



BRITISH COLUMBIA  
CENTRE *for* EXCELLENCE  
*in* HIV/AIDS

# THE THERAPEUTIC GUIDELINES ANTIRETROVIRAL (ARV) TREATMENT OF ADULT HIV INFECTION

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*The BC-CfE Therapeutic Guidelines have remained generally consistent but not identical with the IAS-USA Guidelines since 1996. The current Guidelines are consistent with those published by H.F. Günthard et al. in 2014 (Günthard HF, Aberg JA, Eron JJ, et al. Antiretroviral Treatment of Adult HIV Infection: 2014*

*Recommendations of the International Antiviral Society–USA Panel. JAMA 2014; 312(4):410-425). However, the reader should be aware that the use of antiretroviral drugs for the treatment of HIV infection within the BC-CfE programs is exclusively guided by the 2015 Guidelines as outlined here.*

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# TABLE OF CONTENTS

<b>I</b>	<b>GLOSSARY OF ABBREVIATIONS</b> .....	<b>1</b>
<b>II</b>	<b>SUMMARY</b> .....	<b>2</b>
<b>III</b>	<b>INTRODUCTION</b> .....	<b>3</b>
<b>IV</b>	<b>WHEN TO START</b> .....	<b>4</b>
	A. Recommendations .....	4
	B. Evidence .....	4
	C. Special Considerations .....	6
<b>V</b>	<b>WHAT TO START</b> .....	<b>10</b>
	A. Recommendations .....	10
	B. Background .....	10
	C. Cost issues and generic antiretroviral agents .....	16
	D. Nucleoside/nucleotide reverse transcriptase inhibitors .....	16
	E. Nonnucleoside reverse transcriptase inhibitors .....	17
	F. Protease inhibitors .....	19
	G. Integrase strand transfer inhibitors .....	20
	H. CCR5 Receptor Antagonists .....	21
	I. Special considerations .....	21
<b>VI</b>	<b>MONITORING PATIENTS ON ART</b> .....	<b>26</b>
	A. Recommendations .....	26
	B. Background .....	26
<b>VII</b>	<b>TREATMENT EXPERIENCED PATIENTS</b> .....	<b>28</b>
	A. Recommendations .....	28
	B. Background .....	29
	C. Management of initial virologic failure .....	29
	D. Management of multi-drug resistant virologic failure .....	30
	E. Management of immunologic failure .....	30
	F. Switching for ART Regimens for Toxicity or Improved Tolerability and Adherence .....	31
	G. ART Simplification .....	32
<b>VIII</b>	<b>USE OF ART FOR PREVENTION OF HIV INFECTION</b> .....	<b>32</b>
	A. Introduction .....	32
	B. Treatment as Prevention® .....	32
	C. Post-exposure prophylaxis .....	33
	D. Pre-exposure prophylaxis .....	33
<b>IX</b>	<b>ACKNOWLEDGEMENTS</b> .....	<b>34</b>
<b>X</b>	<b>REFERENCES</b> .....	<b>35</b>
TABLES		
	<b>TABLE 1 ART REGIMEN OPTIONS FOR TREATMENT-NAÏVE ADULTS</b> .....	<b>11</b>
	<b>TABLE 2 ANTIRETROVIRAL DRUG DOSING, ADMINISTRATION, AND KEY DRUG INTERACTIONS</b> .....	<b>12</b>

## I GLOSSARY OF ABBREVIATIONS

ACTG	AIDS Clinical Trial Group
AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral Therapy
AUC	Area under the plasma concentration-time curve
BC-CfE	British Columbia Centre for Excellence in HIV/AIDS
BID, b.i.d.	Twice daily
CCR5	C-C chemokine receptor type 5
CD4	Cluster of differentiation 4
CVD	Cardiovascular disease
CYP450	Cytochrome P450
DF	[tenofovir] disoproxil fumarate
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
FDC	Fixed-dose combination
HBV	Hepatitis B Virus
HIV	Human Immunodeficiency Virus
HIVAN	Human Immunodeficiency Virus-Associated Nephropathy
HCV	Hepatitis C Virus
HIV RNA	Human Immunodeficiency Virus Ribonucleic Acid
HLA-B*5701	Human Leukocyte Antigen B*5701 allele
HPTN	HIV Prevention Trials Network
InSTI	Integrase strand transfer inhibitor
MDR	Multi-class drug resistance
NNRTI	Non-nucleoside reverse Transcriptase Inhibitor
nPEP	Non-occupational post-exposure prophylaxis
nRTI	Nucleoside Reverse Transcriptase Inhibitor
OI	Opportunistic infection
PEP	Post-exposure prophylaxis
PI	Protease Inhibitor
PI/r	Ritonavir-boosted Protease Inhibitor
PJP	<i>Pneumocystis jiroveci</i> pneumonia
PrEP	Pre-exposure prophylaxis
pVL	HIV plasma viral load
RCT	Randomized controlled trial
TB	Tuberculosis or <i>Mycobacterium tuberculosis</i>
TDM	Therapeutic Drug Monitoring
TID, t.i.d.	Three times daily
USA	United States of America
VF	Virologic failure

## II SUMMARY

Treatment is recommended for all HIV infected individuals primarily to reduce the risk of disease progression to AIDS and premature death, and secondarily to prevent transmission of HIV. The strength of the recommendation (based on the quality of the evidence) increases with decreasing CD4 count and under specific circumstances, specifically pregnancy, chronic hepatitis C or B infection, or HIV associated nephropathy. Antiretroviral therapy (ART) is recommended for persons during the acute phase of primary HIV infection, regardless of symptoms. ART is not currently recommended for elite controllers (those with HIV-1 RNA below the level of quantification without ART).

ART today represents a life-long therapeutic proposition. It is therefore important to individualize and optimize decisions regarding when and what to start, when and what to switch, and how to best support adherence to ART. Simpler regimens and fixed-dose combinations are generally preferred as there is some evidence to show that they promote and facilitate adherence.

Preferred recommended initial regimens comprise a backbone of two nucleoside/nucleotide reverse transcriptase inhibitors (nRTIs): tenofovir plus either emtricitabine or lamivudine, or abacavir plus lamivudine (the latter being acceptable if the HLA-B\*5701 screening is negative, but should be used with caution if the baseline HIV-1 RNA level is >100,000 copies/mL, depending on the third agent in the regimen); plus either the non-nucleoside reverse transcriptase inhibitor (NNRTI) efavirenz, or the ritonavir-boosted protease inhibitor (PI/r) atazanavir. Alternative third agents can be used in special clinical circumstances such as specific co-infections or concurrent conditions (e.g. pregnancy), or need for certain concomitant medications, or in the presence of pre-existing drug-resistant HIV. Seeking expert advice is highly encouraged in such circumstances. In certain situations, alternative third agents may include the NNRTIs rilpivirine or nevirapine; the PIs darunavir/ritonavir, darunavir/cobicistat, or lopinavir/ritonavir; or the integrase strand-transfer inhibitors raltegravir, dolutegravir, or elvitegravir/cobicistat; or the CCR5 receptor antagonist maraviroc. When requesting access to alternative third agents, prescribers are expected to justify their recommendation at the time of submitting the prescription for review.

The goal of therapy remains the full suppression of viral replication, indicated by a plasma HIV-1 RNA level (viral load) below 40 copies/mL. However, because of the intermittent occurrence of false positive readings with the current plasma HIV-1 RNA assay, a diagnosis of virologic failure should not be arrived at unless there is definitive proof of viral load greater than 250 copies/mL upon repeat testing, particularly if it is increasing and/or genotypic resistance is identified, while the patient is fully adherent to the ART regimen. CD4 cell count and plasma HIV-1RNA level should be monitored frequently after the start of ART: monthly until plasma HIV-1RNA level is confirmed undetectable (i.e. two consecutive HIV-1 RNA results <40 copies/mL at least 2 weeks apart), and every three to four months thereafter. In an adherent, clinically stable patient, if the CD4 is consistently >350 cells / $\mu$ L and the viral load is consistently <40 copies/mL for at least 2 years, plasma viral load can be monitored at intervals up to every six months and monitoring CD4 cell counts is optional. CD4 monitoring should be reinitiated in the presence of virologic failure (plasma viral load consistently >250 copies/mL), a change in the patient's clinical condition (in relation to HIV or any co-morbid conditions), and/or other clinical indications (e.g. concomitant immunosuppressive therapy).

Other parameters that need to be considered include: entry into and retention in care, ART adherence and refill compliance, HIV drug resistance at baseline and upon virologic rebound (confirmed plasma viral

load >250 copies/mL), HLA-B\*5701 screening prior to initiation of abacavir, tropism assay prior to initiation of maraviroc, and impact on concomitant medications and co-morbidities. Safety monitoring for emergent tolerability issues, adverse drug reactions and laboratory toxicities should be done at regular intervals, typically in tandem with the CD4 and plasma HIV-1 RNA monitoring. Therapeutic drug monitoring is not recommended in routine care; however, selected patients might benefit from this intervention.

Confirmed treatment failure (defined by failure to suppress viral load to <40 copies/mL after at least 6 months on ART, or confirmed rebound of viral load >250 copies/mL after initial suppression) should be addressed promptly, taking into account prior treatment history, adherence, co-morbidities, results of resistance testing, and patient preferences, among other factors. An immediate change in the regimen may not be necessary unless new resistance is documented on genotypic testing. It is critically important that the underlying reasons precipitating the failure of the regimen be understood so that these determinants can be adequately addressed before they can similarly affect the outcome of the next regimen. Treatment failures may occur due to virologic, toxicity, tolerance, pharmacological or adherence reasons. Seeking expert advice is strongly encouraged in the assessment and management of treatment failure.

Maintenance of virologic suppression is paramount when switching the regimen to improve tolerability, reduce toxicity, or improve convenience.

