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

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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. At present, there are approximately 13,000 HIV-positive individuals in the province,[1] of which approximately only 5,400 are receiving antiretrovirals.[2]

In response to the need to expand the treatment of HIV-positive individuals and requests from the larger community of primary care providers, the British Columbia Centre for Excellence in HIV/AIDS (BCCfE) has developed 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

Panel Composition

An expert panel composed of primary care and infectious disease physicians, a nurse practitioner, a pharmacist, and a person living with HIV prepared these guidelines.

Process Overview

Panel members were instructed to perform a detailed review of existing HIV primary care guidelines in Canada and the United States. They were asked to reconcile differences between what is currently being advised in existing guidelines and the general recommendations from the BCCfE, and to create recommendations in the absence of existing guidelines. Panel members searched for relevant literature on PubMed and/or other online search engines, particularly examining literature published between 2009 and 2010. Only articles printed in English were included in the literature review. Evidence accumulated during the literature search was ranked using a systematic weighing of the quality of evidence and the recommendation strength. The table below and the ranking strategy were adapted from the Strength of Recommendation Taxonomy (SORT) grading scale developed by Ebell and colleagues.[3]

Consensus Development on the Basis of Evidence

The panel met a total of eight times. Panel members developed sections and presented their work at panel meetings, where all recommendations were discussed until consensus was reached. The final report manuscript was reviewed by all panel members as well as by external primary care providers to ensure applicability prior to dissemination.

Table 1: Strength of Recommendation Taxonomy (SORT) [adapted from Ebell 2004][3]

Assessment	Type of Evidence
Strength of Recommendation	
Grade A	Consistent, good quality patient-oriented evidence
Grade B	Inconsistent or limited-quality patient-oriented evidence
Grade C	Consensus, disease-oriented evidence, usual practice, expert opinion, or case series for studies of diagnosis, treatment, prevention, or screening
Quality of evidence	
Level I	Evidence from at least 1 properly designed randomized, controlled trial
Level II	Evidence from at least 1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 centre); from multiple time series; or from dramatic results of uncontrolled experiments
Level III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

Conflicts of Interest

Panel members were asked to report any conflicts of interest. Rolando Barrios, Aida Sadr, Martin Payne, Paul Kerston and Linda Akagi have no conflicts to disclose.

Disclosures: Marianne Harris has received honoraria for advisory board participation, other honoraria, and/or consultancies including continuing education and speaking engagements from Abbott, Bristol-Myers Squibb, Gilead, GlaxoSmithKline/ViiV, Merck Frosst, and Tibotec; and research funding from the Canadian Institutes for Health Research (CIHR) and CIHR-CTN. Neora Pick has received support from Abbott Laboratories as well as research funding from CIHR. Peter Phillips has received honoraria or participated in advisory boards for the following companies: Pfizer Inc., Janssen Pharmaceutica, Schering-Plough, Fujisawa, Merck, and Astellas. Silvia Guillemi has received honoraria for advisory board participation, other honoraria, and/or consultancies including speaking engagements for Abbott, Bristol-Myers Squibb, Gilead, Merck Frosst, Tibotec, and ViiV.

SUMMARY OF RECOMMENDATIONS FOR THE MANAGEMENT OF HIV-POSITIVE INDIVIDUALS

Medical History and Physical Examination of HIV-Positive Individuals

1. All HIV-positive individuals should be evaluated by a primary care clinician with knowledge and experience in the management of HIV infection at all stages, including treatment initiation, change in treatment regimen and treatment failure. (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, medication/social/family history, and a review of systems upon patient entry into care. (A-III)
3. A physical examination should be performed at baseline and annually for all HIV-positive individuals, with an emphasis on systems affected by HIV. (CIII)
4. Clinicians should schedule routine monitoring visits at least every 3-6 months for all HIV-positive individuals who are clinically stable and on antiretroviral therapy. More frequent visits should be scheduled for those who are clinically unstable or not on antiretroviral therapy. (CIII)

HIV Disease-Specific Testing

5. 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. (A-III)
6. 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)
7. All patients should be assessed for transmitted drug resistance using genotypic drug resistance testing regardless of the estimated duration of the infection. This should be ideally done by testing the first available HIV plasma viral load sample (AIII). Note that genotypic resistance testing can be performed on archived plasma samples.
8. If antiretroviral therapy is deferred, repeat genotypic drug resistance testing close to the time of initiation of therapy is recommended because of the potential for superinfection (CIII).
9. 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)
10. All patients should be screened for HLA-B*5701 prior to initiating therapy with abacavir. (AI).
11. Although not all patients will be exposed to abacavir, in British Columbia, HLA-B*5701 testing is recommended at baseline, and results should be recorded for future use (CIII). This testing only needs to be performed once per patient.
12. HLA-B*5701-positive patients should not receive abacavir. (AII)
13. 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)

Screening for Co-Morbidities

14. All HIV-positive individuals should be screened at baseline for Mycobacterium tuberculosis (TB) infection. (AI) Screening involves reviewing previous history of TB or exposure to TB, previous chest x-rays, and previous tuberculin skin test (TST) results. (AIII)
15. A TST should be performed using purified protein derivative (PPD) unless there is documented history of a previous positive TST, documented TB or a previous severe reaction to PPD. Positive test results should be followed by treatment for latent TB infection (once active TB is ruled out). Induration of ≥ 5 mm is considered a positive result for HIV-positive individuals. (AI)
16. The TST should be repeated annually for individuals with negative baseline TST results and more frequently if there is evidence of new exposure to TB. (AIII) Individuals with advanced HIV disease who initially had negative TST results are also recommended for repeat testing if their CD4 cell counts increase to >200 cells/mm3, indicating immunocompetence sufficient to mount a response to the test. (AIII)
17. All HIV-positive individuals should have a chest x-ray at baseline. (CIII)
18. All HIV-positive individuals should be screened at baseline for *Toxoplasma* IgG antibodies to determine prior exposure to *Toxoplasma (T.) gondii*. (BIII)
19. HIV-positive individuals should be screened at baseline for hepatitis A virus (HAV) using total anti-HAV antibodies. (CIII)
20. 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)
21. 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)
22. HIV-positive individuals should be screened at baseline for syphilis using RPR. (AIII) RPR positive screening results should be verified by FTA-ABS or TP-PA confirmatory test (AI). 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)
23. All HIV-positive individuals should be screened for gonorrhoea and chlamydia (GC) using Nucleic Acid Amplification Test (NAAT) in first void urine specimen for males and cervical swab for females, or in a urine specimen for women without a cervix or those who wish to avoid pelvic examinations. (AII)

Immunizations and HIV

24. All HIV-positive individuals who are susceptible (anti-hepatitis A [HAV] negative) should be vaccinated against HAV. (BII)
25. The HAV vaccine should be administered intramuscularly at the standard dose (AI), at 0, 1 and 6 months. (AII) 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. (BII)
26. 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)

27. In the situations described above, HBV vaccine should be administered intramuscularly at double the regular dose (AI), at 0, 1, and 6 months. (AII)
28. All HIV-positive individuals should be vaccinated against pneumococcal disease using standard vaccine doses. (AI)
29. Vaccination should be given regardless of the CD4 cell counts and repeated once 5 years after the first dose. (AII)
30. 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)
31. All HIV-positive individuals should be offered a tetanus and diphtheria (Td) toxoid booster every 10 years. (AII)

Schedule of Care for HIV-Positive Individuals

32. All HIV-positive individuals not on antiretroviral therapy should have CD4 cell counts and plasma viral loads (pVL) measured every 3 to 4 months. (BII)
33. All individuals initiating antiretroviral therapy should have CD4 cell counts and pVL measured on a monthly basis until pVL is <40 copies/mL, at which time monitoring can occur every 3 to 4 months. Once pVL is consistently <40 copies/mL for one year and CD4 cell counts are consistently over 350 cells/mm^3, monitoring may be extended to once every 6 months in patients with dependable antiretroviral adherence. (CIII)
34. Antiretroviral toxicity should be monitored monthly after initiation of therapy and may be undertaken every 6 months once the patient has been stabilized on an antiretroviral regimen, depending on the known potential toxicities of specific drugs, concomitant medications, and underlying co-morbidities (refer to Table 5). (CIII)

Special Consideration for Women with HIV

35. Pregnancy plans and contraception should be discussed with all women of childbearing potential upon initiation of HIV care and routinely thereafter, as it may affect the choice and timing of antiretrovirals. (AIII)
36. Pregnant women should be treated for HIV infection, regardless of their immunologic or virologic status, to prevent infection of their fetus. (AI)
37. Breastfeeding is not recommended for HIV-positive women in Canada. (AI)
38. Contraceptive counselling should be included as a critical aspect of postpartum care. (AIII)
39. Cervical Pap smear should be done upon initiation of care and should be repeated 6 months later. If results are normal in both tests, the cervical Pap smear should be done annually thereafter. (AI)
40. If Pap smear results are abnormal, women should be referred for colposcopy and directed biopsy, with further treatment as indicated by results. (AII)
41. Mammography for HIV-positive women should follow standard BC guidelines and should be performed annually in women aged 40-49 years and every 2 years for women over 50 years of age. (AI)
42. Providers should perform individualized assessments of breast cancer risk for women aged 40-49 years and inform women of the potential benefits and risks of screening mammography. (BII)

43. Hormone replacement therapy, particularly if prolonged, has been associated with a small increased risk of breast cancer and cardiovascular and thromboembolic morbidity, and its routine use in HIV-positive women is not currently recommended. (AI)
44. Hormone replacement therapy may be considered in women 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)
45. Clinicians should avoid prescribing efavirenz to pregnant women who are in their first trimester, to women who wish to become pregnant, and to women who do not use effective and consistent contraception. (AIII)
46. Clinicians should not prescribe nevirapine to antiretroviral-naïve women who have CD4 cell counts >250 cells/mm^3 or who are pregnant. (AI)
47. Clinicians should avoid prescribing stavudine and didanosine to women due to increased risk of lactic acidosis, unless the benefit outweighs the risk. (CIII)

Long-Term Complications of Antiretroviral Therapy

48. 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)
49. Assess fasting lipids (total, HDL, LDL cholesterol, and triglycerides) at baseline and every 3-4 months once patient begins antiretrovirals, increasing to 6-month intervals when stable. (AIII)
50. Antiretroviral therapy should not be withheld, stopped, or interrupted based on perceived risk of cardiovascular disease. (AI)
51. Fasting blood glucose should be performed in all HIV-positive individuals at baseline and thereafter during antiretroviral therapy at the same intervals as fasting lipids (i.e. every 3-4 months initially, increasing to 6-month intervals when stable). Abnormalities in fasting glucose should be evaluated and managed according to Diabetes Canada guidelines. (AIII)
52. Initial management of blood glucose abnormalities in HIV-positive individuals involves lifestyle changes (weight loss, diet, exercise). (AIII)
53. Insulin-sensitizing agents and insulin should be used as required, keeping in mind drug interactions with some antiretrovirals. (AIII)
54. Clinicians should prescribe newer antiretroviral agents to avoid lipodystrophy where possible (AI)
55. All HIV-positive individuals should be considered at risk for osteoporosis/osteopenia. (AII)
56. Clinicians should undertake preventive measures in all HIV-positive individuals, including weight-bearing exercises, maintaining ideal weight, reducing smoking and alcohol consumption, and increasing vitamin D and calcium intake (in the form of diet and supplements). (AIII)
57. Vitamin D supplementation should be considered for all HIV-positive individuals (e.g. 1000-2000 IU/day). (BIII)
58. Clinicians should consider a dual energy X-ray absorptiometry (DXA) scan to assess bone mineral density at baseline for HIV-positive men and women aged 50 years and older. DXA scan should be repeated at 3-5 year intervals. (BIII)
59. Renal function and risk of renal disease should be assessed in all HIV-positive individuals at baseline and reassessed at least every 6 months (depending on degree of risk). (AIII)

60. Clinicians should monitor blood pressure (BP), creatinine, estimated glomerular filtration rate (eGFR), urinalysis for protein and sediment, and spot urine for albumin to creatinine ratio (UACR) at baseline and every 3-4 months once patients begin antiretrovirals, increasing to 6-month intervals when stable (and increase frequency in cases at high risk of renal disease). (AIII)
61. In case of renal dysfunction, clinicians should adjust doses of medications, including antiretrovirals that are renally cleared. An exception is tenofovir, 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)
62. Patients should be advised to maintain adequate hydration to prevent kidney stones during treatment with indinavir (AIII) or atazanavir. (CIII)

