicines, including complementary and alternative medicines and hormones  
| Vaccination history including hepatitis A and B series, pneumococcal vaccine, flu shots, tetanus  
| Reproductive history, including pregnancies, births, termination of pregnancy; current contraceptive use and needs  
| Partner information for disclosure of HIV status  
| Allergies  
| Travel history/place of birth  
| Occupational history and hobbies  
| Pets/animal exposures |

| HIV Related History | HIV exposure history  
| Date and place of the diagnosis  
| Route of exposure, if known  
| Most recent viral load and CD4 cell count  
| Seroconversion illness  
| Nadir CD4 cell count and peak viral load  
| Drug-resistance testing (Genotype)  
| Current and previous antiretroviral regimens and date of initiation of ARV therapy  
| Previous adverse ARV drug reactions  
| Opportunistic infections  
| Previous adverse reactions to drugs used for opportunistic infection prophylaxis  
| Providers who have been involved in the patient’s HIV treatment  
| Patient’s understanding of HIV disease and treatment |

| Mental Health History | Mental health diagnoses, especially:  
| Depression  
| Anxiety  
| Post-traumatic stress disorder  
| Suicidal/violent behaviour  
| Severe and persistent mental illness  
| Psychotropic medications  
| Past psychiatric hospitalizations  
<p>| Contact information for mental health providers if applicable |</p>
<table>
<thead>
<tr>
<th>Substance Use History</th>
<th>Types of drugs; past and current use</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>o Street drugs—marijuana, cocaine, heroin, methamphetamine, ecstasy, etc.</td>
</tr>
<tr>
<td></td>
<td>o Illicit use of prescription drugs</td>
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<tr>
<td></td>
<td>o Alcohol</td>
</tr>
<tr>
<td></td>
<td>o Tobacco</td>
</tr>
<tr>
<td></td>
<td>Frequency of use and usual route of administration</td>
</tr>
<tr>
<td></td>
<td>Risk behaviours—drug/needle sharing, exchanging sex for drugs, sexual risk-taking while under the influence of drugs or alcohol</td>
</tr>
<tr>
<td></td>
<td>History of treatment and barriers to treatment</td>
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<tr>
<td>Sexual History</td>
<td>Current sexual activity</td>
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<tr>
<td></td>
<td>History of sexually transmitted infections—syphilis, herpes simplex, genital warts, chlamydia, gonorrhea, chancroid</td>
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<tr>
<td></td>
<td>Sexual practices—vaginal, anal, oral</td>
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<td></td>
<td>Gender identity</td>
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<tr>
<td></td>
<td>Past and current partners</td>
</tr>
<tr>
<td></td>
<td>Risk behaviour assessment, including use of latex or polyurethane barriers, number of partners</td>
</tr>
<tr>
<td>Psycho-social Assessment</td>
<td>Housing status</td>
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<td></td>
<td>Employment and insurance status</td>
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<td>Educational level</td>
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<td>Family and partner contacts</td>
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<tr>
<td></td>
<td>Stability of personal relationships</td>
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<td>o Domestic violence screening</td>
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<td></td>
<td>Immigration status</td>
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<tr>
<td>Review of Systems</td>
<td>Constitutional—weight loss, malaise, fevers, night sweats, changes in appetite, changes in sleep, adenopathy</td>
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<tr>
<td></td>
<td>Eyes—change in vision, including blurry vision, double vision, flashes of light, or loss of vision</td>
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<tr>
<td></td>
<td>Ears, nose, throat—dysphagia, odynophagia, hearing loss, discharge, dental pain, periodontal disease, oral herpes simplex, oral thrush, oral hairy leukoplakia</td>
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<tr>
<td></td>
<td>Pulmonary—cough, dyspnea at rest or on exertion, hemoptysis, sputum</td>
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<tr>
<td></td>
<td>Cardiac—chest pain, palpitations, heart murmur</td>
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<tr>
<td></td>
<td>Abdominal—nausea, vomiting, diarrhea, constipation, blood per rectum, hemorrhoids</td>
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<td></td>
<td>Genitourinary:</td>
</tr>
<tr>
<td></td>
<td>o Vaginal or penile discharge, vaginal pain, dysuria, genital/rectal warts (Human Papilloma Virus), classic and atypical herpes simplex virus</td>
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<tr>
<td></td>
<td>o Obstetrics/gynaecology - menstrual status, bleeding, infections, last Pap test and result</td>
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<tr>
<td></td>
<td>o Anal Pap status</td>
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<td></td>
<td>Extremities—muscle wasting, muscle weakness, muscle pain, joint swelling</td>
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<td></td>
<td>Neurologic—cognitive changes; tingling, burning, pain, or numbness in the extremities; weakness</td>
</tr>
</tbody>
</table>