### III INTRODUCTION

Confirmed Remarkable advances have taken place over the last 25 years with regard to the potency, tolerability, and simplicity of antiretroviral therapy (ART).<sup>1</sup> As a result, in the developed world where ART is available, the rates of opportunistic diseases and deaths have declined markedly.<sup>2</sup> More recently, it has been definitively shown that ART-driven viral suppression reduces HIV transmission by more than 96% at the individual<sup>3</sup> and population level.<sup>4</sup> Together, these developments have led to the call for the “beginning of the end of AIDS”.<sup>5</sup>

The 2015 BC Centre for Excellence in HIV/AIDS (BC-CfE) Antiretroviral Therapy Guidelines represents an update of the 2013 edition, and aims to capitalize on improved therapeutic options that have become available in the intervening period. Since 1996, the guidelines have been generally consistent with those published by the International Antiviral Society-USA (formerly known as the International AIDS Society-USA) Panel.<sup>6</sup> However, the reader should be aware that the use of antiretroviral drugs for the treatment of HIV infection within the BC- CfE programs is exclusively guided by the Guidelines as outlined here.

## IV WHEN TO START

### A. Recommendations

- Patient readiness for treatment should be carefully considered and optimized. Special effort should be taken to ensure that the patient has adequate adherence education and support.
- ART should be offered on an immediate basis during the acute phase of primary HIV infection, regardless of symptoms or CD4 cell count.
- In chronic HIV infection, ART should be offered regardless of CD4 cell count. The strength of the recommendation increases as CD4 cell count decreases. ART is most strongly recommended on a more urgent basis in the following situations:
  - Symptomatic HIV infection, including AIDS-defining opportunistic infections or cancers
  - Pregnancy
  - Chronic hepatitis B (HBV) co-infection
  - Chronic hepatitis C (HCV) co-infection
  - HIV-associated nephropathy (HIVAN)
  - Lower CD4 cell counts
  - Higher viral loads (>100,000 copies/mL)
  - The HIV-infected member of a serodiscordant couple, regardless of symptoms or CD4 count, to prevent transmission to the HIV-uninfected partner

### B. Evidence

Patient ART should be offered to all HIV infected individuals regardless of their CD4 cell count, with the exception of elite controllers (HIV-1-RNA below the level of quantification without ART). Patients with symptomatic HIV disease or AIDS-defining opportunistic infections or cancers should be offered ART. The strength of the recommendations to start therapy in asymptomatic HIV infection (based on the quality of the evidence) increases with decreasing CD4 count and under specific circumstances (pregnancy, chronic hepatitis C or B infection, or HIV associated nephropathy).

The recommendation to initiate ART regardless of CD4 cell count is supported by data from three randomized controlled trials (RCTs) showing that immediate use of ART is associated with clinical benefit to the individual.

- The HIV Prevention Trials Network (HPTN) 052 study of 1763 HIV serodiscordant couples with CD4 cell counts between 350/ $\mu$ L and 550/ $\mu$ L showed that immediate ART initiation resulted in a 41% reduction in the combined endpoint of disease progression and death<sup>3</sup>.

- In the Temprano randomized controlled trial (ANRS 12136) in Côte d'Ivoire, 2056 HIV-infected adults (78% women) with CD4 nadir <800 cells/μL (median CD4 nadir 465/μL) were randomized to receive ART either immediately or when indicated according to WHO guidelines at the time (i.e. when CD4 <200 from 2008-2009, CD4<350 from 2010-2012, and CD4<500 from 2013-2015)<sup>7</sup>. The risk of severe morbidity (defined as AIDS-defining illness, non-AIDS defining malignancy, or non-AIDS-defining invasive bacterial disease) was 44% lower in the group randomized to receive immediate ART. The same degree of benefit was observed when the analysis was restricted to patients entering the study with CD4 >500 cells/μL.
- More recently, the large, international INSIGHT START trial demonstrated the benefit of initiating ART immediately in patients with CD4 >500 cells/μL as compared to deferring ART initiation until the CD4 had declined to 350 cells/μL.<sup>8</sup> The primary composite endpoint was any serious AIDS-related event, serious non-AIDS-related event (cardiovascular disease, end-stage renal disease, decompensated liver disease, or non-AIDS defining cancer), or death from any cause. After a mean of 3 years of follow-up, the primary endpoint occurred in 1.8% of the patients randomized to immediate ART initiation (42 events / 2326 patients) as compared to 4.1% of the
- patients randomized to deferred ART initiation (96 events/ 2359 patients), for a hazard ratio of 0.43 (95% confidence interval 0.30 to 0.62, p<0.001). In view of the overwhelming clinical benefit demonstrated for early ART initiation among patients with CD4 cell counts >500/ μL, a decision was made to stop the study in May 2015 and offer all participants immediate ART.

As a secondary benefit, immediate ART has also been shown to decrease the likelihood of sexual transmission of HIV by 96% in the HPTN 052 RCT<sup>3</sup>, as well as decreasing HIV transmission within cohorts of injection drug users.<sup>9,10</sup>

There is no CD4 count threshold above which starting therapy is contraindicated, and no demonstrated harm of early ART initiation. Ongoing observational cohorts continue to accumulate data confirming that the benefits of HIV treatment are maximized when it is started earlier in the course of the disease. A combined analysis of 6699 ART-treated individuals in the Multicenter AIDS Cohort Study (MACS) and the Women's Interagency HIV Study (WIHS) showed that those who started treatment early (at CD4>350 /μL) were less likely to die of AIDS-related causes, and more likely to die at an older age, than those who started treatment late (at CD4 <200 /μL) (22% from AIDS causes vs. 51% from AIDS causes, respectively; and median 72 years vs. 66 years, respectively).<sup>11</sup> An analysis of 8185 BC-CfE Drug Treatment Program participants demonstrated a significant decline in mortality, from 6.4% in 2001-2002 to 3.6% in 2011-2012, in concert with the expansion of HAART in the province<sup>12</sup>. In an adjusted model, every 100-cell higher pre-ART CD4 count lowered the risk of death by 16% (adjusted hazard ratio 0.84, 95% confidence interval 0.78 to 0.91).

Prospective cohort studies are also demonstrating the benefits of ART even among individuals with higher CD4 cell counts. In the Collaboration of Observational HIV Epidemiological Research Europe (COHERE) study, HIV+ individuals with a current CD4 count of 500-749 /μL



had a significantly higher rate of AIDS-defining illness, especially cancers, than those with a CD4 count of 750-999/  $\mu\text{L}$ .<sup>13</sup>

Although there is some evidence to consider treatment for elite controllers (HIV-1-RNA below the level of quantification without ART)<sup>14,15</sup>, at this time ART is not recommended for this group<sup>16</sup>. Such individuals should be monitored at no less than semiannual intervals because they are still at risk of disease progression<sup>17,18</sup>.

It is important to confirm that the patient is ready to commit to what today constitutes life-long therapy with a requirement for a very high level of adherence. This is particularly important in view of the potential negative consequences of incomplete adherence in the setting of HIV (specifically, the emergence of drug-resistant virus, which is permanently archived in the individual). Special efforts should be taken to ensure that the patient has adequate adherence education and support.<sup>19</sup> These issues should be regularly evaluated and proactively optimized.

## C. Special Considerations

### 1. Pregnancy

The B.C. Centre for Excellence in HIV/AIDS has updated the recommendations for use of antiretroviral therapy (ART) in pregnancy.<sup>20</sup> ART is indicated for all pregnant women for the mother's health and to prevent mother-to-child HIV transmission. Women on ART at conception should remain on therapy and those not on ART should be started on fully suppressive therapy as soon as possible to reduce the risk of transmission. Teratogenicity concerns and the potential for non-adherence due to morning sickness should not be considered impediments to starting therapy. Few women (0.3%-2.0%) experience hyperemesis gravidarum<sup>21</sup> and adherence appears to be improved rather than reduced during pregnancy.<sup>22,23</sup> ART should not be discontinued postpartum given both the potential benefits for the mother's health and the risks associated with HIV transmission during breastfeeding and with treatment interruption. Treatment of HIV positive women who are pregnant or planning to become pregnant should be done under expert guidance.<sup>24</sup> In BC, practitioners may contact the Oak Tree Clinic at BC Women's and Hospital and Health Centre (604-875-2212; toll free 1-888-711-3030) for advice.

### 2. Opportunistic infections (OIs)

Initiation of ART early after starting active OI treatment has been generally associated with improved survival.<sup>25,26</sup> However, regardless of the OI in question, the potential for drug interactions must be considered (see <http://www.hiv-druginteractions.org> or [http://www.hivclinic.ca/main/drugs\\_home.html](http://www.hivclinic.ca/main/drugs_home.html)).

#### i. Cryptococcal meningitis

The Published data have raised concerns about the timing of ART initiation in the context of cryptococcal meningitis. In a randomized controlled trial (RCT) of 54 patients, ART was begun within 72 hours after diagnosis of cryptococcal meningitis or delayed until completion of 10 weeks of antifungal treatment. The risk of death was 2.85 times higher in the early ART group.<sup>27</sup> Immune reconstitution inflammatory syndrome (IRIS) occurred in patients in both groups, but the increased mortality was

not attributable solely to IRIS. However, this study was conducted in Zimbabwe at a time when patients with cryptococcal meningitis were receiving initial treatment with fluconazole, which has been associated with a slower rate of clearance of cerebrospinal fluid infection and higher mortality compared to amphotericin B plus 5-flucytosine.<sup>28</sup>

In contrast, in another small RCT, 27 patients in Botswana with cryptococcal meningitis receiving induction therapy with amphotericin B were randomized to early (within 7 days) vs late (after 28 days) ART; IRIS occurred in 54% (7/13) and none (0/14), respectively<sup>29</sup>. However, there was no increase in mortality associated with early ART (2/13, 15%) compared to late ART (5/14, 36%;  $p=0.39$ ). The largest RCT to address the optimal timing of ART in cryptococcal meningitis was conducted in Uganda and South Africa<sup>30</sup>. This study included 177

HIV patients who received induction therapy with amphotericin B plus fluconazole and randomized to receive early (1-2 weeks after cryptococcal meningitis diagnosis) or deferred (5 weeks after diagnosis) ART. A similar proportion of patients in each group were recognized to develop IRIS (20% and 13%, respectively;  $p=0.32$ ). However, the 26 week mortality was significantly higher with early vs deferred ART (45% vs 30%; hazard ratio for death 1.73, 95% confidence interval 1.06-2.82;  $p=0.03$ ), particularly among those with few white cells in the cerebrospinal fluid (hazard ratio 3.87). In contrast, pooled data from 9 clinical trials included an evaluation of determinants of mortality in HIV-related cryptococcal meningitis<sup>28</sup>. There was no significant difference in mortality after 1 year between the early (within 31 days) and late (after 31 days) ART initiation groups ( $p=0.3$ ). However, it should be noted that many of the “early” ART group started ART after 3 weeks of antifungal therapy, significantly later than in the above-mentioned studies.