Optimizing Adherence to Antiretroviral Therapy

63. All HIV-positive individuals should have timely access to routine and urgent care that is linguistically and culturally sensitive to patient needs. (BII)
64. An interdisciplinary team model with a primary provider for each patient should be utilized to promote trusting relationships between the patient and his or her health care team. (BII)
65. Potential barriers to adherence such as depression, substance abuse, and mental health conditions, should be identified and addressed prior to initiation of antiretroviral therapy and re-evaluated on an ongoing basis. (BII)

Special Consideration for HIV-Positive Individuals with Addictions

66. All HIV-positive individuals should be asked about substance use at baseline and at least annually. Those with a history of substance use should be re-evaluated for drug and alcohol use at least quarterly. (CIII)
67. 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)
68. HIV-positive substance users receiving concurrent methadone and antiretroviral therapy should be monitored for potential drug-drug interactions. (AII)
69. Substance users are at 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)

Psycho-Social Implications of HIV infection

70. All HIV-positive individuals should have timely access to primary care and treatment. (BII)
71. HIV care and patient education should be provided in a socially, culturally, and gender-appropriate manner using a collaborative and interdisciplinary chronic illness care model which fosters trusting patient-provider relationships. (CIII)
72. Clinicians should perform thorough assessments of the social circumstances of HIV-positive individuals at baseline and re-evaluate annually. (CIII)
73. All individuals living with HIV should be offered referral to an AIDS service organization (ASO) for counselling, social, and peer support. (CIII)

I. Background

A. Introduction

HIV infection has long been seen as a continuous spectrum that follows a well-characterized natural history. Left untreated, HIV will certainly lead to death. Treatment with appropriate antiretroviral combination therapy effectively puts the disease in long-term remission. The advent of potent antiretroviral therapy in 1996, accompanied by advances in prophylaxis against opportunistic infections and access to care, significantly improved the management of HIV infection and led to substantial reductions in HIV/AIDS-related morbidity and mortality.[4] In order for the treatment to be effective, individuals must be fully engaged in care, from diagnosis, linkage, initial engagement, retention, and timely initiation of antiretroviral therapy and effective psychosocial support systems.

The clinical course of HIV infection can be highly variable, with extremes of disease progression from onset of acquired immune deficiency syndrome (AIDS) within 12 months after seroconversion to continuous asymptomatic infection for more than 20 years. The loss of CD4+ T-lymphocytes (CD4 cells) is one of the hallmarks of HIV infection and ultimately leads to immunodeficiency. There remains some debate regarding the mechanism by which CD4 cells are lost, but a process involving direct virus-mediated cell death as well as virus-driven chronic immune activation and increased cell turnover is now well accepted.[5] For both mechanisms, the level of HIV in the plasma (viral load) seems to be the driving force. The clinical course of HIV infection is therefore determined by the HIV viral load, which itself is determined by the interplay between viral and host factors, including genetic factors. More recently it has become apparent that the often clinically asymptomatic interval between HIV infection and the development of AIDS is characterized by active ongoing inflammation. This is often characterized by marked elevation of inflammatory markers, including hs-CRP, IL2, and d-dimmer. More importantly, this is now widely regarded as the driver of endothelial dysfunction and end organ damage associated with untreated HIV infection. Of interest, the magnitude and therefore the consequences of this inflammatory state have also been correlated with the level of the plasma HIV viral load.

Presently, HIV infection is considered a chronic disease, and the life expectancy of HIV-positive individuals has significantly increased since the introduction of antiretroviral therapy. In 2007, Lohse and colleagues[6] showed that survival in HIV-positive individuals in Denmark improved significantly from 1995 to 2005. However, life expectancy was still 10 years shorter for HIV-positive individuals compared with HIV-negative controls. Thus, living with HIV, despite the availability of therapy, appears to still be associated with a measurable decrease in life expectancy.

B. HIV Expertise in Clinical Care

Many studies have demonstrated that better outcomes are achieved in HIV-positive outpatients cared for by a clinician with HIV expertise [4, 7-11], 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.

C. Modes of HIV Transmission

The key modes of HIV transmission - sexual contact, exposure to infected blood through sharing of injection drug use paraphernalia or receipt of contaminated blood products, and perinatal transmission—were clarified early in the AIDS epidemic. In untreated HIV-positive individuals, HIV is present in significant concentrations in blood, semen, cervical mucus, and other body fluids such as breast milk. The likelihood of HIV transmission by different routes varies, as shown in Table 2 (adapted from Garcia-Tejedor and Lewthwaite).[12, 13]

Table 2: Methods of HIV Transmission

Method	Risk of Acquisition per 100 exposures (%)*
Sexual	0.2-0.5
Parenteral (blood or blood product recipient)	90
Vertical	18-25
Intravenous Drug Use	0.5-1.0
Occupational Injury	0.2

* 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.[14-18] 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 his/her HIV status
- The nonspecific "flu-" or "mono-like" symptoms of acute HIV infection may be either absent or unrecognized as an indication of HIV infection

Detection of acute HIV infection provides an opportunity to follow patients prospectively soon after infection and thereby reduce disease progression and incidence of opportunistic infections. Patients with a recent diagnosis of HIV are more likely to reduce risk behaviours if they are

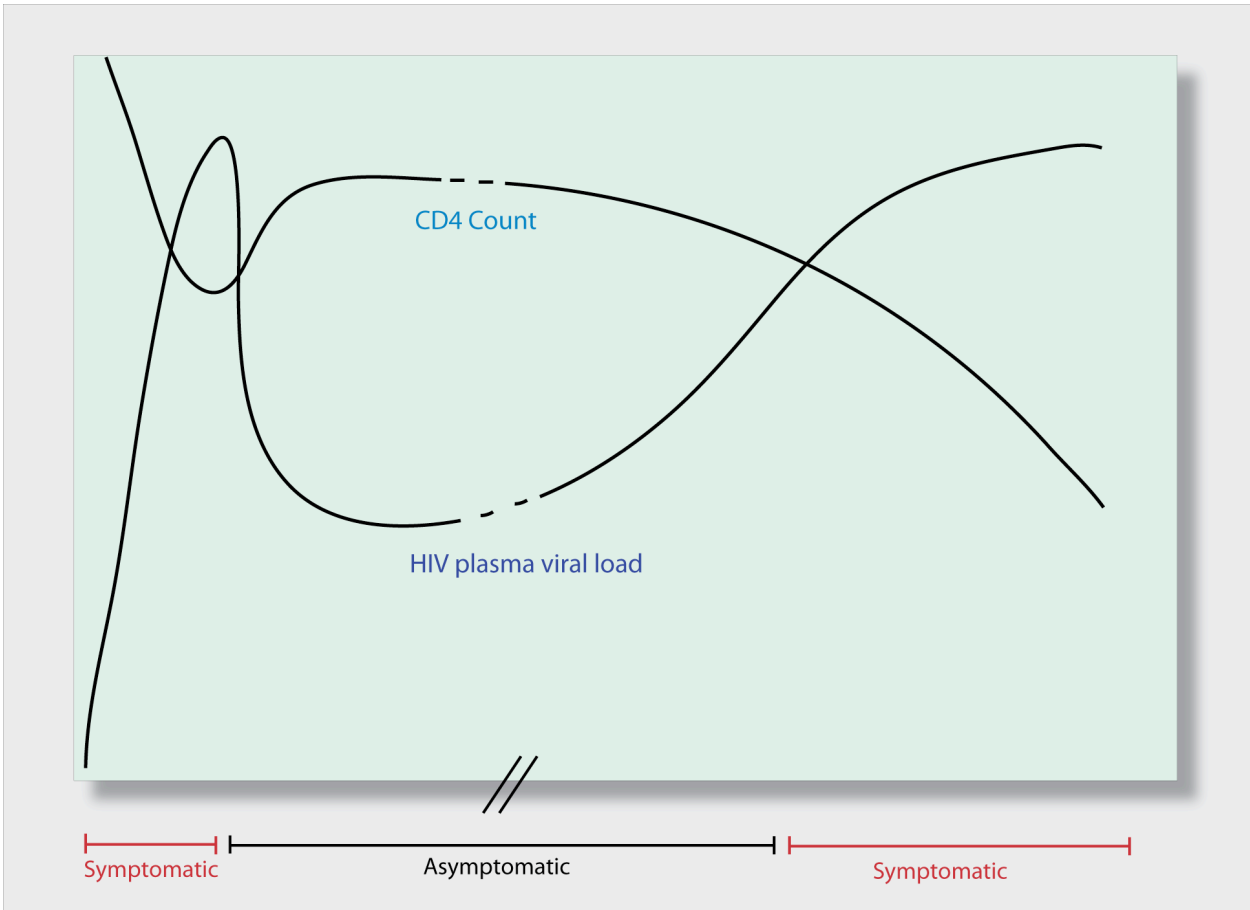
linked to primary HIV care than if they are not receiving care. Thus, early detection may also be a critical component of preventing further transmission.[19] The transmission of HIV through exposure to the bodily fluids of a positive individual is clearly established. Recent treatment with antiretroviral therapy reduces HIV-1 RNA plasma concentrations predictably to undetectable concentrations in most treated patients. Furthermore, the use of antiretroviral treatment leads to a marked reduction in HIV-1 RNA concentrations in both the female genital tract and in semen.

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 ecological evidence.[20] 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.[20] 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.[2]

D. Natural History of HIV/AIDS

After the initial drop in CD4 cell counts and peak of viremia during seroconversion, CD4 cell counts will increase to levels typically below pre-infection levels, and viral load will decrease and stabilize to a set point for several years (Figure 1). There is considerable variability in time to onset of symptoms and late-stage disease. Patients whose CD4 cell counts stabilize above 500 cells/mm^3 may remain healthy for years before CD4 cell counts begin to decline. For some patients, CD4 cells counts will drop rapidly after infection; however, the usual scenario is one in which CD4 cell counts decline over approximately an eight-year period until symptoms begin to appear.[13] A small number of individuals (5-10%), called "long-term non-progressors," will maintain low viral load and stable CD4 cell counts for decades without specific treatment.[13]

Figure 1: Natural History of HIV/AIDS (Adapted from Lewthwaite, 2005)[13]



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 stage, viral replication is occurring in lymphoid tissue and thrombocytopenia may occur. HIV may also begin to affect co-morbid conditions such as hepatitis B and C, accelerating 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) (CDC classification category C disease) is defined by the development of specified opportunistic infections and cancers.

In addition, uncontrolled HIV replication and immune activation leads to a chronic inflammatory state, resulting in end-organ damage and co-morbid conditions. It has been shown that the decrease in life expectancy for HIV-positive individuals is also related to chronic immune activation and potentially permanent immune damage.[21, 22]

E. Acute HIV Infection (revised from New York State Department of Health, 2010)[23]

Other terms for acute HIV infection are acute retroviral syndrome, acute HIV seroconversion, and primary HIV infection. Primary care providers should maintain a high index of suspicion of acute HIV infection when certain patients present with flu-like symptoms: those who request HIV testing; those who have had recent 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 unsafe sexual practices with men; those who report needle-use; those who present with a newly diagnosed sexually transmitted infection; those who present with aseptic meningitis; and women who are pregnant or breastfeeding. Unexplained rash, mucocutaneous ulcers, oropharyngeal candidiasis, and meningismus should also alert providers to the possibility of acute HIV infection. Appendix 1 further describes common symptoms and the frequency of their occurrence in individuals who are symptomatic. The mean time from HIV exposure to onset of acute seroconversion illness is generally 2 to 4 weeks, with a range of 5 to 29 days, [24] although only an estimated 34% of HIV-positive individuals will experience symptomatic seroconversion illness.[25]

F. Diagnosis

In HIV testing, the window period refers to the interval between the time when a person is infected and the time at which standard laboratory antibody tests can detect HIV infection (approximately 3 to 6 weeks). At the British Columbia Provincial Public Health Reference Laboratory, the first HIV test applied to a blood specimen is a third-generation enzyme immunoassay (EIA) antibody test.[26] This test has high sensitivity and is used as a screening test. To confirm or to rule out HIV infection, any degree of reactivity on EIA testing leads to a series of further tests, including:

- Fourth-generation EIA test: The fourth-generation EIA test has a shorter window period compared to third-generation EIA tests and is used as a supplemental test in the standard HIV test protocol (i.e. performed when the third-generation EIA test used for screening is reactive).
- Western Blot test: The Western Blot test is considered the gold standard for confirmation of HIV infection. Specimens that are reactive on both EIA screening tests and on Western Blot are considered to be confirmed HIV- positive.
- Individual RNA Nucleic Acid Amplification Test (NAAT): If there is a weak signal on EIA testing and the Western Blot is non-reactive or indeterminate, an individual RNA NAAT is performed. A negative RNA NAAT result can rule out HIV infection.

For further information, please refer to the Other Guidelines Table (Table 8).