*Adapted from: Primary Care Approach to the HIV-Infected Patient. Office of the Medical Director, New York State Department of Health AIDS Institute. November 2014.*
## Appendix 4: HIV-Related Physical Examination (Appendix updated March 2015)

<table>
<thead>
<tr>
<th>Blood Pressure, Weight, and Symptoms&lt;sup&gt;2&lt;/sup&gt;</th>
<th>• Assess at each visit</th>
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<tbody>
<tr>
<td>Pain Assessment</td>
<td>• Assess at each visit</td>
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<tr>
<td>General</td>
<td>• Body habitus, obesity, wasting, lipodystrophy, frailty, and ambulatory ability.</td>
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</tbody>
</table>
| Ophthalmologic                                | • If possible perform or refer for a funduscopic examination<sup>3</sup> when CD4 cell count <50 cells/mm<sup>3</sup>  
• Pallor or icterus                             |
| 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, petechial, herpes simplex and zoster infections. |
| Lymph Nodes<sup>4</sup>                       | • 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, click, 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/gynaecology - careful pelvic examination (refer to Section VI: Special Consideration for Women and Transgender Individuals with HIV) |
| Rectal                                        | • Visible anal lesions or evidence of skin abnormality around the anus, ulcers, warts, fissures, haemorrhoids, tumors  
• 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 and substance use assessment  |

*Adapted from: Primary Care Approach to the HIV-Infected Patient. Office of the Medical Director, New York State Department of Health AIDS Institute. November 2014.

1 Assessment of symptoms may require direct questioning because patients may not consider their symptoms important until after the symptoms have already caused significant morbidity.  
2 Except where indicated, each element should be performed at baseline and at least annually.  
3 Patients with CD4 cell counts <50 cells/mm$^3$ should be examined by an ophthalmologist at baseline and every 6 months.  
4 Significant abnormalities may present as clusters of large nodes, asymmetry, tenderness, or sudden increase in size or firmness of nodes.
### Appendix 5: Screening for non-infectious comorbid conditions in HIV-positive individuals

(Appendix updated March 2015, Adapted from EACS guidelines for Prevention and Management of Non-infectious Co-morbidities in HIV, version 7.0)

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Pre-ART baseline</th>
<th>Follow-up on ART*</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Medical History</td>
<td>Personal and family history of relevant comorbid conditions (e.g. premature cardiovascular disease, hypertension, diabetes, osteoporosis, liver disease, chronic kidney disease)</td>
<td>+</td>
<td>Update all at each visit (≤q 6mos)</td>
</tr>
<tr>
<td></td>
<td>Concomitant medications</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lifestyle (smoking, alcohol, recreational drugs, diet, exercise)</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>Risk assessment (Framingham risk score)</td>
<td>+</td>
<td>At each visit (≤q 6mos)</td>
</tr>
<tr>
<td></td>
<td>Blood pressure</td>
<td>+</td>
<td>≤q 6mos</td>
</tr>
<tr>
<td></td>
<td>Fasting lipids (total, HDL, and LDL cholesterol, triglycerides) or apolipoprotein B</td>
<td>+</td>
<td>q6 mo</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Fasting blood sugar or HbA1C</td>
<td>+</td>
<td>Q 6 months</td>
</tr>
</tbody>
</table>