Based on these data, early initiation of ART (before 5 weeks) in the setting of cryptococcal meningitis is not recommended (particularly in patients with  $< 5$  white cells per cubic millimeter in their cerebrospinal fluid), and should be considered only in patients who are receiving appropriate antifungal therapy (amphotericin B plus flucytosine), frequent monitoring, appropriate management of high intracranial pressure, and careful management of other underlying conditions that might influence mortality.

## ii. Tuberculosis (TB)

The Three randomized trials evaluating when to start ART during tuberculosis (TB) treatment demonstrated that early ART improved AIDS-free survival compared with initiating ART after completion of TB treatment. The greatest benefit was achieved in persons with CD4 counts of less than 50 cells/ $\mu$ L, and for this subgroup the optimal time of ART initiation was within the first 2 weeks of TB treatment.<sup>31,32,33</sup> Individuals presenting with higher CD4 counts who deferred ART until 8 to 12 weeks after starting TB treatment had lower rates of IRIS and other adverse events. In all 3 studies, trends toward improved AIDS-free survival were observed across all CD4 count strata, with greatest benefit demonstrated among those with most advanced immunosuppression,

as were rates of IRIS, although deaths attributable to IRIS were few. TB-IRIS can be managed with corticosteroids.<sup>34</sup>

Those persons with CD4 counts > 50 cells/ $\mu$ L should have already initiated ART by the time they have reached 8-12 weeks of TB treatment. The optimal timing of ART for patients with TB meningitis is less certain. An RCT was conducted in Vietnam in which 253 persons with HIV and TB meningitis were randomized to receive standard antituberculous therapy plus either immediate or deferred (2 months later) ART<sup>35</sup>. There was no survival benefit, but a higher rate of grade 4 adverse events (102 vs 87;  $p=.04$ ) in the immediate ART group. In TB meningitis, ART should be started within the first 2 to 8 weeks of diagnosis and managed in consultation with experts.

### iii. **Pneumocystis jiroveci pneumonia (PJP)**

The ART should be initiated within 2 weeks of starting treatment of *Pneumocystis jiroveci* pneumonia (PJP). The ACTG study A5164 was a randomized clinical trial which demonstrated that “early ART” (within 14 days of starting acute opportunistic infection [OI] therapy, median 12 days) was associated with fewer AIDS progression/deaths (odds ratio 0.51; 95% confidence interval 0.27-0.94) compared to “deferred ART” (started after acute OI treatment was completed, median 45 days) after 48 weeks of follow-up<sup>25</sup>. Among the 282 evaluable patients in this study, PJP was the most common OI (63%).

## 3. **Hepatitis B virus (HBV)**

Initiation of ART increases the risk of liver-related morbidity and mortality in persons also infected with HBV. Furthermore, the ability to treat both infections with the same medications (namely tenofovir, emtricitabine, and lamivudine) provides a compelling argument for the concomitant treatment of all HIV and HBV co-infected persons. Prior to initiation of ART, all patients who test positive for hepatitis B surface antigen (HBsAg) should be tested for hepatitis B virus (HBV) DNA to determine the level of HBV replication. Failing treatments may expose the individual to an increased risk for the development of HBV resistance to dually active agents. Discontinuation of ART with anti-HBV activity may cause serious hepatocellular damage resulting from reactivation of HBV; patients should be advised against self-discontinuation and carefully monitored during interruptions in HBV treatment<sup>36</sup>. Alternative treatments for hepatitis B infection should be considered<sup>37,38</sup>.

## 4. **Hepatitis C virus (HCV)**

All HIV-infected patients should be screened for hepatitis C virus (HCV) infection, preferably before starting ART. HIV increases the risk of liver-related morbidity and mortality in persons also infected with HCV. In some, but not all studies, treatment of HIV reduces progression of HCV-related liver disease and ART improves HCV treatment response.<sup>39,40,41</sup> In a recent analysis of the Veterans Affairs Cohort of 10,000 co-infected male patients, initiation of ART reduced the risk of hepatic decompensation on average by 28- 41%.<sup>42</sup> If the CD4 cell count is above 500 cells/ $\mu$ L, ART initiation may be deferred until HCV treatment is completed, especially if there are potential

drug interactions or overlapping toxicities between the two regimens. Canadian guidelines for the management of HIV-HCV co-infection were updated in 2014.<sup>43</sup>

#### **5. HIV-serodiscordant couples**

The concentration of HIV in both blood and seminal plasma correlates with the probability of transmission of HIV to a sexual partner.<sup>44</sup> Reducing levels of HIV with ART decreases the probability of transmission, as confirmed by the HPTN 052 study, which showed ART to be more than 96% effective in reducing HIV transmission from an HIV-infected person to his or her HIV-uninfected partner<sup>3</sup>. A preliminary analysis of the PARTNER Study showed no new cases of HIV among sexual partners of virologically suppressed, HIV-positive ART recipients (586 heterosexual and 308 men who have sex with men) after regular, unprotected sex over a median of 2 years<sup>45</sup>. However, viral suppression in plasma does not guarantee suppression in semen, especially in the presence of inflammation (for example, due to the presence of other sexually transmitted infections),<sup>46</sup> underscoring the importance of continued promotion of safer sex practices, including condom use, in high risk populations.

#### **6. Acute HIV Infection**

Prompt initiation of ART should be offered to all people who are diagnosed in the early or acute stage of HIV infection. Studies have shown that early treatment is associated with reduced lymphoid tissue pathology, conserved lymphocyte function,<sup>47</sup> decreased cell-associated HIV-1DNA,<sup>48</sup> and a transient reduction of viral setpoint after treatment interruption.<sup>49</sup> Randomized controlled trials of immediate versus deferred ART for recently infected individuals have shown a delayed rate of CD4 decline after treatment interruptions of 6 to 15 months, compared with deferred treatment.<sup>50,51</sup> Individuals with acute infection have higher levels of HIV-1 RNA in blood and sexual fluids, increasing the risk of transmission per sexual contact.<sup>52</sup> Discontinuing ART after the acute phase is not recommended<sup>6</sup>.

## V WHAT TO START

### A. Recommendations

- Patient Preferred recommended initial regimens comprise a backbone of two nucleoside/-tide reverse transcriptase inhibitors (nRTIs): tenofovir disoproxil fumarate (DF) plus either emtricitabine or lamivudine, or abacavir plus lamivudine (the latter being acceptable if the HLA-B\*5701 screening is negative and preferably the baseline HIV-1-RNA level is < 100,000 copies/mL, depending on the third agent in the regimen); plus either the non-nucleoside RTI (NNRTI) efavirenz, or the ritonavir-boosted protease inhibitor (PI/r) atazanavir/ritonavir (see Table 2 on page 20-22 for usual drug dosages). Alternative third agents may be used if justified in specific circumstances (see Table 1, page 19).
- In patients with established cardiovascular disease or at high risk for cardiovascular disease, lopinavir/ritonavir should be avoided. The use of abacavir may be considered in this setting, depending on the availability of a suitable alternative.
- Tenofovir DF should be avoided in patients with impaired renal function (estimated glomerular filtration rate [eGFR] < 50 mL/min). If treatment for hepatitis B (HBV) is required, consult an expert for advice.
- Tenofovir DF should be used with caution in post-menopausal women and others with established osteoporosis or at high risk for osteoporosis.
- Efavirenz plus two nRTIs is the recommended initial ART regimen in the setting of rifampin-based tuberculosis (TB) treatment. The use of a 3-month once weekly regimen of isoniazid with rifapentine for treatment of latent TB infection should be avoided among HIV-infected patients receiving ART.
- Tenofovir DF plus emtricitabine or lamivudine should be included as the nRTI background for HIV/HBV co-infected persons. Consideration should be given to the continued use of these agents even if the HIV regimen is altered for whatever reason, including HIV resistance to any or all of tenofovir DF, emtricitabine, or lamivudine. Consult an expert for the treatment of HBV in the setting of impaired renal function (eGFR < 50 mL/min).

### B. Background

The specific components of ART should be individualized. HIV resistance testing at baseline plays a key role in deciding what to start with. Also, given that at this time ART represents a life-long therapeutic proposition, the choice of regimen must take into account convenience, tolerability issues, potential toxicities and drug interactions as they relate to existing co-morbidities. The aim of therapy continues to be full, life-long, and continuous suppression

of HIV replication, as demonstrated by a sustained HIV-1 RNA level <40 copies/mL, to prevent emergence of resistance, promote optimal immune recovery, prevent disease progression and prevent premature death. Drug interactions between ART and other medications represent a growing challenge as persons with HIV age and require additional medications for co-morbid conditions.<sup>53,54,55</sup> Wider availability of effective generic drugs will have a strong influence on the choice of the initial antiretroviral regimen, as discussed below.<sup>56</sup>

Initial therapy continues to be based on a combination of two nucleoside/-tide analogue reverse transcriptase inhibitors (nRTIs) and a potent third agent, typically a nonnucleoside analogue reverse transcriptase inhibitor (NNRTI), or a ritonavir-boosted protease inhibitor (PI/r). Under special circumstances, an integrase strand transfer inhibitor (InSTI) may be considered. For each component of a regimen, specific situations can dictate different recommended and alternative agents (Tables 1 and 2, pages 19-22).