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 acute infection. HIV is a reportable infection, and the British Columbia Centre for Disease Control (BCCDC) provides assistance in contact tracing. Baseline HIV genotypic testing should be undertaken. 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.[23]

H. 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.[27]

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).[27, 28] In British Columbia, AIDS and HIV are reportable conditions. To facilitate reporting, the BC Centre for Excellence in HIV/AIDS (BCCfE) mails a specially designed form (Appendix 2) and a pre-paid return envelope to all health care providers at the time they enrol patients in the Drug Treatment Program (DTP) and annually thereafter. This process was established with two goals in mind: first, to help providers meet their obligations to report all AIDS cases, and second, to ensure that public health agencies are provided comprehensive surveillance data.

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 at all stages, including treatment initiation, change in treatment regimen, and treatment failure. (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, medication/social/family history, and a review of systems upon patient entry into care. (A-III)
3. A physical examination should be performed at baseline and annually for all HIV-positive individuals, with an emphasis on systems affected by HIV. (CIII)
4. Clinicians should schedule routine monitoring visits at least every 3-6 months for all HIV-positive individuals who are clinically stable and on antiretroviral therapy. More frequent visits should be scheduled for those who are clinically unstable or not on antiretroviral therapy. (CIII)

Evidence (adapted from NYSD, 2007 & Aberg, 2009)[29, 30]:

A comprehensive current and past medical history should be obtained, with an emphasis on HIV-specific issues (Appendix 3). Important elements include HIV exposure history (date and place of diagnosis, route of exposure), history of acute seroconversion illness, history of prior opportunistic infections or AIDS-related events, antiretroviral regimen history and date of initiation, prior resistance testing, adverse antiretroviral drug reactions, and a patient's understanding of HIV disease and treatment. 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.

Clinicians should perform a comprehensive physical examination at baseline and annually, with particular attention to systems potentially affected by HIV (Appendix 4).

Clinicians should assess patients' vital signs and weight at each visit. Patients with CD4 counts <50 cells/mm^3 should be examined by an ophthalmologist at baseline and every 6 months until CD4 > 100 cells/mm^3. Patients with visual disturbances or unremitting ocular symptoms, regardless of CD4 cell count, should be referred to an ophthalmologist. Regular oral exams should include assessing patients for oral candidiasis, Kaposi's sarcoma lesions, and oral hairy leukoplakia, all of which may be independent indicators of advanced immunosuppression. Clinicians should pay special attention to the examination of a patient's skin, looking for evidence of seborrheic dermatitis, Kaposi's sarcoma, folliculitis, fungal infections, psoriasis and prurigo nodularis. Generalized lymphadenopathy is a common finding during all stages of HIV disease. Lymph nodes should be examined for asymmetry, clustering, sudden increase in size, firmness, and tenderness, which may be indicative of infection, malignancy, or opportunistic infections. Thorough cardiac, pulmonary, and abdominal assessments should be completed for all patients.

An anogenital examination for evidence of rectal cancer in all patients at risk, prostate cancer in men, and sexually transmitted infections, including condylomata and *Herpes simplex* infection, should be performed at baseline and annually thereafter. Regarding neurological examinations, clinicians should examine for sensory and motor abnormalities, cerebellar function, motor and sensory abnormalities, especially peripheral neuropathy, and cognitive impairment. Mental health and substance use assessments should be performed at baseline and annually thereafter. For more information on aspects of physical examinations specific to women, please refer to the Special Consideration for Women section of this document.

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. (A-III)
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 drug resistance using genotypic drug resistance testing regardless of the estimated duration of the infection. This should be ideally done by testing the first available HIV plasma viral load sample (AIII). Note that genotypic resistance testing can be performed on archived plasma samples.
4. If antiretroviral therapy is deferred, 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[30, 31] or outside of their local jurisdiction (i.e. in a different province or country), resulting in an absence of prior documentation.[32] There is also the possibility of testing errors (specimen handling or mislabelling) among individuals identified as HIV-positive for the first time.[31] Patients may also be unclear about whether an HIV test has been performed or may present with misinformation regarding previous test results.[33, 34]

CD4 cell counts (absolute and fraction) are significant clinical indicators of immunocompetence in patients with HIV infection.[32, 33, 35] These markers are used to stage HIV disease initially and subsequently are used as a predictor of disease progression and survival.[36, 37] They 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.[38] Moreover, CD4 cell counts are key factors in determining the need for antiretroviral therapy[26, 32, 34, 35] and to evaluate patient response to therapy.[39] 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/uL (or cells/mm^3) and fraction of lymphocytes expressed as a percentage (e.g. absolute CD4 cell count: 500 cells/uL (or cells/mm^3), and fraction: 25%). The less common measure uses fraction numbers of cells x 10*9/L (e.g. absolute CD4 cell count: 0.500 cells x 10*9/L and the fraction: 0.25), requiring some calculations to convert to the more explicit method of absolute cell count.

Plasma viral load testing is another useful way to assess patient prognosis[32] and to determine a patient's need for antiretroviral therapy.[35] The association between a decrease in plasma viremia and improved outcomes has been well-established [39]; thus, HIV plasma viral load is an essential indicator of therapeutic response and for identifying patients who are failing therapy.[37, 40] HIV plasma viral load is also useful in predicting clinical progression.[41, 42]

Current laboratory assays in use for quantifying HIV plasma viral load have good correlation across their linear range. However, concordance at the lower level of quantification is generally poor.[43] This is of particular interest in British Columbia because after the introduction of the Roche TaqMan test (range from 40 - 10,000,000 copies/mL), a significant number of specimens with low-level viremia have been reported. This makes the interpretation of such results and their relevance to the clinical management of HIV-positive individuals receiving antiretroviral therapy challenging. In this setting, review of a patient's adherence level and close monitoring (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.

Drug-resistant virus can be transmitted from one person to another and lead to suboptimal virological response to initial antiretroviral therapy.[44-47] Results of drug resistance testing are useful in guiding initial antiretroviral therapy and assessing failing therapy[23, 48] and have been shown to improve the outcomes of people taking antiretrovirals.[48] 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. However, it is a test that has relevance when considering the use of CCR5-receptor antagonist drugs, such as maraviroc. For more information about indications and type of tropism testing, please consult the BCCfE Therapeutic Guidelines.[35]

*C. HLA-B*5701*

Recommendations:

1. All patients should be screened for HLA-B*5701 prior to initiating therapy with abacavir. (AI).
2. Although not all patients will be exposed to abacavir, in British Columbia, HLA-B*5701 testing is recommended at baseline, and results should be recorded for future use (CIII). This testing only needs to be performed once per patient.
3. HLA-B*5701-positive patients should not receive abacavir. (AII)
4. 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)

Evidence:

HLA-B*5701 is not a specific HIV viral test. However, screening for HLA-B*5701 identifies persons at 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 formulations). 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 previously undertaken for patients re-initiating abacavir following a gap in therapy who had previously tolerated the drug, due to the potential for HSR in this setting.[49-53] 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. For more information about indications for abacavir and screening for HLA-B*5701, please consult the BCCfE Therapeutic Guidelines.[35]

Table 3: HIV Disease Specific Tests

	Test	Baseline	Follow-up Before Antiretroviral Initiation	After Antiretroviral Initiation
HIV Infection Status	HIV Diagnostic test			
Immunologic Assessment	CD4 absolute count and percentage	√	Every 3 - 4 months	Monthly until HIV pVL undetectable, then every 3-6 months
HIV Plasma Viral Load	Quantitative RNA testing	√	Every 3 - 4 months	Monthly until HIV pVL undetectable, then every 3-6 months
Drug Resistance Testing	HIV genotypic drug resistance	√ (At the time of first HIV pVL)	At the time of initiation of ARV	Test if ARV treatment failure or incomplete pVL suppression (>250 HIV copies/mL)
Other	HLA-B*5701	√	At baseline or before initiating or restarting therapy with abacavir, if not previously done	Test patients not previously screened and currently taking abacavir
Other	Tropism testing		When considering a CCR5 antagonist	

Abbreviations:
HIV = Human Immunodeficiency Virus
ARV = Antiretrovirals
HIV pVL= HIV plasma Viral Load
HSR = Hypersensitivity Reaction

IV. Screening and Immunization for Selected Co-morbid Infections

PART 1: SCREENING FOR CO-MORBIDITIES

A. Tuberculosis Screening

Recommendations:

1. All HIV-positive individuals should be screened at baseline for *Mycobacterium tuberculosis* (TB) infection. (AI) Screening involves reviewing previous history of TB or exposure to TB, previous chest x-rays, and previous tuberculin skin test (TST) results. (AIII)
2. A TST should be performed using purified protein derivative (PPD) unless there is documented history of a previous positive TST, documented TB, or a previous severe reaction to PPD. Positive test results should be followed by treatment for latent TB infection (once active TB is ruled out). Induration of ≥ 5 mm is considered a positive result for HIV-positive individuals. (AI)
3. The TST should be repeated annually for individuals with negative baseline TST results and more frequently if there is evidence of new exposure to TB. (AIII) Individuals with advanced HIV disease who initially had negative TST results are also recommended for repeat testing if their CD4 cell counts increase to >200 cells/mm3, indicating immunocompetence sufficient to mount a response to the test. (AIII)

Evidence:

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.[54] The risk of acquiring TB increases with advancing immunosuppression and decreases in patients receiving effective antiretroviral therapy.[55, 56] 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.[57] Thus, the identification of latent TB infection (LTBI) and the implementation of measures to prevent 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 to 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 the HIV-positive individual.[57] The sensitivity of the TST decreases in parallel with a patient's CD4 cell count. However, TST remains the standard method of diagnosing LTBI.[57]

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; those with major viral infections (excluding HIV); 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.[57]

Review of the previous chest x-rays, TST results, and history of tuberculosis disease or exposure is part of the TB screening for the HIV-positive individual.[38] 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.[58] A systematic review including eleven clinical trials concluded that treatment of LTBI significantly reduces the risk of active TB in HIV-positive individuals with a positive TST.[59]

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 increased risk of having radiographic abnormalities.[30] Because of the potentially high prevalence of these risk factors in the HIV-positive population in BC, it is important to perform chest x-ray at baseline in all HIV-positive individuals not only to rule out abnormalities but also to be used as 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.[38] Toxoplasma encephalitis is the most frequent clinical manifestation of central nervous system (CNS) disease in HIV-positive individuals.[60] While positive serology identifies individuals at greater risk, up to 16% of those presenting with CNS toxoplasmosis will have negative serology.[60] 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%.[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 through ingestion of 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.[61] In Canada, the number of cases of HAV has steadily declined since 2003.[62] 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.[62-64] Pre-immunization serologic testing is only cost-effective in populations that have a seroprevalence of >30%.[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.[62] 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 injection drug users [IDU]), sexual (anal, vaginal and oral) and vertical transmission.[61] The reported prevalence of HIV-HBV co-infection is between 6-10%, with higher rates observed in IDU, in MSM, and in individuals from endemic areas.[65] HIV-HBV co-infection is associated with an 8-fold increase in risk of mortality compared to HBV mono-infection.[66] Therefore, traditional HBV markers such as HBsAg (surface antigen), anti-HBs (surface antibodies) and anti-HBc (core antibodies) will assist in distinguishing those 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 hepatitis B infection should follow standard international guidelines (Refer to Table 8: Other Guidelines).

In Canada, the prevalence of HIV-hepatitis C (HCV) co-infection ranges from 20% to almost 90% in certain subgroups.[67] HCV is highly prevalent among IDU; a review of international studies suggests that between 50-95% of IDU are infected with HCV.[68] Canadian studies report HCV rates as high as 82% among IDU.[69, 70] If left untreated, HCV infection becomes chronic in 50-85% of co-infected individuals, potentially leading to death.[68] A meta-analysis of 17 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.[71] The probability of survival is also reduced among HIV-HCV co-infected individuals compared to those who are HIV mono-infected.[72] Anti-HCV antibody is the standard screening test; however, approximately 6% of HIV-HCV co-infected patients do not develop HCV antibodies.[30] 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 used needles) or those with unexplained abnormally elevated liver enzymes. Patients with confirmed HIV-HCV co-infection should be managed according to current guidelines.[73]

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

Recommendations:

1. HIV-positive individuals should be screened at baseline for syphilis using RPR. (AIII) RPR-positive screening results should be verified by FTA-ABS or TP-PA confirmatory test (AI). 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. All HIV-positive individuals should be screened for gonorrhoea and chlamydia (GC) using Nucleic Acid Amplification Test (NAAT) in first void urine specimen for males and cervical swab for females, or in a urine specimen for women without a cervix or those who wish to avoid pelvic examinations. (AII)

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).[74]

The prevalence of STIs in British Columbia is increasing. In 2009, 11,173 cases of genital chlamydia (251.1 per 100,000 population) and 1,307 cases of genital gonorrhea (29.4 per 100,000 population) were reported in BC, and the provincial prevalence of infectious syphilis decreased for the first time to 4.9 (216 cases) from 7.5 per 100,000 population (328 cases) in 2008. The prevalence of syphilis decreased primarily due to a decrease of syphilis among MSM.[31] The prevalence of asymptomatic syphilis in a cohort of MSM ranged from 2.9% at baseline, 3.2% at 6 months, and 3.2% at 12 months.[74] Syphilis screening for HIV-positive individuals has generally been recommended to be performed at baseline and repeated at least

annually. [30, 75] 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.[74]

Prevalent and incident asymptomatic STIs are common among HIV-positive MSM and 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.[76] Screening for syphilis in British Columbia is performed by using a rapid plasma reagin (RPR) test (a non-treponemal test) confirmed by a specific treponemal test such as TPPA (Treponema pallidum particle agglutination) test.