- Framingham Risk Score may underestimate risk in HIV
- Consider using Reynolds Risk Score
- Consider measuring apolipoprotein B especially in patients with hypertriglyceridemia
- Manage hypertension and dyslipidemia per general population guidelines; NB 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

- Manage blood glucose abnormalities per Diabetes Canada guidelines, with lifestyle changes first (weight loss, diet, exercise)
- NB potential drug interactions with ART
## Appendix 5: Screening for non-infectious comorbid conditions in HIV-positive individuals (Continued)

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Pre-ART baseline</th>
<th>Follow-up on ART*</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bone disease</strong> (osteopenia/osteoporosis)</td>
<td></td>
<td></td>
<td>● FRAX not validated for use in Canada or in patients with HIV</td>
</tr>
<tr>
<td>Osteoporosis risk assessment (family history, exercise, weight, smoking, alcohol, calcium and vitamin D intake)</td>
<td>+</td>
<td>At each visit (≤q 6 months)</td>
<td>● Recommend supplementation with Vitamin D 1000-2000 IU/day for prevention</td>
</tr>
<tr>
<td>Fracture risk assessment (FRAX)</td>
<td>+</td>
<td>At each visit (≤q 6 months)</td>
<td>● Recommend calcium supplementation if dietary intake inadequate</td>
</tr>
<tr>
<td>DXA scan</td>
<td>+ for post-menopausal women, men age ≥50 years</td>
<td>Intervals determined by BC guidelines</td>
<td>● Perform DXA in HIV+ patients of any age with a history of fragility fractures or significant risk factors for osteoporosis</td>
</tr>
<tr>
<td><strong>Renal disease</strong></td>
<td></td>
<td></td>
<td>● 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</td>
</tr>
<tr>
<td>Risk assessment including nephrotoxic medications</td>
<td></td>
<td>≤q 6months</td>
<td>● Increased risk of renal toxicity with certain antiretrovirals, particularly tenofovir DF and indinavir, also possibly with atazanavir, lopinavir/ritonavir</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>+</td>
<td>≤q 6months</td>
<td>● Diagnosis of abnormalities may require referral to a nephrologist and possible renal biopsy</td>
</tr>
<tr>
<td>Serum creatinine and eGFR; urinalysis; spot urine for albumin to creatinine ratio</td>
<td>+</td>
<td>q3-4 mo initially, then q6 mo when stable</td>
<td></td>
</tr>
<tr>
<td><strong>Hypogonadism</strong></td>
<td></td>
<td></td>
<td>● 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</td>
</tr>
<tr>
<td>Morning serum total testosterone</td>
<td>+ Only in symptomatic men</td>
<td>Only in symptomatic men</td>
<td></td>
</tr>
<tr>
<td><strong>Lung disease</strong></td>
<td></td>
<td></td>
<td>● If symptomatic</td>
</tr>
<tr>
<td>Chest X-ray</td>
<td>+</td>
<td></td>
<td>Q 6 mo if HBV+ (any stage fibrosis) or HCV+ with cirrhosis</td>
</tr>
<tr>
<td>Liver disease</td>
<td></td>
<td></td>
<td>● consider chest CT in presence of significant symptoms, especially in smokers</td>
</tr>
<tr>
<td>Abdominal ultrasound</td>
<td>+ (if HBV+ or HCV+)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
* Frequency of laboratory monitoring may be adjusted according medical 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
CT, computed tomography
DXA, dual energy absorptiometry
ECG, electrocardiogram
eGFR, estimated glomerular filtration rate
HbA1C, glycated hemoglobin
NSAIDs, non-steroidal anti-inflammatory drugs