There is no evidence that drug efficacy differs among different subtypes of HIV-1.<sup>57</sup> Co-formulations of drugs and complete regimens in fixed-dose combinations (FDCs), increasingly used once daily, are often preferred for convenience which may promote improved adherence.<sup>58</sup> There has been substantial interest over the years regarding nRTI-sparing regimens; however, the evidence accumulated to date supports retaining the dual nRTIs as the preferred backbone of contemporary ART. PI monotherapy is not recommended, because of lower rates of virologic suppression and increased risk of virologic failure.<sup>59,60</sup>

**TABLE 1. ART REGIMEN OPTIONS FOR TREATMENT-NAIVE ADULTS**

(See Table 2 for details re: dosing, administration, and drug interactions)

	RECOMMENDED <sup>a</sup>	ALTERNATIVE 3 <sup>rd</sup> Agent <sup>a,b</sup>
<b>Non-nucleoside reverse transcriptase inhibitor (NNRTI)</b>	Efavirenz/emtricitabine/tenofovir DF Efavirenz/lamivudine /tenofovir DF Efavirenz/lamivudine /abacavir *  *if HLA-B*5701 negative and preferably baseline plasma viral load (pVL) < 100,000 copies/mL	Nevirapine * Rilpivirine **  *men with CD4<400 cells/mm <sup>3</sup> , women with CD4<250 cells/mm <sup>3</sup>  **if baseline pVL< 100,000 copies/mL
<b>Boosted protease inhibitor (PI/r)</b>	Atazanavir/ritonavir + either emtricitabine/tenofovir DF or lamivudine/tenofovir DF or lamivudine /abacavir *  *if HLA-B*5701 negative and preferably baseline pVL< 100,000 copies/mL	Darunavir/ritonavir Darunavir/cobicistat Lopinavir/ritonavir

	RECOMMENDED <sup>a</sup>	ALTERNATIVE 3 <sup>rd</sup> Agent <sup>a,b</sup>
<b>Integrase Inhibitors</b>		Raltegravir BID Elvitegravir /cobicistat* Dolutegravir  *Only available as FDC with emtricitabine/tenofovir DF
<b>CCR5 receptor antagonist</b>		Maraviroc BID

- a. Administered once daily unless specified to be given twice daily (BID)  
b. With either emtricitabine/tenofovir DF, lamivudine/tenofovir DF, or lamivudine/abacavir FDC, fixed-dose combination initiation

**TABLE 2. ANTIRETROVIRAL DRUG DOSING, ADMINISTRATION, AND KEY DRUG INTERACTIONS**

	Generic name	Brand Name <sup>**</sup>	Usual dose in first line	Dosing/ Administration Issues	Key Drug Interactions
<b>Nucleoside/ tide Reverse transcriptase inhibitor (NRTI)</b>	abacavir	Ziagen <sup>®</sup>	600mg daily	Avoid if HLA-B*5701 positive	
	didanosine	Videx-EC <sup>®</sup>	400mg daily		
	lamivudine	3TC <sup>®</sup>	300mg daily		
	stavudine	Zerit <sup>®</sup>	40mg BID	30 mg BID if weight <60kg	
	tenofovir DF	Viread <sup>®</sup>	300mg daily		didanosine; caution nephrotoxic drugs
	zidovudine	Retrovir <sup>®</sup>	300mg BID		

	<b>Generic name</b>	<b>Brand Name**</b>	<b>Usual dose in first line</b>	<b>Dosing/ Administration Issues</b>	<b>Key Drug Interactions</b>
<b>NRTI combination products</b>	emtricitabine-tenofovir DF	Truvada®	1 tablet daily		didanosine; caution nephrotoxic drugs
	Tenofovir alafenamide-emtricitabine	Descovy®	1 tablet daily		Potent p-glycoprotein inducers*
	abacavir-lamivudine	Kivexa®	1 tablet daily	Avoid if HLA-B*5701 positive	
	zidovudine-lamivudine	Combivir®	1 tablet BID		
	zidovudine-lamivudine-abacavir	Trizivir®	1 tablet BID	Avoid if HLA-B*5701 positive	
<b>Non-nucleoside reverse transcriptase inhibitor (NNRTI)</b>	delavirdine	Rescriptor®	400mg TID		CYP450 metabolized drugs*
	efavirenz	Sustiva®	600mg daily	Take at bedtime, preferably on an empty stomach to minimize side effects	CYP450 metabolized drugs*
	etravirine	Intelence®	200mg BID	Take with food	CYP450 metabolized drugs*
	nevirapine	Viramune®	400mg daily	Lead in dose (200mg daily) x 14 days	CYP450 metabolized drugs*
	rilpivirine	Edurant®	25mg daily	Take with food	CYP450 metabolized drugs*; proton pump inhibitors



	<b>Generic name</b>	<b>Brand Name**</b>	<b>Usual dose in first line</b>	<b>Dosing/ Administration Issues</b>	<b>Key Drug Interactions</b>
<b>Protease inhibitor (PI)</b>	atazanavir	Reyataz®	400mg daily	Take with food	TDF; proton pump inhibitors
	atazanavir/ ritonavir	Reyataz®/ Norvir®	300mg / 100mg daily	Take with food	CYP450 metabolized drugs*; proton pump inhibitors
	darunavir/ ritonavir	Prezista®/ Norvir®	800mg/rito- navir 100mg daily	Take with food	CYP450 metabolized drugs*
	darunavir- cobicistat	Prezcobix®	800mg / 150mg (1 tablet) daily	Take with food; avoid taking with TDF if eGFR<70 mL/min	CYP450 metabolized drugs*
	fosamprenavir/ ritonavir	Telzir®/Norvir®	1400mg / 100mg daily		CYP450 metabolized drugs*
	indinavir/ ritonavir	Crixivan®/ Norvir®	800 mg/100mg BID	Recom- mended fluid intake 1.5 L/24 hours	CYP450 metabolized drugs*
	lopinavir- ritonavir	Kaletra®	800mg / 200mg daily or 400mg / 100mg BID	Take with food	CYP450 metabolized drugs*
	nelfinavir	Viracept®	1250mg BID or 750mg TID	Take with food	
	saquinavir- HG/ritonavir	Invirase®/ Norvir®	1000mg / 100mg BID	Take with food	CYP450 metabolized drugs*
	tipranavir/ ritonavir	Aptivus®/ Norvir®	500mg/200mg BID		CYP450 metabolized drugs*

	<b>Generic name</b>	<b>Brand Name**</b>	<b>Usual dose in first line</b>	<b>Dosing/ Administration Issues</b>	<b>Key Drug Interactions</b>
<b>Integrase Inhibitors</b>	raltegravir	Isentress®	400mg BID		Rifampin, metformin, iron, calcium, magnesium, aluminum  Multiple*
	dolutegravir	Tivicay®	50mg daily		
<b>CCR5 receptor antagonist</b>	maraviroc	Celsentri®	150, 300, or 600mg BID		
<b>Entry inhibitors</b>	enfuvirtide	Fuzeon®	90mg BID	Subcutaneous injection	
<b>Multi-class combination products</b>	efavirenz-tenofovir DF-emtricitabine	Atripla®	1 tablet daily	Take at bedtime, preferably on an empty stomach to minimize side effects	CYP450 metabolized drugs*; didanosine; caution nephrotoxic drugs
	rilpivirine-tenofovir DF-emtricitabine	Complera®	1 tablet daily	Take with food (>390 kcal)	CYP450 metabolized drugs*; didanosine; proton pump inhibitors; caution nephrotoxic drugs
	elvitegravir-cobicistat-tenofovir DF-emtricitabine	Stribild®	1 tablet daily	Take with food Avoid if eGFR<70 mL/mIn	CYP450 metabolized drugs*; didanosine; caution nephrotoxic drugs
	Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide	Genvoya®	1 tablet daily	Take with food	CYP450 metabolized drugs*
	dolutegravir/abacavir/lamivudine	Triumeq®	1 tablet daily	Avoid if HLA-B*5701 positive	Rifampin, metformin, iron, calcium, magnesium, aluminum

	Generic name	Brand Name**	Usual dose in first line	Dosing/ Administration Issues	Key Drug Interactions
CYP450, Cytochrome P450 BID, twice daily; TID, three times daily eGFR, estimated glomerular filtration rate *Consult with St Paul's Hospital Ambulatory Pharmacy (toll-free) 1-888-511-6222 **generic formulations may also be available					

### C. Cost issues and generic antiretroviral medications

Widespread, effective ART has been shown to be not only cost-saving, but cost-averting.<sup>61</sup> On the other hand, cost concerns are becoming an increasingly important issue, particularly given the fact that ART is necessarily life-long. A number of antiretroviral agents and fixed-dose combinations will become available as generic formulations in Canada over the next few years, representing potentially significant cost-savings compared to their brand-name counterparts. A preliminary analysis suggests that incorporation of generic antiretrovirals into the BC-CfE Drug Treatment Program could save the province more than 200 million dollars over the next 10 years [Julio Montaner and Steven Wong, personal communication].

### D. Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)

#### 1. *Pneumocystis jiroveci* pneumonia (PJP)

*Tenofovir disoproxil fumarate* (DF) and *emtricitabine* are available together in a once-daily FDC with no food restrictions. Tenofovir DF is well tolerated but has been associated with kidney injury, which appears to increase in incidence with long-term administration and concurrent PI/r use.<sup>62,63,64,65</sup> Risk factors may include advanced HIV disease; longer treatment history; low body weight, especially in women<sup>66</sup>; and pre-existing renal impairment.

Renal function (serum creatinine, estimated glomerular filtration rate [eGFR], serum phosphorus, urinalysis, urine albumin and/or protein to creatinine ratio) should be assessed before use and monitored over time.<sup>67</sup> Tenofovir DF should be avoided, if at all possible, in the case of renal impairment (eGFR below 50 mL/min). If tenofovir DF is necessary in patients with eGFR < 50 mL/min, for example in the setting of HBV coinfection, the dosage should be adjusted according to the package insert,<sup>68</sup> with the guidance of the St. Paul's Hospital Pharmacy (1-888-511-6222). Tenofovir DF has been associated with decreases in bone mineral density in the spine and hip, and increased risk of osteoporotic fractures.<sup>69,70</sup> Emtricitabine is clinically similar to lamivudine; however, it has been associated with rashes and gastrointestinal intolerance, particularly among women.<sup>71</sup> If emtricitabine is not tolerated, *lamivudine* can be given with tenofovir DF as separate entities. Lamivudine is extremely well-tolerated.

Emtricitabine/tenofovir alafenamide (AF; Descovy®) is available for patients who require tenofovir-based therapy and who have documented renal or bone toxicity to tenofovir DF. Specific criteria must be met for use of this combination. Patients are eligible for

emtricitabine/tenofovir AF if abacavir cannot be taken due to HLA-B\*5701 positivity, documented resistance, documented abacavir intolerance, or chronic HBV infection, and eGFR <60mL/min, severe hypophosphatemia (serum phosphate <0.32mmol/L), documented osteoporosis (at least one t-score  $\leq$  -2.5 at the hip or spine on DXA scan), occurrence of a fragility fracture, or documented osteomalacia. When completing the prescription request form, prescribers should provide justification for its use and appropriate documentation (i.e. laboratory or DXA scan results).