Rectal and throat swabs (to test for GC) should be considered for patients at-risk (e.g. MSM or women engaging in anal sex).

F. Pap Smear Screening:

Regarding screening for cervical cancer, please see the Special Consideration for Women with HIV section.

Anal cytological screening (anal Pap smear) in HIV-positive women and MSM is not considered standard of care at this time but is being performed in some health care centres. Additional studies of screening and treatment protocols are in progress and will inform the decision to include anal Pap smears as a standard of care.[76]

PART 2: IMMUNIZATIONS AND HIV

Prevention of inter-current illness is a crucial aspect of HIV care.[29, 30] The use of vaccines provides an opportunity to prevent infectious diseases in HIV-positive individuals, who are more susceptible to these diseases.[62] Immunosuppression can reduce the effectiveness of vaccines and potentially increase the risks associated with certain vaccines.[31, 62, 64] 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):[62]

- Tailor immunizations to the needs of each patient
- Make no assumptions about susceptibility or protection
- 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
- Avoid live vaccines unless data are available to support their use or the risk of natural infection is greater than the risk of immunization
- There is no contraindication to the use of inactivated or component vaccines at any CD4 level

A. Hepatitis A

Recommendations:

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

Evidence:

Serologic response rates of all HAV vaccines are between 95-100% amongst HIV-negative individuals.[62] 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).[77, 78] A meta-analysis reported an overall response rate of 64% for HIV-positive individuals.[79] 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.[80] The standard HAV vaccination doses are 1.0 mL intramuscularly (IM).[31]

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. (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 at double the regular dose (AI), at 0, 1, and 6 months. (AII)

Evidence:

The overall seroconversion rate (defined as HBsAb >10 mIU/mL) to standard HBV vaccine dosing (10 ug of Recombivax HB or 20ug of Engerix-B IM [deltoid]) following a 0, 1, and 6 month dosing regimen appears to be on the order of 26-65%.[62, 81-83] 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 count (both ultimate nadir and at time of vaccination), HIV viral load, treatment with antiretrovirals, 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.[80, 84, 85] 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) one month and no longer than 6 months after completion of the initial vaccination series.[86] The intramuscular vaccine delivery route has been shown to be more effective than the intradermal route.[87]

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.[88] Currently, no defined criteria exist for the management of vaccine non-responders; in this situation, consultation with an experienced specialist is encouraged.

C. Pneumococcal Disease

Recommendations:

1. All HIV-positive individuals should be vaccinated against pneumococcal disease using standard vaccine doses. (AI)
2. Vaccination should be given regardless of the CD4 cell counts and repeated once 5 years after the first dose. (AII)

Evidence:

Patients with HIV infection are at higher risk of developing invasive pneumococcal disease than HIV-negative patients.[89-93] *Streptococcus pneumoniae* is the most common agent causing

pneumonia in HIV-positive individuals, followed by gram-negative bacteria, including *Haemophilus influenza, Pseudomonas aeruginosa* and *Legionella pneumophila*.[94, 95] 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, malnutrition, uncontrolled viral replication, and lack of antiretroviral treatment.[96-98]

The efficacy of the pneumococcal vaccine is unclear for HIV-positive individuals with CD4 cell counts <200 cells/mm^3. A study of individuals on antiretroviral therapy showed a failure to induce serotype-specific antibodies when administering the vaccine to patients with CD4 cell counts < 100 cells/mm^3.[99] However, another study demonstrated that although the vaccine failed to prevent the occurrence of invasive pneumococcal disease (IPD), it decreased the severity and mortality of illness related to IPD.[100] Research on the efficacy of the pneumococcal conjugate 7-valent vaccine in HIV-positive individuals has demonstrated the emergence of non-vaccine type pneumococci.[101, 102] There may be a role for a dual vaccination regimen that incorporates the conjugate and polysaccharide vaccine, but further research will need to be done on this topic.[103] The standard pneumococcal vaccination dose is 0.5 mL, subcutaneously (SC) or IM.[31]

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.[62] 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.[62] HIV-positive individuals form part of the group at greatest risk of serious infection, complications, hospitalizations, and/or death from influenza.[62, 104] 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%.[105]

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/mm^3 to 11% in those with lower CD4 cell counts.[106] 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.[106] However, the benefits of the influenza vaccine in preventing severe illness and hospital/intensive care unit admissions prompted the US CDC to recommend the use of the vaccine in HIV-positive individuals regardless of CD4 cell counts or HIV plasma viral load.[107] A single annual intramuscular dose of 0.5 mL is currently

recommended.[31, 62] There is no indication for pre- or post-immunization serology testing.[62] Inactivated influenza vaccine is recommended, and live attenuated intranasal vaccine should not be used in this population.[26, 30, 64]

E. Tetanus and diphtheria

Recommendation:

1. All HIV-positive individuals should be offered a tetanus and diphtheria (Td) toxoid booster every 10 years. (AII)

Evidence:

The recommendations in this section assume 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.[108] 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.[109]

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.[108] After the primary series in immunocompetent individuals, over 99% develop antibody levels that are considered protective against disease.[108] The antitoxin is believed to persist at protective levels for 10 years or more. Titres decline slowly with time but are boosted by additional vaccine doses.[108]

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.[108] The antibody response to tetanus boosters given to adults with HIV or other humoral immune deficiencies is suboptimal.[108]

Table 4: Recommended Vaccines for HIV-positive Adults

Vaccine	Recommendation
Hepatitis A Vaccine (Formalin inactivated Monovalent with an aluminium hydroxide or influenza virosome adjuvant)	**Formulations**: Vaqta®, Havrix®, Avaxim®, EpaxalBerna® **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**: RecombivaxHB ® (10 mcg/1.0 ml) or Engerix B ® (20mcg/1.0ml) **Schedule**: 0, 1, 6 months for susceptible individuals. **Dosage**: 2ml (20 mcg of RecombivaxHB or 40 mcg of Engerix B **Route of administration:** IM
Pneumococcal Vaccine (23-valent pneumococcal polysaccharide vaccine)	**Formulations**: Pneumovax 23®, Pneumo23®, Pnu-immune®. **Schedule**: Initial dose plus a single booster five years after initial vaccination **Dosage**: 0.5 ml **Route of administration:** IM
Influenza Vaccine (Inactivated split-virus vaccine)	**Formulations**: Fluviral ® and Vaxigrip® **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

V. Schedule of Care for HIV-Positive Individuals

Recommendations:

1. All HIV-positive individuals not on antiretroviral therapy should have CD4 cell counts and plasma viral loads (pVL) measured every 3 to 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, at which time monitoring can occur every 3 to 4 months. Once pVL is consistently <40 copies/mL for one year and CD4 cell counts are consistently over 350 cells/mm^3, monitoring may be extended to once every 6 months in patients with dependable antiretroviral adherence. (CIII)
3. Antiretroviral toxicity should be monitored monthly after initiation of therapy and may be undertaken every 6 months once the patient has been stabilized on an antiretroviral regimen, depending on the known potential toxicities of specific drugs, concomitant medications, and underlying co-morbidities (refer to Table 5). (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 contact with and monitoring of individuals is important because individuals engaged in care are more likely to be adherent to their medications and have improved health outcomes.[110] Moreover, risk of virologic failure decreases with duration of viral suppression.[111-113] All antiretroviral agents are associated with potential adverse effects, which can lead patients to switch or cease therapy.[114] Certain factors may increase the risk of adverse effects for some individuals, such as sex, age, baseline CD4 count, concomitant medical conditions, genetics, and interactions with other medications. Often individuals at higher risk of developing adverse effects are not fully represented in clinical trials, resulting in uncertainty around the frequency and severity of adverse events in real-life clinical settings.

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 have faster progression of HIV disease and is less likely to be routinely evaluated for antiretroviral therapy.[115, 116] In addition, higher rates of co-morbid conditions and antiretroviral toxicities have been observed in older HIV-positive individuals.[117, 118] This requires a shift from focusing solely on CD4, pVL, and AIDS-defining illnesses to a more comprehensive care model that is focused on managing a complex, chronic disease.[119]

Table 5: Laboratory Monitoring [1]

	Test	Baseline	Follow up before antiretroviral therapy initiation	After antiretroviral therapy initiation[2]
Hematologic Assessment [3]	Complete blood count (CBC) with differential with CD4 cell counts and HIV plasma viral load (pVL)	√	Every 3 – 4 months	Every 3 – 4 months increasing to 6 month intervals when stable
Renal Function[4]	Creatinine Estimated glomerular filtration rate (eGFR) Sodium, potassium, chloride, bicarbonate (HCO_3) Phosphate Blood urea nitrogen (BUN) Urinalysis Spot urine for albumin to creatinine ratio (UACR)	√	Annually if stable	Every 3 – 4 months increasing to 6 month intervals when stable
Liver Function Enzyme Tests[5]	Alanine aminotransferase (ALT), aspartate aminotransferase (AST), Total bilirubin, International normalized ratio (INR)	√	Annually if stable	Every 3 – 4 months increasing to 6 month intervals when stable
Fasting Lipid Profile[6]	Total cholesterol (TC), high-density cholesterol (HDL), low-density lipoprotein (LDL), triglycerides (TG)	√	Annually if stable	Every 3 – 4 months increasing to 6 month intervals when stable
Blood Glucose[7]	Fasting Glucose	√	Annually if stable	Every 3 – 4 months increasing to 6 month intervals when stable

1 Clinical and laboratory assessment of relevant co-morbid conditions should be performed at baseline, before initiation of antiretroviral (ARV) therapy and during follow up.

2 The frequency of laboratory monitoring for ARV toxicity depends on the known potential toxicities of specific drugs, concomitant medications, and underlying co-morbid conditions. Monitoring may occur 4 weeks after initiation of therapy, decreasing to up to every 6 months once stable on ARV regimen. In most cases the timing of safety laboratory monitoring can be coordinated with monitoring of HIV RNA and CD4 cell counts.

3 Hematologic abnormalities are common among HIV-positive individuals. A complete blood count (CBC) with differential white blood cells and platelet count is recommended at baseline and routinely thereafter (AIII).

4 Renal function is abnormal in about 30% of HIV-positive individuals. Renal function and risk of renal disease should be assessed in all HIV-positive individuals (AIII).

5 Risk factors for chronic liver disease frequently present among HIV-positive individuals include alcohol use, viral hepatitis, obesity, diabetes, insulin resistance, hyperlipidemia, and hepatotoxic drugs. Liver enzymes and liver function should be assessed in all HIV-positive individuals (AIII).

6 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 ARVs may cause dyslipidemia. Fasting lipid testing, including Total Cholesterol (TC), High Density Cholesterol (HDL), Low Density Cholesterol (LDC) and Triglycerides (TG), should be assessed at baseline (AII). Apolipoprotein B (apoB) levels, now a treatment target, should also be monitored (AIII).

7 Diabetes mellitus is more prevalent in the HIV-positive population than in the general population, particularly in those who are hepatitis C co-infected. Fasting blood glucose should be performed at baseline and thereafter during ARV therapy (AIII).

VI. Special Consideration for Women with HIV

For additional guideline information regarding special considerations for women and HIV, such as pregnancy in HIV-positive women, please refer to Other Guidelines Table (Table 8).