*Abacavir* and lamivudine as an FDC offers once-daily administration, no food restriction, and minimal subjective toxicity. Screening for the HLA-B\*5701 allele is required before starting abacavir and this drug should not be prescribed to a patient who is positive for HLA-B\*5701 (for information on HLA-B\*5701 testing, see: <http://www.cfenet.ubc.ca/clinical-activities/lab-tests/hla-b5701>; to order the test in BC, requisition form available at: <http://www.cfenet.ubc.ca/research/laboratory-program/laboratory-test-order-forms>. This strategy markedly reduces the risk of potentially life-threatening hypersensitivity reactions to abacavir. In one randomized controlled trial, initial regimens containing the abacavir/lamivudine backbone had lower rates of viral suppression than regimens containing tenofovir DF/emtricitabine in persons with baseline HIV-1 RNA levels above 100,000 copies/mL.<sup>72</sup> This remains controversial as this effect was not confirmed in a second randomized trial<sup>73</sup>. The current recommendation is to avoid starting abacavir-based regimens in patients with viral load above 100,000 copies/mL; however, abacavir may be used in this situation with close monitoring, if it is judged to be the most suitable option. An exception may be made for regimens including dolutegravir or raltegravir as the third drug, where abacavir-based regimens have proven equally efficacious as tenofovir DF-based regimens, even among subjects with a plasma viral load above 100,000 copies/mL.<sup>74,75,76,77,78</sup> In some non-randomized observational cohort studies, recent use of abacavir has been associated with a higher risk for acute myocardial infarction or other cardiovascular events.<sup>79,80,81</sup> However, other cohort studies and randomized controlled trials have not confirmed this association.<sup>82,83,84</sup> Furthermore, three large meta-analyses of randomized controlled trial data, one of which was conducted by the United States Food and Drug Administration (FDA), failed to find any evidence of an association between abacavir use and increased risk of cardiovascular events,<sup>85,86,87</sup> and a plausible biological mechanism for such an association has yet to be demonstrated. Given the uncertainty of the association, use of abacavir may be considered in the setting of established cardiovascular disease (CVD) or high CVD risk, if a viable alternative is not available.

## 2. **Alternative nRTIs**

*Zidovudine* and lamivudine as an FDC must be used twice daily. Zidovudine commonly causes headache, nausea, anemia, and/or neutropenia, and long-term use is associated with progressive and persistent peripheral lipoatrophy. Its use should be reserved for individuals unable to use abacavir or tenofovir DF, and in some cases during pregnancy<sup>20</sup>.

## E. Nonnucleoside reverse transcriptase inhibitors (NNRTIs)

*Nevirapine*, *efavirenz*, and *rilpivirine* are each available as a single pill for once-daily use; the two latter drugs are available in FDCs with tenofovir DF and emtricitabine. Etravirine is usually reserved for later treatment as it has a higher pill burden.

### 1. Recommended NNRTI

*Efavirenz* is used once daily, preferably without food, at bedtime. Long-term efficacy and safety data are available for the use of *efavirenz* in triple therapy, with rates of virologic failure (VF) in clinical trials similar to those of the comparator arms, including atazanavir/ritonavir<sup>88</sup> and the integrase inhibitors: raltegravir (VF 21% with *efavirenz* vs. 20% with raltegravir at 240 weeks in STARTMRK<sup>89</sup>), elvitegravir/cobicistat (VF 10% with *efavirenz* vs. 7% with elvitegravir/cobicistat at 144 weeks in Gilead study 102<sup>90</sup>), and dolutegravir (VF 7% with *efavirenz* vs. 10% with dolutegravir at week 144 in SINGLE<sup>91</sup>).

*Efavirenz* can cause a rash, which usually, but not always, decreases despite continued treatment. Central nervous system side effects include sleep disturbance, abnormal dreams, and less commonly, depressed mood.<sup>92,93</sup> Recent blinded trials show that the early central nervous system adverse effects of *efavirenz* may persist<sup>83</sup>. An analysis of patients randomized to *efavirenz*-containing vs non-*efavirenz*-containing regimens found a 2.3-fold increased risk of suicidality (suicidal ideation, suicide attempt, or completed suicide) with *efavirenz*<sup>94</sup>. However, an analysis of spontaneous adverse event reports to the United States Food and Drug Administration did not confirm the association between *efavirenz* use and suicidality<sup>95</sup>. Overall, the rate of *efavirenz* discontinuation due to neuropsychiatric or other adverse events is low; in a recent systematic review, more than 90% of patients remained on a first-line *efavirenz*-containing regimen after an overall follow-up time of 78 weeks.<sup>96</sup> Suicidal ideation was rare (0.6%) and there were no completed suicides among the 8466 *efavirenz*-exposed patients included in this review.

### 2. Alternative NNRTIs

*Nevirapine* is available in a 400 mg once-daily formulation. *Nevirapine* requires a two-week lead-in of 200 mg once daily.<sup>97</sup> Rash is more common and may be more severe than with *efavirenz*. Severe hepatotoxicity is occasionally seen with initial use. Both severe rash and hepatotoxicity are more common in women with baseline CD4 cell counts above 250/ $\mu$ L and men with baseline CD4 counts above 400/ $\mu$ L; therefore, *nevirapine* is not recommended in these situations.

*Rilpivirine* is administered once daily. In 2 studies, efficacy of *rilpivirine* was non-inferior to that of *efavirenz*; however, rates of virologic failure were higher with *rilpivirine* and rates of adverse events were higher with *efavirenz*.<sup>98,99</sup> Virologic failure was more common with *rilpivirine* than with *efavirenz* in patients with HIV-1 RNA above 100,000 copies/mL at baseline; *rilpivirine* should be avoided in this population. *Rilpivirine* is formulated both as an individual tablet and in a fixed-dose combination tablet with tenofovir DF/emtricitabine (Complera<sup>®</sup>). Both formulations must be taken with food for optimal absorption (at least 390 kcal with Complera<sup>®</sup>); a protein drink is not an adequate substitute. Concomitant use of proton-pump inhibitors is contraindicated. *Rilpivirine* inhibits tubular transport of creatinine, resulting in an increase in serum creatinine during the first 2 weeks of use, without

affecting renal function.<sup>91, 100</sup> In clinical trials, doses of rilpivirine higher than the currently recommended dose were associated with QTc interval prolongation.<sup>101</sup> An ECG should be performed and monitored periodically (at intervals determined by the degree of risk) in patients taking rilpivirine with one or more PR- or QTc-prolonging drugs<sup>67</sup>.

*Etravirine* is another alternative NNRTI which is rarely used as part of initial ART because it is dosed twice daily. It is generally reserved for use as a component of combination therapy for multi-drug resistant HIV.

## F. Protease Inhibitors (PIs)

Protease inhibitors (PIs) are used in combination with two nRTIs as part of initial ART. Because PIs have limited bioavailability, they are co-administered with a pharmacologic “booster”. Boosting has typically been achieved with a low and virologically inactive dose of ritonavir. Cobicistat, a newer pharmacological booster without inherent anti-HIV activity, is available as a co-formulation with the protease inhibitor darunavir (in Prezco**ix**®), but is not currently available in Canada as a separate boosting agent. Boosted PI-based regimens have demonstrated virologic potency and durability in treatment-naive patients, and a high genetic barrier to resistance.

As a class, PIs may be associated with mild to moderate nausea, diarrhea, and long term toxicities such as dyslipidemia, insulin resistance, and other metabolic disorders. All PIs may be associated with cardiac conduction abnormalities, particularly PR interval prolongation<sup>102</sup>. Some older ritonavir-boosted PIs (saquinavir and lopinavir) have been associated with QTc interval prolongation.<sup>103,104</sup> This may become clinically significant when a ritonavir –boosted PI is co-administered with one or more QTc-prolonging drugs such as methadone, quetiapine, macrolides, quinolones, and/or azoles (for a full list, see: <http://www.azcert.org/medical-pros/drug-lists/drug-lists.cfm>), or PR-prolonging drugs (e.g. digitalis, calcium channel blockers, anti-arrhythmics, and beta-blockers). An ECG should be performed and monitored periodically (at intervals determined by the degree of risk) in patients taking a ritonavir-boosted protease inhibitor with one or more PR- or QTc-prolonging drugs.<sup>67</sup>

All ritonavir- or cobicistat-boosted PIs inhibit the cytochrome P450 3A isoenzyme, which may lead to significant drug-drug interactions with co-administered medications (for information regarding drug interactions, see <http://www.hiv-druginteractions.org> or [http://www.hivclinic.ca/main/drugs\\_home.html](http://www.hivclinic.ca/main/drugs_home.html)).

### 1. Recommended PI

*Ritonavir-boosted atazanavir* is used in initial therapy once daily. It blocks bilirubin conjugation resulting in a nearly universal elevation in indirect bilirubin. Usually modest, this can cause visible jaundice in some individuals but does not represent hepatotoxicity. Atazanavir requires gastric acidity for absorption and should be taken with meals. Proton pump inhibitors should be avoided, or if used, expert advice should be sought for dosing and monitoring recommendations. Therapeutic drug monitoring (TDM) is available to titrate atazanavir dose in selected cases. Expert advice should be sought to optimally

use and interpret TDM. Atazanavir is available for use without boosting, but its potency is reduced and therefore unboosted atazanavir is not recommended for initial treatment.

Atazanavir/ritonavir may be associated with nephrolithiasis<sup>105</sup> and renal dysfunction, independent of tenofovir DF.<sup>63,65</sup> Atazanavir/ritonavir is also associated with cholelithiasis<sup>106,107</sup>. Atazanavir/ritonavir was shown to have similar efficacy to efavirenz-based therapy in a large randomized trial<sup>88</sup>, and to darunavir/ritonavir and to raltegravir in another large randomized trial (ACTG 5257)<sup>108</sup>.

## 2. Alternative PIs

Alternative PIs include *darunavir/ritonavir* and *lopinavir/ritonavir*.