A. Introduction

Globally, over 50% of all people living with HIV are women.[120] In 2008, there were an estimated 14,300 women living with HIV in Canada, accounting for about 22% of the total number of HIV-positive cases nationally and 26% of new infections. The most common mode of transmission for women in Canada is heterosexual transmission, accounting for 71% of cases in 2008, while 29% of HIV cases were attributed to IDU.[121]

The treatment of women with HIV can present certain challenges. Women may have difficulty accessing and maintaining treatment as a result of multiple social determinants, including lack of stable and secure housing, food security, transportation, child care, personal security, and care-giver roles.[122] Many studies have shown that women may experience different and more severe side-effects to antiretroviral therapies compared to men; many women have more difficulty adhering to treatment than men[123], sometimes as a result of side-effects and toxicities.[124] Treatment must be individualized for women, taking into consideration age and reproductive issues such as pregnancy wishes. Importantly, women must be supported in terms of the social and mental health determinants for treatment success.[125]

B. Obstetrical Aspects of Care

Approximately 80% of HIV-positive women are of childbearing age. Since perinatal HIV transmission can be prevented by the appropriate use of antiretroviral therapy, and because of the life-threatening nature of ectopic pregnancy, health care providers should discuss menstrual history, sexual behaviours, and contraceptive practices with their female patients at each visit. The goal of these discussions is to ensure that patients make informed decisions about contraception and reproductive health, and to prevent unintended pregnancies.

C. Contraception and Mother-to-Child Transmission

Recommendations:

1. Pregnancy plans and contraception should be discussed with all women of childbearing potential upon initiation of HIV care and routinely thereafter, as it may affect the choice and timing of antiretrovirals. (AIII)
2. Pregnant women should be treated for HIV infection, regardless of their immunologic or virologic status, to prevent infection of their fetus. (AI)
3. Breastfeeding is not recommended for HIV-positive women in Canada. (AI)
4. Contraceptive counselling should be included as a critical aspect of postpartum care. (AIII)

Evidence:

Pregnancy history should include the number of pregnancies and outcomes (miscarriage, ectopic, preterm, term), significant obstetrical complications, number of living children and the woman's general state of health. Co-infection status (hepatitis B [HBV], hepatitis C [HCV]) should also be assessed and taken into consideration when selecting the antiretroviral regimen to be used. If treatment for HBV is indicated, a full combination regimen for both HIV and HBV should be administered. If a woman takes antiretrovirals for perinatal HIV prophylaxis and she plans to stop therapy postpartum, careful clinical and laboratory monitoring for HBV flare should be performed.[32] Due to limited data on the use of tenofovir in human pregnancy and concerns about potential fetal bone effects, tenofovir should only be used in pregnancy after careful consideration and consultation with an HIV/HBV specialist.

Several protease inhibitors and non-nucleoside reverse transcriptase inhibitors have significant drug interactions with oral contraceptives. Interactions include either a decrease or an increase in blood levels of ethinyl estradiol and/or norethindrone (Tables 14a and 14b, (http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf)), which potentially decrease contraceptive efficacy or increase estrogen- or progestin-related adverse effects, including thrombo-embolic risk. In general, women who are on any of these antiretroviral agents should use an alternative or additional method of contraception (e.g. barrier methods). Similarly, although there is minimal information about drug interactions with 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 are 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.[126, 127] Contraindications to combined hormonal methods, such as diabetes mellitus, hyperlipidemia, and chronic liver disease, are more common in HIV-positive women.

Condom use should be recommended with each sexual act. Condoms reduce the risk of pregnancy, sexually transmitted infections (STIs), and superinfection with different HIV strains. Condoms may reduce risk of HIV infection by approximately 69% [128], but are associated with high rates of failure and are not welcomed by many men. No randomized trials comparing the clinical effectiveness of male and female condoms for prevention of HIV have been performed. Use of female condoms can provide protection from acquisition and transmission of STIs, although data are limited.[129, 130] Female condoms offer an option for individuals and couples who cannot or will not use the male condom. Women should be counseled about the greater effectiveness of condoms when used with a second method of protection. Intrauterine device (IUD) use in the context of HIV remains controversial. It should be avoided in women at increased risk for STIs; however, in low-risk women, the contraceptive benefit of IUD use may outweigh the risk. Spermicides are not recommended for the prevention of HIV transmission because they may increase the risk of HIV acquisition.[131] However, a recent publication indicating that use of tenofovir vaginal gel resulted in a 39% reduction in HIV transmission is the

first evidence that seems promising in this regard[132]; however, further studies are needed to validate results, and the risk of HIV acquisition, though reduced, still exists.

In women who are 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 (Sustiva, Atripla) has been associated with teratogenic effects in primate studies, and there are reports of central nervous system abnormalities in human infants exposed to efavirenz during the first trimester. [133] Other medications occasionally used in women (lithium, ribavirin, statins, angiotensin converting enzyme [ACE] inhibitors and warfarin) are also potentially teratogenic.

If women wish to become pregnant, preconception counseling with a specialized infectious disease obstetrician is recommended, especially for HIV serodiscordant couples who can be counseled 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.

D. Gynaecological care

The incidence and prevalence of gynaecological problems are high among HIV-positive women throughout the course of their HIV disease.[134] 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, STIs and treatments, and prior abnormal Pap results, including subsequent tests and treatments. History of gynecological 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 will by asymptomatic with chlamydia and gonorrhoea infections.

Recommendations:

1. Cervical Pap smear should be done upon initiation of care and should be repeated 6 months later. If results are normal in both tests, the cervical Pap smear should be done annually thereafter. (AI)
2. If Pap smear results are abnormal, women should be referred for colposcopy and directed biopsy, with further treatment as indicated by results. (AII)

Evidence:

Abnormal cervical cytology is ten times more prevalent in HIV-positive women compared with the general female 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 women with HPV infection
- In HIV-positive women who have had a hysterectomy and history of abnormal cervical cytology before or at the time of the procedure. These women are at increased risk for pathological lesion and should undergo screening with vault Pap smears.[135] Although the appropriate interval for screening has not been established, it is reasonable to follow guidelines similar to those for women who have not undergone a hysterectomy, or once yearly.

Specimens that are reported to be unsatisfactory for evaluation should be obtained again as soon as possible. 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.

E. Human Papilloma Virus (HPV)

Over 30 identified strains of Human Papilloma Virus (HPV) are sexually transmitted in both men and women, of which about half are oncogenic. Cervical HPV infections are more prevalent and persistent in HIV-positive women, particularly among women with lower CD4 cell counts.[136] Studies evaluating the impact of antiretrovirals on cervical and anal HPV infection and cytological changes have been inconclusive: some studies have indicated that antiretrovirals were associated with regression of cervical disease [137], while others have not found such an association.[138] Epidemiologic surveys indicate that the overall incidence of invasive cervical cancers has remained unchanged or increased slightly in the era of highly active antiretroviral therapy (HAART). The prevalence of anal HPV is high among HIV-positive women.[139] The clinical significance of these findings is unclear at this time.

A preventive quadrivalent HPV vaccine is currently available for use in Canada in girls and women 13 to 26 years of age. This vaccine includes the HPV strains that are the most common cause of cervical warts (HPV types 6 and 11) and those that are responsible for 70% of cervical cancers (types 16 and 18). There is no evidence that this vaccine has any therapeutic effect on pre-existing cervical dysplasia. In the general population, the vaccine is highly effective in preventing infection and diseases caused by the HPV types included in the vaccine.

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.[140, 141] Due to limited data on safety, immunogenicity and efficacy of the HPV vaccine in HIV-positive women, and lack of data in HIV-positive women over the age of 26, a recommendation for widespread use cannot be made at this time.

The safety, immunogenicity, and efficacy of the HPV vaccine in HIV-positive women is currently being studied in a multicentre Canadian trial in BC, and recruitment is still ongoing in 2011. HPV testing as an adjunct to Pap testing is not currently available in BC outside of research settings.

F. Breast Cancer Screening

Recommendations:

1. Mammography for HIV-positive women should follow standard BC guidelines and should be performed annually in women aged 40-49 years and every 2 years for women over 50 years of age. (AI)
2. Providers should perform individualized assessments of breast cancer risk for women aged 40-49 years and inform women of the potential benefits and risks of screening mammography. (BII)

Evidence:

Breast cancer is the most common cancer among Canadian women and the second-leading cause of cancer-related death in women in the United States. One in 9 Canadian women is expected to develop breast cancer during her lifetime.[142] Breast cancer does not appear to have a higher prevalence among women with HIV, although unusual clinical presentations and rapid progression have been reported, suggesting that breast cancer may behave more aggressively in these patients.[143, 144] As in the general population, screening mammography should be performed before the age of 40 years for women with a personal history of breast cancer, with a first-degree relative with a history of premenopausal breast or ovarian cancer, or with a palpable mass or other suspicious finding on examination.[30]

G. Menopause

Recommendations:

1. Hormone replacement therapy, particularly if prolonged, has been associated with a small increased risk of breast cancer and cardiovascular and thromboembolic morbidity, and its routine use in HIV-positive women is not currently recommended. (AI)
2. Hormone replacement therapy may be considered in women 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)

Evidence:

An increasing number of HIV-positive women are living past menopausal age or are becoming infected when they are over 50 years of age. In Canada, women over 50 years of age constitute 7.6% of the HIV-positive population.[121] A woman is considered menopausal if she has had bilateral oophorectomy with or without hysterectomy, or if she has no menses for 1 year with elevated FSH >40 U/L.[145] 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 women.

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.[146]

Menopausal women are at increased risk of premature bone loss (osteopenia and osteoporosis). 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.[147] The pathogenesis of the reduced bone mineral density noted in HIV-positive individuals is most likely multi-factorial. 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. Both HIV infection and certain medications used commonly in HIV-positive individuals, as well as antiretroviral therapy regimens, have been implicated in the pathogenesis of osteoporosis. Longer follow-up will be needed to clarify factors associated with the high prevalence of osteoporosis/osteopenia in HIV-positive individuals. Periodic bone density screening every 3-5 years should be considered in this setting.[148] For additional information on management of bone loss please refer to the Long-term Complications of Antiretroviral Therapy section.

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.[149] Thus, it is important for physicians to discuss safer sex practices with women of all ages and to consider HIV diagnosis in women above the age of 40 years and those who are menopausal.

H. Special Consideration of Antiretroviral Therapy for Women

Recommendations:

1. Clinicians should avoid prescribing efavirenz to pregnant women who are in their first trimester, to women who wish to become pregnant, and to women who do not use effective and consistent contraception. (AIII)
2. Clinicians should not prescribe nevirapine to antiretroviral-naïve women who have CD4 cell counts >250 cells/mm^3 or who are pregnant. (AI)
3. Clinicians should avoid prescribing stavudine and didanosine to women due to increased risk of lactic acidosis, unless the benefit outweighs the risk. (CIII)

Evidence:

The indications for and goals of antiretroviral therapy are the same for men and women, excluding pregnancy.[32] The risk of teratogenic events of efavirenz was recently estimated in 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.[133] Nevirapine has been associated with an increased risk of symptomatic, potentially

fatal, and often rash-associated liver toxicity among antiretroviral-naïve individuals. Women with higher CD4 cell counts appear to be at greatest risk: a meta-analysis of nevirapine-related clinical trials found that a CD4 cell count of >250 cells/mm^3 at the time of nevirapine initiation was associated with a 9.8-fold increase in symptomatic hepatic events compared with lower CD4 cell counts in women.[150] Introducing nevirapine during pregnancy resulted in higher rates of toxicity and is currently not recommended.[151, 152]

Although lactic acidosis is less common with newer antiretroviral agents, there appears to be a female predominance in the increased incidence of symptomatic and even fatal lactic acidosis associated with prolonged exposure to nucleoside analogues, particularly stavudine and/or didanosine. Women should be warned about the signs and symptoms of lactic acidosis, and levels of liver enzymes and electrolytes should be monitored on a periodic basis.[153]

Several studies indicate that women experience metabolic complications associated with antiretroviral therapy use differently than men. HIV-positive women are more likely to experience increases in central fat with antiretroviral therapy and are at higher risk of developing particular patterns of lipodystrophy.[154] However, women are less likely to have triglyceride elevations on treatment.[155] In addition, women have an increased risk of osteopenia/osteoporosis, particularly after menopause, and this risk may be exacerbated by HIV and antiretroviral therapy.[147, 156]

Table 6: Vaccinations to consider in HIV-positive women

Vaccine	Recommendation
MMR	Recommended if patient was born after 1957, has no evidence of immunity, CD4 >200 cells/mm^3 and is not pregnant. Contraindicated if CD4 <200 cells/mm^3.
Varicella	Recommended if patient has CD4 >200 cells/mm^3 and is not pregnant. Contraindicated if CD4 <200 cells/mm^3. Adults without evidence of immunity to Varicella should receive 2 doses of single-antigen Varicella vaccine if not previously vaccinated, or the second dose if they have received only one dose, unless they have a medical contraindication.[157]
Influenza	Influenza may be associated with greater morbidity in pregnancy, so immunization is recommended.[158] The vaccine should be given routinely, but especially in pregnancy.