*Darunavir/ritonavir* is used once daily in initial regimens and should be taken with a meal to improve bioavailability. Darunavir contains a sulfonamide moiety and may produce hypersensitivity reactions, especially in people with a known sulfonamide allergy. Darunavir is available in a FDC (Prezcobix<sup>®</sup>) with an alternative pharmacokinetic booster, cobicistat. Darunavir 800mg/cobicistat 150mg has been shown to be bioequivalent to darunavir 800mg/ritonavir 100mg<sup>109</sup>, and is safe and effective in HIV-positive patients who do not harbor darunavir-associated resistance mutations<sup>110</sup>.

*Lopinavir* is only available as a FDC (Kaletra<sup>®</sup>) with ritonavir. Fewer individuals randomized to lopinavir/ritonavir in combination with tenofovir DF/emtricitabine maintained their HIV-1 RNA below 50 copies/mL at 48 and 96 weeks as compared to those randomized to darunavir/ritonavir or atazanavir/ritonavir.<sup>111</sup> Lopinavir/ritonavir causes more frequent gastrointestinal side effects than the other PIs currently in use. It can be used once daily in initial regimens and does not require administration with food to optimize absorption, although food may mitigate gastrointestinal intolerance. Lopinavir/ritonavir has been associated in cohort studies with increased risk of renal dysfunction<sup>63,65</sup> and cardiovascular events.<sup>79,82</sup>

## G. Integrase Strand Transfer Inhibitors (InSTIs)

Protease InSTIs are the newest class of potent antiretroviral drugs used with a dual nRTI backbone. Similar to the NNRTIs, some current InSTIs may have a relatively low genetic barrier to resistance when compared to the PI/r class. However, this may not be a class effect<sup>112</sup>.

*Raltegravir* has demonstrated durable virologic efficacy over 5 years in clinical trials<sup>89</sup>. It should be used twice daily as once-daily dosing diminishes efficacy.<sup>113</sup> Raltegravir does not require concomitant food consumption. It is well-tolerated with minimal metabolic impact or other long-term toxicities. Raltegravir plasma concentrations are lower when administered simultaneously or staggered from aluminum and/or magnesium containing antacids and administration of raltegravir with these products is not recommended. It has few drug interactions with other concomitant medications, including chemotherapeutic agents and newer agents used to treat HCV (see <http://www.hep-druginteractions.org/>).

*Elvitegravir* must be boosted to achieve sufficient potency and thus is co-formulated with the new boosting agent cobicistat and with the nRTIs tenofovir DF and emtricitabine.<sup>114</sup> This FDC



(Stribild®) is administered once daily. Because of the boosting, the FDC can cause substantial drug-drug interactions, as cobicistat inhibits cytochrome p450 3A4, as does ritonavir. Cobicistat causes an immediate increase in serum creatinine level during the first two weeks of use, without affecting true measured creatinine clearance.<sup>115</sup> Like ritonavir, cobicistat is associated with gastrointestinal side effects. Because cobicistat inhibits CYP3A, it interacts with a number of medications that are metabolized by this enzyme (see <http://www.hiv-druginteractions.org> or [http://www.hivclinic.ca/main/drugs\\_home.html](http://www.hivclinic.ca/main/drugs_home.html)). Elvitegravir plasma concentrations are lower when it is administered simultaneously with aluminum-, magnesium-, or calcium-containing antacids; administration should be separated by at least 2 hours. At this time, elvitegravir and cobicistat are not available as separate entities (outside the FDC with tenofovir DF/emtricitabine) in Canada.

The once-a-day combination drug elvitegravir/cobicistat/emtricitabine/tenofovir AF (Genvoya®) is available for patients who require tenofovir-based therapy and who have documented renal or bone toxicity to tenofovir DF. Specific criteria must be met for use of this combination. When completing the prescription request form, prescribers should provide justification for its use and appropriate documentation (i.e. laboratory or DXA scan results). This combination should be taken with food for optimal absorption. As this combination contains cobicistat, a strong inhibitor of cytochrome P450, assess for drug-drug interactions when prescribing (see <http://www.hiv-druginteractions.org> or [http://www.hivclinic.ca/main/drugs\\_home.html](http://www.hivclinic.ca/main/drugs_home.html)).

*Dolutegravir* is administered once daily without the need for a pharmacologic booster, and has demonstrated non-inferior efficacy and similar safety to raltegravir, efavirenz, and darunavir/ritonavir in clinical trials.<sup>74-78, 116</sup> Dolutegravir is generally well-tolerated. The most common adverse reactions of moderate to severe intensity with an incidence of  $\geq 2\%$  in the clinical trials were insomnia and headache. Dolutegravir should be administered 2 hours before or 6 hours after taking medications containing polyvalent cations (i.e. certain antacids, calcium supplements or buffered medications). Dolutegravir may increase plasma levels of metformin, potentially necessitating metformin dose adjustment when the two drugs are co-administered. Dolutegravir has a similar effect on serum creatinine to that of cobicistat and rilpivirine. It is available as a single agent and in the form of an FDC with abacavir and lamivudine (Triumeq®).

## H. CCR5 Receptor Antagonists

Drugs that block the CCR5 co-receptor have antiretroviral activity only if the individual is infected with HIV that exclusively utilizes CCR5 to enter human cells. Therefore, HIV tropism screening is required before considering the use of a CCR5 antagonist (for information on tropism testing, see: <http://www.cfenet.ubc.ca/clinical-activities/lab-tests/ccr5-tropism>; to order the test in BC, requisition form available at: <http://www.cfenet.ubc.ca/research/laboratory-program/laboratory-test-order-forms>). The phenotypic assay that measures tropism is expensive and time consuming, but genotypic tropism testing is faster and readily available.<sup>117</sup> *Maraviroc* is the only currently approved CCR5 attachment inhibitor. It is used twice daily and has no food restrictions.

## I. Special Considerations

### 1. Pregnancy



The B.C. Centre for Excellence in HIV/AIDS has updated the recommendations for use of antiretroviral therapy (ART) in pregnancy.<sup>20</sup> The choice of ART in pregnant women should take into consideration the same benefits and risks as in all HIV-infected adults as well as any special considerations associated with the pregnancy. The Antiretroviral Pregnancy Registry of more than 15,000 HIV exposures reported from January 1989 through July 2014 notes no increase in the rates of congenital birth defects with exposure to ART, including to efavirenz, even in the first trimester.<sup>118</sup> However, in BC, efavirenz is still not recommended to be given to women of child-bearing potential or during the first trimester of pregnancy, based on primate teratogenicity data and anecdotal reports of neural tube defects in humans.<sup>20,119</sup> Management of HIV positive women who are pregnant or planning to become pregnant should be conducted under expert guidance.<sup>24</sup> In BC, health care providers can contact the Oak Tree Clinic at BC Women's and Hospital and Health Centre (604-875-2212; toll free 1-888-711-3030) for further information.

## 2. **Opportunistic infections (OIs).**

Drug interactions and tolerability of OI treatment together with ART regimens are key considerations in the context of acute OIs. Drug interactions with triazole antifungal drugs and those associated with the rifamycins are among the most important. The recommended regimen in the setting of TB is rifampin-based TB therapy with efavirenz plus nRTIs. Data are conflicting about the effect of rifampin co-administration on efavirenz concentrations. Early studies reported a 26% reduction in efavirenz exposure,<sup>120</sup> but more recent studies in patients with HIV and TB co-infection have not shown a clinically significant effect of rifampin on efavirenz exposure.<sup>121,122,123,124</sup> The current FDC with 600 mg of efavirenz is associated with good HIV and TB outcomes regardless of weight,<sup>125</sup> and is the recommended dose in patients receiving rifampin-based TB therapy. If efavirenz cannot be used, rifabutin-based TB therapy with a ritonavir-boosted PI plus two nRTIs is recommended. Rifabutin reportedly has little effect on atazanavir/ritonavir<sup>126</sup> or lopinavir/ritonavir,<sup>127</sup> results in only modest increases in darunavir/ritonavir,<sup>128</sup> and has no clinically meaningful effect on raltegravir.<sup>129</sup> However, serum concentrations of rifabutin and its major metabolite are markedly increased by all ritonavir-boosted PIs, requiring dose adjustment of rifabutin in this setting. Rifabutin 150 mg every other day resulted in increased rates of acquired rifamycin resistance when used with a ritonavir-boosted PI regimen<sup>130,131</sup> and lower than expected concentrations of rifabutin. Two recent pharmacokinetic studies have indicated that, for persons with HIV and TB who received lopinavir/ritonavir-based ART, the optimal dose of rifabutin was 150 mg once daily (rather than three times a week).<sup>132,133</sup> Raltegravir concentrations are decreased when co-administered with rifampin, and it has been suggested that if a raltegravir-based ART regimen is used, then the raltegravir dose should be increased to 800 mg twice daily. However, a recent open-label RCT included 153 persons co-infected with HIV and TB who were randomized to receive rifampin-based TB therapy in addition to an ART backbone (tenofovir plus lamivudine) with raltegravir 400 mg twice daily, or raltegravir 800 mg twice daily, or efavirenz 600 mg once daily<sup>134</sup>. At 48 weeks of follow-up, virologic suppression (<50 copies/mL) was not significantly different among the three groups (76%, 63%, and 67%, respectively). The slightly higher success rate with standard dose raltegravir (400 mg twice

daily) was related to better tolerability and possibly adherence compared to the higher dose. In support of these findings, pharmacokinetic observations in patients receiving raltegravir co-administered with rifampin-based TB treatment showed no change in raltegravir's area under the plasma concentration curve (AUC) and only a 31% decrease in trough concentration<sup>135</sup>. In summary, raltegravir at standard dose may be an alternative to efavirenz in patients with HIV/TB co-infection receiving rifampin-based treatment.

Dolutegravir may be used together with rifampin or rifabutin based on a pharmacokinetic study<sup>136</sup>. Dolutegravir concentrations are decreased when co-administered with rifampin and a dose of dolutegravir 50 mg twice daily is recommended in integrase-naïve and experienced patients. However, dolutegravir has not been studied in HIV-infected individuals with active TB. There are no data on elvitegravir/cobicistat with rifamycin drugs, but these drugs should not be used together because of a likely interaction.