I. HIV infection in young women

As a result of increasing survival of HIV-positive individuals, many new challenges have emerged. Youth vertically infected with HIV have to cope with many issues, including stigma, adherence issues, loss of family members, distortion of body image, and negotiation of sexual activity. Special attention needs to be paid to risk reduction counseling and secondary prevention in early adolescence, especially in young women who have been vertically infected and are currently struggling with growing to be young women and potentially mothers themselves.

VII. Long-Term Complications of Antiretroviral Therapy

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.[159] 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.[30] 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.

The frequency of lab monitoring for antiretroviral toxicity depends on the known potential toxicities of specific drugs, concomitant medications, and underlying co-morbid conditions. Lab monitoring may occur every 4 weeks after initiation of therapy, decreasing to up to every 6 months after stabilization of the patient on their antiretroviral regimen.[160] 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. (AI)
2. Assess fasting lipids (total, HDL, LDL cholesterol, and triglycerides) at baseline and every 3-4 months once patient begins antiretrovirals, increasing to 6-month intervals when stable. (AIII)
3. Antiretroviral therapy should not be withheld, stopped, or interrupted based on perceived risk of cardiovascular disease. (AI)

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).[159] Uncontrolled HIV infection, including during antiretroviral therapy interruption, is associated with an unfavourable lipid profile and increased risk of cardiovascular events.[159, 161] However, antiretrovirals are also associated with increased CVD risk, with the rate of CV events increasing by 16% per year of exposure to antiretroviral therapy, particularly protease inhibitors.[162] This 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 CV risk

factors such as age and smoking.[163, 164] The Canadian Cardiovascular Society Guidelines now recognizes HIV as a significant risk factor for premature CVD and an indication for screening for CV risk factors, including lipids.[165] High CV risk is an indication to start antiretroviral therapy in antiretroviral-naïve patients regardless of CD4 cell count.[160] For the same reasons, antiretroviral therapy should not be stopped due to concern over perceived high CV risk e.g. to correct dyslipidemia.[30, 162]

Apolipoprotein B (apoB) measurement is subject to less laboratory error than LDL cholesterol, particularly in patients with hypertriglyceridemia[165] (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.[165]

Elevated levels of some inflammatory biomarkers, notably high-sensitivity C-reactive protein (hsCRP), are independently associated with a high risk of myocardial infarction in the HIV-positive population,[166] as in the general population.[167] 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 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,[165] but may underestimate CV risk in the setting of HIV infection.[168] The Reynolds Risk Score (www.reynoldsriskscore.org), which incorporates family history and hsCRP as well as traditional CV risk factors, may be a more accurate alternative but has not yet been validated in a Canadian population nor in HIV.[165] Regardless of underlying CV 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.[165] Smoking cessation is particularly critical[30] and has been demonstrated to reduce clinical CV events in a large HIV-positive population.[169] Dyslipidemia, where present, should be managed according to current general population guidelines,[165] taking into account potentially significant drug-drug interactions between lipid-lowering agents and antiretrovirals (e.g. statins and protease inhibitors) (www.hiv-druginteractions.org). Of note, HIV-positive individuals may not reach desirable lipid targets with conventional statin therapy[170] and combination therapy may be necessary.

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

Recommendations:

1. Fasting blood glucose should be performed in all HIV-positive individuals at baseline and thereafter during antiretroviral therapy at the same intervals as fasting lipids (i.e. every 3-4 months initially, increasing to 6 month intervals when stable). Abnormalities in fasting glucose should be evaluated and managed according to Diabetes Canada guidelines. (AIII)

2. Initial management of blood glucose abnormalities in HIV-positive individuals involves lifestyle changes (weight loss, diet, exercise). (AIII)
3. Insulin-sensitizing agents and insulin should be used as required, keeping in mind drug interactions with some antiretrovirals. (AIII)

Evidence:

DM is more prevalent in the HIV-positive population than in the general population, particularly in those who are co-infected with hepatitis C.[30, 171] 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.[30] Traditional risk factors for DM remain relevant in HIV-positive individuals.

D. Lipodystrophy

Recommendations:

1. Clinicians should prescribe newer antiretroviral agents to avoid lipodystrophy where possible (AI)

Evidence:

HIV-associated lipodystrophy encompasses fat loss (lipoatrophy) in the face, buttocks, extremities and/or fat gain (lipohypertrophy) in the trunk.[172] Lipoatrophy is mainly due to the mitochondrial toxicity of older nucleoside reverse transcriptase inhibitors (NRTIs) (stavudine, zidovudine)[173] and is less common with the use of new NRTIs (tenofovir, abacavir).[174] Lipohypertrophy is mainly associated with exposure to older protease inhibitors[175] and appears to be a less common complication with the use of newer protease inhibitors and other drug classes (nonnucleoside reverse transcriptase inhibitors, integrase inhibitors); however, it is still observed to some extent with regimens currently in use.[174, 176-180] Of concern is that lipodystrophy may result in an increase in visceral adipose tissue (VAT) mass; in the general population, increased VAT is associated with CVD, type-2 diabetes, and all-cause mortality.[181-183] Lifestyle changes (diet and exercise) may be partially effective in reducing VAT and its associated risk of metabolic disorders in the general population,[184, 185] but have less effect on HIV-associated lipohypertrophy. For HIV-positive individuals with signs of lipodystrophy on an older antiretroviral regimen, a switch to newer agents should be considered early, because treatment of established lipodystrophy is difficult, costly, and may be only partially effective. For lipoatrophy, surgical fillers (e.g. polylactic acid) may be of short-term benefit, while growth hormone[186] or the growth-hormone releasing factor tesamorelin[187] may be useful in cases of lipohypertrophy, although these agents are administered by injection and their effect wanes after treatment is discontinued.

E. Bone disease

Recommendations:

1. All HIV-positive individuals should be considered at risk for osteoporosis/osteopenia. (AII)
2. Clinicians should undertake preventive measures in all HIV-positive individuals including weight-bearing exercises, maintaining ideal weight, reducing smoking and alcohol consumption, and increasing vitamin D and calcium intake (in the form of diet and supplements). (AIII)
3. Vitamin D supplementation should be considered for all HIV-positive individuals (e.g. 1,000-2,000 IU/day). (BIII)
4. Clinicians should consider a dual energy X-ray absorptiometry (DXA) scan to assess bone mineral density at baseline for HIV-positive men and women aged 50 years and older. DXA scan should be repeated at 3-5 year intervals. (BIII)

Evidence:

HIV-positive individuals are at greater risk of fractures than non-infected individuals [188] The loss of bone density associated with normal aging is accelerated by HIV infection and by exposure to antiretrovirals.[189] The role of specific antiretrovirals in causing bone loss is controversial and inconsistent, with most evidence pointing to tenofovir and possibly ritonavir-boosted protease inhibitors as the leading culprits.[190] 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. Regarding the use of 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.[191] Osteoporosis cannot be diagnosed using DXA alone in men aged less than 50 years or in premenopausal women;[192] 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[190, 193] – although in this context, HIV may be considered a sufficient risk factor.

With or without DXA results, a patient's 10-year risk of fracture can be assessed using the World Health Organization (WHO) Fracture Risk Assessment tool (http://www.sheffield.ac.uk/FRAX/); however, this instrument has not been validated for use in Canada or in patients with HIV.

Most HIV patients have low vitamin D levels,[194] as does the general North American population;[195] therefore, there is insufficient evidence to support routine measurement of vitamin D levels in HIV-positive individuals. Supplementation with vitamin D at doses of 1,000 to 2,000 international units daily is inexpensive, safe, and is not associated with known interactions with antiretroviral drugs. If dietary calcium intake is inadequate, a calcium supplement should be considered.

F. Renal disease

Recommendations:

1. Renal function and risk of renal disease should be assessed in all HIV-positive individuals at baseline and reassessed at least every 6 months (depending on degree of risk). (AIII)
2. Clinicians should monitor blood pressure (BP), creatinine, estimated glomerular filtration rate (eGFR), urinalysis for protein and sediment, and spot urine for albumin to creatinine ratio (UACR) at baseline and every 3-4 months once patients begin antiretrovirals, increasing to 6-month intervals when stable (and increase frequency in cases at high risk of renal disease). (AIII)
3. In case of renal dysfunction, clinicians should adjust doses of medications, including antiretrovirals that are renally cleared. An exception is tenofovir, 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)
4. Patients should be advised to maintain adequate hydration to prevent stones during treatment with indinavir (AIII) or atazanavir. (CIII)

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, hypertension, hepatitis B or C, and other liver disease).[196] Classic HIV-associated nephropathy (HIVAN), due to direct infection of renal epithelial cells with HIV, is relatively uncommon in BC. 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.[160] Despite a small potential for nephrotoxicity, overall large studies show that current antiretroviral therapy is beneficial for renal function.[159, 197]

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
- Related to nephrotoxic medications (notably nonsteroidal anti-inflammatory drugs) including some antiretrovirals
- Drug interactions, e.g. tenofovir/didanosine (tubular dysfunction); 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, especially in patients with other risk factors or eGFR <90 mL/min at baseline[198]
- Other NRTIs (didanosine, stavudine, and lamivudine) rarely associated with tubular disorders

- Nephrolithiasis risk with indinavir (4%)[199] and atazanavir (rare).[200] Indinavir is not recommended in current treatment guidelines.[160]
- Rarely, acute interstitial nephropathy (AIN) with reversible acute renal failure has been described in association with hypersensitivity reactions to abacavir, efavirenz, and atazanavir

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 are often 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; maraviroc) 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 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 should be discontinued if possible and replaced with another agent (e.g. abacavir if HLA-B*5701 negative) rather than dose-reduced.

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 sensitive to patient needs. (BII)
2. An interdisciplinary team model with a primary provider for each patient should be utilized to promote trusting relationships between the patient and his or her health care team. (BII)
3. Potential barriers to adherence such as depression, substance abuse, and mental health conditions, should be identified and addressed prior to initiation of antiretroviral therapy and re-evaluated on an ongoing basis. (BII)

Evidence:

High levels of adherence to antiretroviral therapy (≥95%) are necessary to ensure the optimum effect of treatment on HIV disease progression.[201] Near perfect adherence (80-95%) leads to a high probability of the development of drug resistance; therefore, patients must be encouraged to take their medications regularly as prescribed. However, 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.[202] 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.[203] 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.[204] Mixed results have been observed regarding the effects of directly observed therapy on adherence and clinical outcomes in hard-to-treat populations.[205, 206] A comprehensive model of HIV care that addresses medical and social issues is essential for providing care to marginalized populations.[110, 207-209] If appropriate, simplification of therapy (e.g. decreased number of daily doses) may enhance adherence to antiretroviral therapy.[210, 211]

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. 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 concurrent methadone and antiretroviral therapy should be monitored for potential drug-drug interactions. (AII)
4. Substance users are at 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.[212] Substance abuse is associated with decreased access to and use of health care, reduced likelihood of being prescribed antiretrovirals, and reduced adherence to antiretrovirals.[213] HIV-positive individuals should be screened annually for substance use even if their baseline screen is negative. Individuals with a known history of substance dependence are at 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.[214] 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 injection drug users (IDU).[215] Methadone maintenance therapy (MMT) is another intervention that has been shown to increase access and adherence to antiretroviral drug treatment among IDUs.[216, 217] Clinicians should closely monitor HIV-positive IDs concurrently receiving antiretroviral therapy and MMT. Common antiretrovirals known to interact with methadone include zidovudine, efavirenz, nevirapine, and lopinavir.[218] For a complete list, please refer to Table 14 (a, b, and c) in the DHHS 2009 guidelines (http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf) or seek advice from a pharmacist with antiretroviral expertise.

There are a number of common co-morbidities among HIV-positive drug 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.[219, 220] 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 drug users are

concentrated, such as the urban poor.[221] Several studies have documented an elevated risk of bacterial pneumonia in HIV-positive drug users.[222-224] The most common IDU-related infectious disease complications are skin and soft tissue infections, which include cellulitis and abscesses.[225-227] Endocarditis is independently associated with HIV infection among IDU.[226] High rates of depressive disorders have also been reported among IDU.[228, 229] 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.

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 BC, 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, for a number of reasons. 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. Indications for prophylaxis, agents of choice, and criteria for discontinuing and restarting primary prophylaxis for Pneuomocystis pneumonia (PCP), Toxoplasma, Mycoplasma (M.) tuberculosis, and M. avium complex (MAC) are shown in Table 7.