The 3-month once weekly isoniazid-rifapentine regimen<sup>137</sup> may be used for the treatment of latent TB infection in HIV-infected patients who are not taking antiretroviral therapy. However, given the numerous drug interactions of rifapentine (as for other rifamycins) which have not been fully evaluated for antiretrovirals, this regimen is not recommended in those patients receiving antiretroviral therapy. For such patients, isoniazid monotherapy for 9 months is recommended. In contrast, it is important that a rifamycin (rifampin or rifabutin) is included in the treatment regimen for active TB infection in order to achieve optimal outcomes.

### 3. **HBV**

The optimal ART regimen for HIV and HBV co-infected persons should include tenofovir DF and emtricitabine (or lamivudine) as the nRTI background because these agents are also effective against HBV. If renal insufficiency occurs in HBV and HIV co-infected persons, expert advice should be sought with regard to the use of tenofovir DF. Entecavir has been used safely in co-infected patients, but has impaired activity against lamivudine-resistant HBV, and can select for M184V in HIV reverse transcriptase.<sup>37,138,139</sup> In persons without lamivudine-resistant HBV, entecavir is an alternative to tenofovir DF if used with a fully suppressive ART regimen. Regimens containing lamivudine or emtricitabine as the only antivirals with activity against HBV provide suboptimal efficacy and should not be used in individuals with HIV/HBV co-infection, as they typically result in nRTI-resistant HBV.<sup>140,141</sup>

### 4. **HCV**

Canadian guidelines for the management of HIV-HCV co-infection were updated in 2014<sup>43</sup>. At this time Peginterferon alfa and ribavirin remain treatment options for HCV genotypes 2 and 3 in HIV co-infected persons. Ribavirin has overlapping toxicity with zidovudine, and should similarly not be used in conjunction with stavudine or didanosine. A new oral NS5B polymerase inhibitor, sofosbuvir, has recently been approved by Health Canada for the treatment of HCV. Sofosbuvir is highly efficacious and well tolerated, with minimal potential for drug-drug interactions, particularly with regard to antiretrovirals<sup>142</sup>. An oral FDC of sofosbuvir with the NS5A inhibitor, ledipasvir, has also shown remarkably high response rates, even in the setting of HIV/HCV coinfection<sup>143,144,145</sup> and is now standard

of care for HCV genotype 1. Ledipasvir should be used with caution in those receiving tenofovir DF and boosted PI regimens due to risk for increased tenofovir levels, and if possible regimens should be adjusted. Prior HIV virologic failure and previous evidence of nRTI resistance mutations may limit switches away from a boosted PI regimen due to increased risk of HIV virologic failure in this setting. Additional updated drug interaction information can be accessed at <http://www.hep-druginteractions.org>.<sup>146</sup> The HCV PIs telaprevir, boceprevir, and simeprevir are no longer considered standard of care, or are not available for the treatment of genotype 1 chronic HCV.

## 5. Co-morbid conditions

Pre-existing risks for or existence of particular co-morbidities influence the choices among otherwise equally effective recommended initial regimens. Co-morbidities may be exacerbated by the potential toxicity of individual ART drugs, and treatment for these conditions may be subject to drug-drug interactions with antiretroviral agents.

### a. Cardiovascular disease (CVD).

In HIV-infected patients, CVD is a major cause of morbidity and mortality, accounting for one-third of serious non-AIDS conditions and at least 10% of deaths<sup>147,148</sup>. In addition, persons living with HIV infection also have higher rates of traditional CVD risk factors, particularly smoking and dyslipidemia, than HIV-uninfected individuals.

As noted above, data linking abacavir with an increased risk of CVD are inconsistent and no explanatory mechanism has been identified. Lopinavir/ritonavir has been associated with CVD risk in cohort studies<sup>79,82</sup>; treatment with this boosted PI has been associated with a proatherogenic lipid profile,<sup>149</sup> making this association biologically plausible. The same cohort analyses have not found associations between CVD risk and use of tenofovir DF, efavirenz, nevirapine, or atazanavir/ritonavir.<sup>79,80,150</sup> Sufficient cohort data to analyze CVD risks associated with darunavir/ritonavir, raltegravir, dolutegravir or rilpivirine are not yet available.

In summary, use of lopinavir/ritonavir should be avoided if possible in patients at high risk for CVD. Given the uncertainty of the association, use of abacavir may be considered in this setting, if a viable alternative is not available.

As noted above, PIs may be associated with cardiac conduction abnormalities that may become clinically significant in the setting of co-administered QTc-prolonging drugs such as methadone, quetiapine, macrolides, quinolones, and/or azoles (<http://www.azcert.org/medical-pros/drug-lists/drug-lists.cfm>) or PR-prolonging drugs (e.g. digitalis, calcium channel blockers, anti-arrhythmics, and beta-blockers). An ECG should be performed and monitored periodically (at intervals determined by the degree of risk) in patients taking a ritonavir-boosted protease inhibitor and/or rilpivirine with one or more PR- or QTc-prolonging drugs.<sup>67</sup>

**b. Renal disease**

In patients with reduced renal function, prolonged use of tenofovir DF is associated with cumulative nephrotoxicity,<sup>63-65,151</sup> and should be avoided. Atazanavir/ritonavir and lopinavir/ritonavir have each been associated in cohort studies with loss of renal function, either in the setting of concomitant tenofovir DF<sup>62,151</sup> or independent of it.<sup>63,65</sup> The clinical significance of this finding remains to be elucidated. Initiation of elvitegravir/cobicistat/tenofovir DF/emtricitabine is not recommended for patients with an estimated creatinine clearance of less than 70 mL/min, and discontinuation is recommended if creatinine clearance is less than 50 mL/min.<sup>152</sup>

HIV-associated nephropathy (HIVAN) presents as a rapidly progressive nephrotic syndrome occurring in the setting of advanced untreated HIV disease; it is an indication for immediate initiation of ART.<sup>6</sup>

**c. Bone disease**

Compared with uninfected individuals, patients with HIV infection are at increased risk of osteoporotic fragility fractures. In addition to traditional factors associated with bone loss, use of tenofovir DF and lopinavir/ritonavir have been found to be independent risk factors for fractures in some recent studies.<sup>70,153</sup> Although all initial ART regimens are associated with a rapid reduction in bone mineral density during the first year of treatment, the effect is more pronounced with tenofovir DF-containing regimens.<sup>69,154</sup> Notably, in postmenopausal women, both HIV infection and tenofovir DF use are independently associated with higher rates of bone loss.<sup>155</sup> Given their increased risk of fragility fractures it may be prudent to consider avoiding tenofovir DF as part of initial therapy in postmenopausal women and others with established or high risk for osteoporosis. Adequate intake of calcium and vitamin D should be considered in all HIV-infected patients<sup>156</sup>. For specific recommendations, refer to the Primary Care Guidelines for the Management of HIV/AIDS in British Columbia (<http://www.cfenet.ubc.ca/therapeutic-guidelines/primary-care>).

**d. Cirrhosis**

In persons with cirrhosis but without encephalopathy, coagulation disorders, or liver synthetic abnormalities, there are no restrictions on ART. In persons with hepatic failure, HIV PIs and some other antiretroviral drugs should be avoided or used with caution. Raltegravir combined with tenofovir DF/emtricitabine is an attractive option for patients with chronic liver disease, because of its low propensity to cause hepatotoxicity and absence of significant interactions with drugs used to treat HCV.<sup>157,158</sup>

**e. Malignancy**

The concomitant use of anticancer drugs and ART is associated with overlapping toxicities and the potential for substantial drug interactions. Raltegravir-

and dolutegravir-based regimens may be considered in this setting due to their favourable drug interaction profile.<sup>157, 159,160</sup>.

## VI MONITORING PATIENTS ON ART

### A. Recommendations

- Plasma HIV-1 RNA levels should be assessed before ART initiation and monitored frequently afterwards: monthly until suppression of viral load to below 40 copies/mL is confirmed, and every 3-4 months thereafter. The same monitoring strategy applies when ART is initiated or changed for any reason. CD4 counts should be monitored in tandem with plasma HIV-1 RNA levels initially.
- Once the regimen is well-tolerated, the viral load is suppressed for at least 2 years, and CD4 cell counts are stable at  $\geq 350/\mu\text{L}$ , HIV-1-RNA can be monitored at intervals of up to 6 months and CD4 cell count monitoring is optional as long as the patient's clinical condition remains stable.
- Detectable HIV-1-RNA (more than 40 copies/mL) during therapy should be confirmed in a subsequent sample at least 2 to 4 weeks afterwards and prior to making management decisions. Sustained elevation of HIV-1-RNA between 40 and 250 copies/mL should prompt evaluation of factors leading to failure and consideration of switching of ART. Genotypic testing for resistance should be performed in all treatment-naive patients at baseline and in cases of confirmed virologic rebound when HIV-RNA is over 250 copies/mL. (For information on HIV resistance testing, see: <http://www.cfenet.ubc.ca/clinical-activities/lab-tests/drug-resistance-testing> ; to order the test in BC, requisition form available at: <http://cfenet.ubc.ca/research/laboratory-program/laboratory-test-order-forms>).
- Therapeutic Drug monitoring (TDM) is recommended in selected clinical situations, such as kidney or liver impairment, potential drug-drug interactions, virologic failure in the absence of resistance, and pregnancy. (For information on TDM , see: <http://www.cfenet.ubc.ca/clinical-activities/lab-tests/therapeutic-drug-monitoring>).

### B. Background

Effective therapy should result in full suppression of plasma HIV-1-RNA (below lower limit of quantification of the commercially available PCR assays) by at least 24 weeks, regardless of previous treatment experience. The optimal frequency of monitoring has not been thoroughly evaluated.<sup>161,162</sup> In general, it is recommended that plasma HIV-1 RNA levels be measured at entry of care (pre-treatment viral load level is an important factor in the selection of an initial ART regimen, given the different potency of certain antiretroviral regimens) and initiation of antiretroviral therapy, and monitored frequently thereafter, typically monthly until suppression

of plasma viral load to below 40 copies/mL is confirmed, and every 3-4 months initially thereafter, as long as treatment is stable and the patient is clinically well and adherent.

CD4 counts are initially monitored in tandem with plasma HIV-1 RNA levels. The same monitoring strategy applies when antiretroviral therapy is initiated or changed for any reason.