Table 7: 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 (adapted from MMWR, 2009)[76]

Pathogen*	Indication	First choice	Alternative	Criteria for discontinuing primary prophylaxis	Criteria for restarting primary prophylaxis
Pneumocystis pneumonia (PCP)	CD4 cell count <200 cells/mm^3 **or** oropharyngeal candidiasis **or** CD4 cell count <14% or history of AIDS-defining illness **or** CD4 cell count >200 but <250 cells/ mm^3 if monitoring CD4 cell count every 1-3 months is not possible	Trimethoprim-sulfamethoxazole (TMP-SMX), 1 double strength (DS) per os (by mouth) (PO) daily; or 1 single strength (SS) PO daily	TMP-SMX 1 DS PO 3 times a week; or Dapsone 100 mg PO daily or 50 mg PO bid; or Aerosolized pentamidine 300 mg via Respigard 11^{TM} nebulizer every month	CD4 cell count >200 cells/mm^3 for >3 months in response to antiretroviral therapy (ART) **or** CD4 cell count 100-200 cells/mm^3 for >3 months in response to ART, and HIV RNA <400 copies/mL[230]	CD4 cell count <200 cells/mm^3, if HIV RNA≥400 copies/mL; **or** CD4 <100 cells/mm^3 if HIV RNA <400 copies/mL
Toxoplasma gondii encephalitis	Toxoplasma IgG positive patients with CD4 cell count <100 cells/mm^3 Seronegative patients receiving PCP prophylaxis not active against toxoplasmosis should have toxoplasma serology retested if CD4 cell count declines to <100 cells/mm^3. Prophylaxis should be initiated if seroconversion occurred	TMP-SMX, 1 DS PO daily	TMP-SMX 1 DS PO 3 times a week; **or** Dapsone 50 mg PO daily + pyrimethamine 50 mg PO weekly + leucovorin 25 mg PO weekly	CD4 cell count >200 cells/mm^3 for >3 months in response to ART, and HIV RNA <400 copies/mL	CD4 cell count < 100-200 cells/mm^3
Mycobacterium tuberculosis infection (TB) [Treatment of latent TB infection (LTBI)]	(+) diagnostic test for LTBI, no evidence of active TB, and no prior history of treatment for active or latent TB (-) diagnostic test for LTBI, but close contact with a person with infectious pulmonary TB and no evidence of active TB 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 50 mg PO daily; **or** For persons exposed to drug-resistant TB, selection of drugs after consultation with public health authorities	Rifampin (RIF) 600 mg PO daily x 4 months; **or** Rifabutin (RFB) (dose adjusted based on concomitant ART) x 4 months	Not applicable	Not applicable
Disseminated *Mycobacterium avium* complex (MAC) disease	CD4 cell count <50 cells/mm^3 after ruling out active MAC infection¶	Azithromycin 1200 mg PO once weekly **or** Clarithromycin 500 mg PO bid **or** Azithromycin 600 mg PO twice weekly	RFB 300 mg PO daily (dosage adjustment based on drug-drug interactions with ART); rule out active TB before starting RFB	CD4 cell count >100 cells/mm^3 for ≥3 months in response to ART	CD4 cell count <50 cells/mm^3

* 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

The development of best practices for the delivery of primary care for HIV-positive individuals necessitates an understanding of the importance of a coordinated care approach. Delivery of HIV care, which includes testing and treatment, must be informed by an array of psycho-social considerations stemming 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. 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.

A. Eligibility and timely access to treatment

Recommendation:

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

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, 231] Currently, all residents of British Columbia are eligible for care and treatment of HIV. However, visitors and persons residing in Canada illegally are not included in this provision. Care providers who are faced with the ethical dilemma of caring for any person not eligible for treatment or care should advocate on their behalf for coverage of the cost of medical treatment.

B. Model of care

Recommendation:

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

Evidence:

The use of a collaborative and interdisciplinary chronic illness model is indicated for HIV primary care; such a model coordinates care of the client at a clinic, community, and individual level.[232, 233] While clinical services begin in the primary care clinic setting, the interdisciplinary collaborative model of care allows for the conceptualization of all the factors and supports that impact the clinical outcomes of successful chronic disease management.[232, 233]

The collaborative and interdisciplinary chronic illness model of care should strengthen and support self-care while assuring effective medical care, prevention, and health maintenance.[234] 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.[32, 234-237] It is essential to this type of health care management that collaborative definitions of problems, goals and planning are clearly established.[33, 234-237]

In addition to having an interdisciplinary team approach, HIV care should foster the development of a strong and trusting patient-provider relationship, preferably between the patient and a primary case manager.[238, 239] 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.[238, 239]

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 referral to an AIDS service organization (ASO) for counselling, social, and peer support. (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.[33] Moreover, clinicians should ensure that individuals' 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. 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 for a list of provincial ASOs.

OTHER GUIDELINES

Table 8: Guidelines related to the care of HIV-positive individuals

Title	URL	Issuing Agency
Antiretroviral Treatment of Adult HIV Infection	http://cfenet.ubc.ca/our-work/initiatives/therapeutic-guidelines/adult-therapeutic-guidelines	BC Centre for Excellence in HIV/AIDS
Therapeutic Guidelines for HIV Exposed and Infected Children	http://cfenet.ubc.ca/sites/default/files/uploads/docs/Pediatric_Therapeutic_Guidelines.pdf	BC Centre for Excellence in HIV/AIDS
Canadian consensus guidelines for the management of pregnant HIV-positive women and their offspring	http://www.bcwomens.ca/NR/rdonlyres/F4FFE776-2CE2-4759-9C6C-DAB0CDCD5301/11075/consensus1.pdf	Canadian HIV Trials Network Working Group on Vertical HIV Transmission
Therapeutic Guidelines for Opportunistic Infections	http://cfenet.ubc.ca/sites/default/files/uploads/docs/Opportunistic_Infection_Therapeutic_Guidelines.pdf	BC Centre for Excellence in HIV/AIDS
Accidental Exposure Guidelines	http://cfenet.ubc.ca/sites/default/files/uploads/docs/Accidental_Exposure_Therapeutic_Guidelines.pdf	BC Centre for Excellence in HIV/AIDS
Drug Interactions in HIV Disease	http://www.hivclinic.ca/main/drugs_interact.html http://www.hiv-druginteractions.org/interactions.aspx	Toronto General Hospital, University Health Network Liverpool HIV Pharmacology Group, at the University of Liverpool
Communicable Disease Control Manual	Immunization Program http://www.bccdc.ca/dis-cond/comm-manual/CDManualChap2.htm Tuberculosis Manual http://www.bccdc.ca/NR/rdonlyres/B17BA4E2-605D-47D7-9B23-053791D9BA7A/0/BCC_TB_Manual_FinalJune2010.pdf Sexually Transmitted Infections (Section I) http://www.bccdc.ca/dis-cond/comm-manual/CDManualChap5.htm HIV testing, reporting, counselling and follow-up, and guidelines on point of care testing http://www.bccdc.ca/dis-cond/comm-manual/CDManualChap5.htm	BC Centre for Disease Control
HIV Laboratory Testing: A Resource for Health Professionals	http://www.bccdc.ca/NR/rdonlyres/2982E293-BD82-436D-B193-F929B5CEEBEC/0/HIVTestinginBCResourceDocumentforHealthProfessionalsJune2010.pdf	BC Centre for Disease Control
Canadian Guidelines on Sexually Transmitted Infections.	http://www.phac-aspc.gc.ca/std-mts/sti-its/pdf/sti-its-eng.pdf	Expert Working Group for the Canadian Guidelines on Sexually Transmitted Infections. Public Health Agency of Canada
Canadian Immunization Guide	http://www.phac-aspc.gc.ca/publicat/cig-gci/pdf/cig-gci-2006_e.pdf	National Advisory Committee on Immunization Public Health Agency of Canada
Canadian Tuberculosis Standards	http://www.phac-aspc.gc.ca/tbpc-latb/pubs/pdf/tbstand07_e.pdf	Public Health Agency of Canada and Canadian Lung Association

1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults	www.cdc.gov/mmwr/[revoew/mmwrhtml/00018871.htm	US Centres for Disease Control and Prevention
Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents	http://aidsinfo.nih.gov/guidelines	US Department of Health and Human Services
Antiretroviral Treatment of Adult HIV Infection: 2010 Recommendations	http://jama.ama-assn.org/cgi/reprint/304/3/321.pdf	International AIDS Society, US Panel
Antiretroviral Drug Testing in Adult HIV-1 Infection: 2008 Recommendations	http://www.iasusa.org/pub/resistance2008.pdf	International AIDS Society, US Panel
Guidelines for the Management of Chronic Kidney Disease in HIV-Infected Patients	http://www.journals.uchicago.edu/doi/abs/10.1086/430257	HIV Medicine Association of the Infectious Diseases Society of America
Hepatitis B and co-infection	http://www.easl.ch/PDF/cpg/EASL_HBV_CPGs.pdf http://www.bhiva.org/HepBC2010.aspx http://www.europeanaidsclinicalsociety.org/guidelines.asp http://www.aasld.org/practiceguidelines/documents/bookmarked%20practice%20guidelines/chronic_hep_b_update_2009%208_24_2009.pdf	European Association for the Study of the Liver British HIV Association European AIDS Clinical Society American Association for the Study of Liver Disease
Hepatitis C and co-infection	http://www.bhiva.org/HepBC2010.aspx http://www.europeanaidsclinicalsociety.org/guidelines.asp http://www.hepatology.ca/cm/FileLib/hepC.pdf http://www.matecmichigan.com/resource/10.Hepatitis/C%20Care%20of%20patients%20coinfected%20with%20HIV%20and%20HCV%202007.pdf	British HIV Association European AIDS Clinical Society Management of Chronic Hepatitis C: Consensus Guidelines International AIDS Society Hepatitis C Co-infection Guidelines 2007
Diabetes Clinic Practice Guidelines 2008	http://www.diabetes.ca/for-professionals/resources/2008-cpg	Canadian Diabetes Association
Canadian Hypertension Guidelines: 2010	http://hypertension.ca/chep/wp-content/uploads/2010/04/FullRecommendations2010.pdf	Canadian Hypertension Education Program
Guidelines for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease in the adult – 2009 recommendations	http://www.ccsguidelineprograms.ca/images/stories/Dyslipidemia_Program/Guidelines/2009_dyslipidemia-guidelines.pdf	Canadian Cardiovascular Society
2010 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada	http://www.cmaj.ca/cgi/rapidpdf/cmaj.100771v1?ijkey=ab94499c2341afa8cc5a2577e9d6c9d4b78ea7bb&keytype2=tf_ipsecsha	The Scientific Advisory Council of Osteoporosis Canada
A practical guide to nutrition for people living with HIV (2007)	http://www.catie.ca/ng_e.nsf/	Canadian AIDS Treatment Information Exchange
BCPWA Healthy Living Manual (2009)	http://www.bcpwa.org/sectionNew.php?section=resources&page=healthy_living_manual	BC Persons with AIDS Society

CONTACT LIST

Organization	Local Number	Other Number	Website
BC Centre for Excellence in HIV/AIDS For HIV treatment and management or guideline inquiries	604-806-8477	HIV/AIDS Treatment Program Information Line 604-806-8515 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	N/A	1-800-665-7677	N/A
HIV preceptorship training opportunities – Dr. Silvia Guillemi	604-806-8415	N/A	Email: sguillemi@cfenet.ubc.ca
BC Centre for Disease Control For HIV testing inquiries	604-707-5600	N/A	www.bccdc.ca
Oak Tree Clinic Inquiries regarding specialized HIV care for postive women, pregnant women, partners, children, and youth	604-875-2212	1-888-711-3030	www.bcwomens.ca/Services/HealthServices/OakTreeClinic/

Provincial AIDS Service Organizations

Organization	Local Number	Other Number	Website
BC Persons With AIDS Society	604-893-2200	1-800-994-AIDS	www.bcpwa.org
Positive Women's Network	604-692-3000	1-866-692-3001	www.pwn.bc.ca
YouthCO AIDS Society	604-688-1441	1-877-968-8426	www.youthco.org
Healing Our Spirit BC Aboriginal HIV/AIDS Society	604-879-8884	1-866-745-8884	www.healingourspirit.org
Western Canadian Pediatric AIDS Society	604-684-1701	N/A	www.campmoomba.com

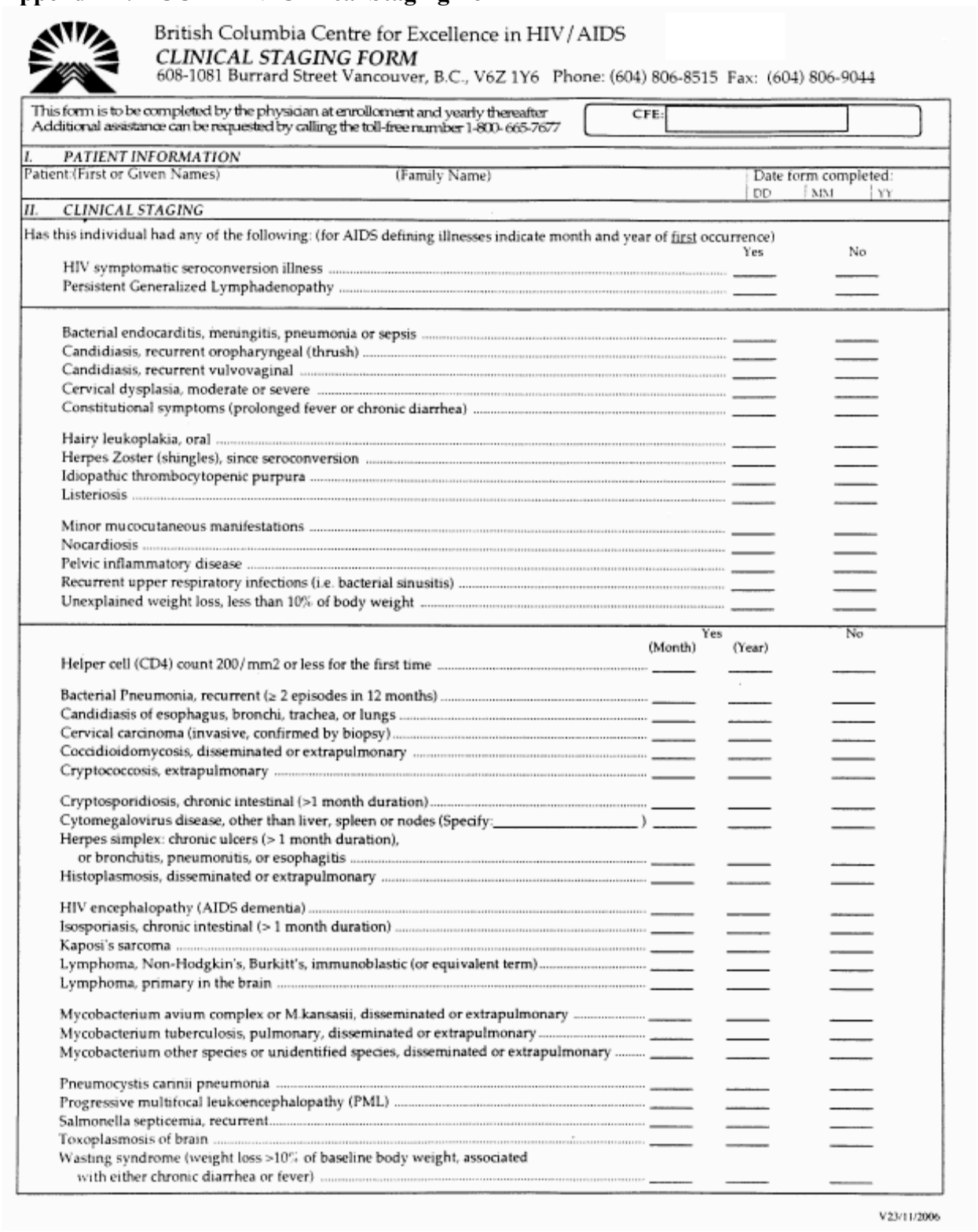
APPENDICES

Appendix 1: Signs and symptoms associated with HIV Seroconversion Syndrome / Acute Retroviral Syndrome*

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

*Adapted from HIV Clinical Resource, New York State Department of Health AIDS Institute (http://www.hivguidelines.org/clinical-guidelines/adults/diagnosis-and-management-of-acute-hiv-infection/) with data from Hecht FM, Busch MP, Rawal B, et al. Use of laboratory tests and clinical symptoms for identification of primary HIV infection. AIDS 2002;16:1119-1129.

Appendix 2: BCCfE HIV Clinical Staging Form



British Columbia Centre for Excellence in HIV / AIDS

CLINICAL STAGING FORM

608-1081 Burrard Street Vancouver, B.C., V6Z 1Y6 Phone: (604) 806-8515 Fax: (604) 806-9044

This form is to be completed by the physician at enrollement and yearly thereafter
Additional assistance can be requested by calling the toll-free number 1-800-665-7677

CFE:

I. PATIENT INFORMATION

Patient:(First or Given Names) (Family Name) Date form completed: DD MM YY

II. CLINICAL STAGING

Has this individual had any of the following: (for AIDS defining illnesses indicate month and year of first occurrence)

	Yes	No
HIV symptomatic seroconversion illness		
Persistent Generalized Lymphadenopathy		
Bacterial endocarditis, meningitis, pneumonia or sepsis		
Candidiasis, recurrent oropharyngeal (thrush)		
Candidiasis, recurrent vulvovaginal		
Cervical dysplasia, moderate or severe		
Constitutional symptoms (prolonged fever or chronic diarrhea)		
Hairy leukoplakia, oral		
Herpes Zoster (shingles), since seroconversion		
Idiopathic thrombocytopenic purpura		
Listeriosis		
Minor mucocutaneous manifestations		
Nocardiosis		
Pelvic inflammatory disease		
Recurrent upper respiratory infections (i.e. bacterial sinusitis)		
Unexplained weight loss, less than 10% of body weight		

	Yes (Month)	Yes (Year)	No
Helper cell (CD4) count 200/mm2 or less for the first time			
Bacterial Pneumonia, recurrent (≥ 2 episodes in 12 months)			
Candidiasis of esophagus, bronchi, trachea, or lungs			
Cervical carcinoma (invasive, confirmed by biopsy)			
Coccidioidomycosis, disseminated or extrapulmonary			
Cryptococcosis, extrapulmonary			
Cryptosporidiosis, chronic intestinal (>1 month duration)			
Cytomegalovirus disease, other than liver, spleen or nodes (Specify:_____)			
Herpes simplex: chronic ulcers (> 1 month duration), or bronchitis, pneumonitis, or esophagitis			
Histoplasmosis, disseminated or extrapulmonary			
HIV encephalopathy (AIDS dementia)			
Isosporiasis, chronic intestinal (> 1 month duration)			
Kaposi's sarcoma			
Lymphoma, Non-Hodgkin's, Burkitt's, immunoblastic (or equivalent term)			
Lymphoma, primary in the brain			
Mycobacterium avium complex or M.kansasii, disseminated or extrapulmonary			
Mycobacterium tuberculosis, pulmonary, disseminated or extrapulmonary			
Mycobacterium other species or unidentified species, disseminated or extrapulmonary			
Pneumocystis carinii pneumonia			
Progressive multifocal leukoencephalopathy (PML)			
Salmonella septicemia, recurrent			
Toxoplasmosis of brain			
Wasting syndrome (weight loss >10% of baseline body weight, associated with either chronic diarrhea or fever)			

V23/11/2006

Appendix 3: HIV-Related History

TABLE 1* HIV-RELATED HISTORY	

General History	• Review sources of past medical care; obtain medical records whenever possible
	• Past hospitalizations, past and current illnesses
	• Tuberculosis history
	  o Possible recent exposure to tuberculosis
	  o 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
	  o Date and place of the diagnosis
	  o 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:
	  o Depression
	  o Anxiety
	  o Post-traumatic stress disorder
	  o Suicidal/violent behaviour
	  o Severe and persistent mental illness
	• Psychotropic medications
	• Past psychiatric hospitalizations
	• Contact information for mental health providers, if applicable

Substance Use History	• Types of drugs; past and current use
	  o Street drugs—marijuana, cocaine, heroin, methamphetamine, ecstasy etc.
	  o Illicit use of prescription drugs
	  o Alcohol
	  o Tobacco
	• Frequency of use and usual route of administration
	• Risk behaviours—drug/needle sharing, exchanging sex for drugs, sexual risk-taking while under the influence of drugs or alcohol
	• History of treatment and barriers to treatment

Sexual History	• Current sexual activity • History of sexually transmitted infections—syphilis, herpes simplex, genital warts, chlamydia, gonorrhea, chancroid • Sexual practices—vaginal, anal, oral • Gender identity • Past and current partners • Risk behaviour assessment, including use of latex or polyurethane barriers, number of partners
Psychosocial Assessment	• Housing status • Employment and insurance status • Educational level • Family and partner contacts • Stability of personal relationships o Domestic violence screening • Immigration status

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

**Adapted from: Primary Care Approach to the HIV-Infected Patient. Office of the Medical Director, New York State Department of Health AIDS Institute. March 2007.*

Appendix 4: HIV-Related Physical Examination

TABLE 2* HIV-RELATED PHYSICAL EXAMINATION [1]	
Blood Pressure, Weight, and Symptoms [2]	• Assess at each visit
Pain Assessment	• Assess at each visit
Ophthalmologic	• Perform or refer for a funduscopic examination[3] when CD4 cell count <50 cells/mm^3
Head, Ears, Nose, Throat	• Sinus infection, odynophagia, dysphagia, hearing loss
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, maceration of the gluteal cleft, Kaposi's sarcoma, onychomycosis, diffuse folliculitis with pruritus, melanoma, medication-related rash
Lymph Nodes [4]	• Particular attention to axillary, posterior cervical chain, supraclavicular, submental, axillary, epitrochlear, femoral
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
Abdominal	• Hepatosplenomegaly, multiple lipomata in the subcutaneous fat, increased visceral fat, abdominal masses or tumours
Genital	• Genitourinary - vaginal or penile discharge, vaginal pain, ulcerative genital disease - venereal warts • Obstetrics/gynaecology - careful pelvic examination *(refer to Special Consideration for Women with HIV Section)*

Rectal	• Visible anal lesions or evidence of skin abnormality around the anus • Digital rectal exam • Symptoms - itching, diarrhea, pain
Musculoskeletal	• Extremities, muscle wasting • Joint inflammatory changes • Peripheral pulses • Evidence of peripheral vascular disease • Peripheral edema
Neuropsychological	• Reflex, sensory, motor, and cerebellar function • Signs of multifocal motor and sensory nerve abnormalities, especially peripheral neuropathy • Cranial nerves • Cognitive status examination • 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. March 2007.*

[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 long-term complications of antiretroviral therapy
(Adapted from EACS guidelines for Prevention and Management of Non-infectious Co-morbidities in HIV, version 5.2)

	Assessment	Pre-ART baseline	Follow-up on ART	Comments
General Medical History	• Personal and family history of relevant co-morbid conditions (e.g. premature cardiovascular disease, hypertension, diabetes, osteoporosis, liver disease, chronic kidney disease) • Concomitant medications • Lifestyle (smoking, alcohol, recreational drugs, diet, exercise)	+ + +	• Update all at each visit (≤q 6mos)	
Cardiovascular disease	• Risk assessment (Framingham risk score) • Blood pressure • Fasting lipids total, HDL, and LDL cholesterol; triglycerides)	+ + +	• At each visit (≤q 6mos) • ≤q 6mos • q 3-4 mo initially, then q6 mo when stable	• 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

Continued on next page…

	Assessment	Pre-ART baseline	Follow-up on ART	Comments
Diabetes	• Fasting blood sugar	+	• q3-4 mo initially, then q6 mo when stable	• Manage blood glucose abnormalities per Diabetes Canada guidelines, with lifestyle changes first (weight loss, diet, exercise) • NB potential drug interactions with ART
Bone disease (osteopenia/ osteoporosis)	• Osteoporosis risk assessment (family history, exercise, weight, smoking, alcohol, calcium and vitamin D intake) • Fracture risk assessment (FRAX) • DXA scan	+ + + for age ≥50 years	• At each visit (≤q 6months) • At each visit (≤q 6months) • 3-5 years (age ≥50 years)	• FRAX not validated for use in Canada or in patients with HIV • Recommend supplementation with Vitamin D 1000-2000 IU/day for prevention • Recommend calcium supplementation if dietary intake inadequate • Use caution in interpreting T-scores in this population
Renal disease	• Risk assessment, including nephrotoxic medications • Blood pressure • Serum creatinine and eGFR; urinalysis; spot urine for albumin to creatinine ratio	+ + +	• ≤q 6months • ≤q 6months • q3-4 mo initially, then q6 mo when stable	•Increased risk for renal disease associated with family history, black race, age ≥50 years, advanced HIV disease (low CD4 nadir), diabetes, hypertension, hepatitis B/C, other liver disease, concomitant nephrotoxic medications, including NSAIDs and some recreational drugs •Increased risk of renal toxicity with certain antiretrovirals, particularly tenofovir and indinavir, also possibly with atazanavir, lopinavir/ritonavir •Diagnosis of abnormalities may require referral to a nephrologist and possible renal biopsy

ART, antiretroviral therapy
DXA, dual energy absoptiometry
eGFR, estimated glomerular filtration rate
NSAIDs, non-steroidal anti-inflammatory drug

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