Once the viral load is suppressed for 2 years and CD4 cell counts are stable at  $\geq 350/\mu\text{L}$ , plasma HIV-1-RNA levels can be monitored at intervals of up to 6 months and CD4 cell count monitoring is optional in clinically stable, adherent patients. For further details regarding appropriate monitoring of patients receiving ART, refer to the Primary Care Guidelines for the Management of HIV/AIDS in British Columbia (<http://www.cfenet.ubc.ca/therapeutic-guidelines/primary-care>).

The currently used HIV-1 RNA assay has a lower limit of quantification of 40 copies/mL, and can report qualitative RNA detection below these cutoffs. In addition, many patients on stable suppressive treatment show residual viremia of 1 to 10 copies/mL using research-based assays. The source, significance, and prognostic value of detectable viremia below 50 copies/mL during treatment are not well defined. Persistent HIV-1 RNA levels of 50 to 200 copies/mL may be associated with increased risk of virologic failure<sup>163</sup>, although this was not confirmed in a recent large observational study<sup>164</sup>. As a result, monthly monitoring of plasma- HIV-1 RNA levels in such cases is warranted. However, there is little evidence regarding the optimal management of patients with detectable HIV-1 RNA levels below 250 copies/mL.

In practice, it is recommended that a detectable HIV-1 RNA during therapy should be confirmed in a subsequent sample, usually within 2 to 4 weeks, prior to making management decisions. Virologic failure is defined as a confirmed detectable HIV-1 RNA of more than 250 copies/mL after virologic suppression or failure to achieve viral load below 40 copies/mL by at least 24 weeks of therapy.<sup>165</sup> An immediate change in the regimen may not be necessary unless new resistance is documented on genotypic testing. Genotypic resistance testing is advised for all patients with plasma viral load  $>250$  copies/mL, and may be also requested for patients with consistently detectable plasma viral load between 200 and 250 copies/mL; these levels of viremia have been shown in some studies to be predictive of later virologic failure<sup>163,164</sup>. However, the success of genotypic testing decreases at lower viral loads<sup>166</sup>. For information on HIV resistance testing, see: <http://www.cfenet.ubc.ca/clinical-activities/lab-tests/drug-resistance-testing>; to order the test in BC, requisition form available at: <http://cfenet.ubc.ca/research/laboratory-program/laboratory-test-order-forms>. Expert advice should be sought for the management of patients with persistently detectable HIV-1 RNA levels below 250 copies/mL.

Levels of transmitted drug resistance in BC remain stable at around 8-10% overall. The most common clinically important transmitted resistance concerns the NNRTIs, at about 5% of new antiretroviral naïve patients, and slowly increasing [PR Harrigan, personal communication]. However, the presence of transmitted drug resistance may be underestimated if a resistance test is performed in chronically infected individuals, who may be months to years away from early infection. Some drug resistant mutants may persist for a long time (e.g. mutations conferring resistance to NNRTIs). Other drug resistant mutants are replaced promptly by wild-type virus, because they are associated with impaired viral fitness (e.g. M184V). Patients with resistance mutations detected prior to initiation of ART have a 3-



5-fold greater risk of virologic failure, which highlights the importance of pre-therapy resistance testing.<sup>167,168</sup> For confirmed virologic failure, resistance testing is essential and should, when possible, be performed while the patient is still receiving the failing regimen.

Therapeutic drug monitoring (TDM) is not generally recommended, but it may be useful in some settings, such as patients with kidney or liver impairment, to minimize overexposure and adverse effects, manage potential drug-drug interactions, or to evaluate virologic failure in the absence of resistance<sup>169,170,171,172</sup>. TDM may also prove valuable in the management of pregnant women, and children. Random untimed serum drug levels have been useful to assess adherence in selected situations, as well<sup>173</sup>. For information on TDM, see: <http://www.cfenet.ubc.ca/clinical-activities/lab-tests/therapeutic-drug-monitoring>.

Increasing attention has been focused on the monitoring of and interventions to improve ART adherence and in the rates of engagement of HIV-infected patients in the cascade of care. Ongoing initiatives<sup>174,175</sup> have generated quality of care indicators, including in the areas of follow-up of patients under treatment. Finally, management by physicians experienced in HIV medicine is increasingly recognized as a critical contributor to improved health outcomes.<sup>176,177</sup>

## VII TREATMENT EXPERIENCED PATIENTS

### A. Recommendations

- In the setting of confirmed virologic failure (HIV RNA >250 copies/mL at least twice consecutively, particularly if new drug resistance mutations are identified on genotypic testing), changing to a new regimen should be considered promptly. However, this should be tempered by the ability to fully address the determinants of treatment failure, the availability of a fully active (non-cross-resistant) regimen, and the patient's willingness and ability to commit to the new regimen.
- A new regimen should be constructed using resistance testing, both past and present, treatment history, and consideration of tolerability and adherence issues.
- Initial regimen failures should be changed to regimens including a minimum of two and ideally three fully active drugs.
- The management of multidrug resistance is complex, and expert advice should be sought.
- In virologically suppressed patients, switching single agents for toxicity or prevention of anticipated adverse reactions or drug interactions is generally safe and effective. Maintenance of virologic suppression is paramount when switching the regimen to improve tolerability, reduce toxicity, and improve convenience.
- Intensification of or switching therapy has not been successful in improving suboptimal CD4 count responses in the setting of durable virologic suppression and is not recommended.
- Treatment interruptions should be avoided due to increased risk of death, AIDS, and serious non-AIDS morbidity associated with untreated HIV infection. The management of multidrug resistance is complex, and expert advice should be sought.
- Ritonavir-boosted protease inhibitor (PI/r) monotherapy is associated with an increased risk of virologic failure and is not recommended.

## B. Background

New regimens for ART-experienced patients should include fully active drugs, based on previous and recent resistance testing. The regimen should be constructed taking into account prior treatments and adverse effect history, and future ART regimen options. It is critical to fully understand and correct the determinants of prior treatment failure to avoid compromising the potential efficacy of the new regimen. Potential reasons for treatment failures may include virologic failure, adverse effects, exacerbation of co-morbidities, drug- drug interaction, pill burden, or adherence reasons. Seeking expert advice is strongly encouraged in the assessment and management of treatment failure.

## C. Management of Initial Virologic Failure

Management of virologic failure of an initial regimen calls for a new regimen with at least two and preferably three active drugs. On confirmation of virologic failure, a change of regimen should be considered promptly. However, this should be tempered by the ability to fully address the determinants of treatment failure, the availability of a fully active (non-cross- resistant) regimen, and the patient's willingness and ability to commit to the new regimen.

### 1. **Initial NNRTI-based regimens.**

NNRTI and/or nRTI resistance mutations are more likely to emerge upon failure of these regimens than with PI based regimens<sup>178,179</sup>. Delaying a treatment change allows the accumulation of additional nRTI and NNRTI mutations that may limit future treatment options within these classes. Generating a new regimen with three active agents is attainable using a PI/r and active nRTIs. If the choice is limited by resistance, HLA-B\*5701 carriage, or adverse reactions, use of agents from other classes such as InSTIs or CCR5 inhibitors are options.

### 2. **Initial ritonavir-boosted PI-based regimens.**

Initial virologic failure of a ritonavir-boosted PI-based regimen is typically not associated with emergent PI mutations; however, it may be associated with limited nRTI (most often M184V) mutation(s). The presence of the M184V mutant does not preclude ongoing response to a lamivudine- or emtricitabine-containing ritonavir-boosted PI- based therapy, as long as the PI and the second agent are fully active. If the nRTI backbone is otherwise compromised, NNRTIs or raltegravir should be used with caution due to their low genetic barrier to resistance. Darunavir/ritonavir may be preferable in this situation, since is associated with a lower incidence of virologic failure than lopinavir/ritonavir in treatment-experienced patients.<sup>180</sup> In the presence of PI-resistance- associated drug mutations, darunavir/ritonavir should be administered twice daily instead of once daily to achieve higher drug concentrations.<sup>181</sup>

### 3. **Initial Integrase-inhibitor-based regimens.**

There are several available treatment options with three fully active drugs from classes not used in an initial raltegravir-based regimen. Standard genotypic tests do not include the integrase region; however, this is available upon request from the BC-CfE



Virology Laboratory. Raltegravir and elvitegravir are almost completely cross-resistant. Prompt discontinuation of these drugs in a failing regimen will increase the potential utility of dolutegravir, as discussed below.

#### D. Management of Multi-Drug Resistant Virologic Failure

Following virologic failure of second and later regimens, the presence of multi-class drug resistance (MDR) becomes increasingly likely. MDR can also be found among ART naïve patients who present with transmitted drug resistance to three classes, although this is currently rare in BC. Effective regimens will usually include a PI/r with activity against resistant strains, such as darunavir/ritonavir, combined with raltegravir and potentially etravirine (all given twice daily), depending on the spectrum of NNRTI mutations detected.<sup>182</sup> Upon request, the BC-CfE Virology Laboratory can reevaluate past resistance tests to include estimates of etravirine or rilpivirine resistance if this was not included in the original report. The entry inhibitor enfuvirtide also was used successfully in salvage regimens in the past, but is rarely used now because of cost, inconvenience and poor tolerability due to injection site reactions. Maraviroc is a potentially effective option if the MDR virus is CCR5-tropic. In patients with MDR and very few treatment options, continuation of some nRTIs, such as lamivudine or emtricitabine and/or tenofovir DF, might be considered even if resistance is present, because residual activity of these compounds has been demonstrated in this setting.<sup>183</sup> Expert advice should be sought in the management of MDR virus.

Dolutegravir appears to have substantial activity against raltegravir- and elvitegravir-resistant viruses, but reduced susceptibility has been reported for viruses with the Q148 or G140 mutations.<sup>184,185</sup> With high-level raltegravir resistance, there is no clinical benefit from continuing raltegravir.<sup>186</sup> In the presence of drug resistance-associated mutations, dolutegravir should be given twice daily instead of once daily to achieve higher drug concentrations<sup>187</sup>.

Treatment interruptions are strongly discouraged as they have been shown to be associated with increased risk of disease progression and death.<sup>188,189</sup> Treatment interruptions are acceptable in specific situations, including very short interruptions due to surgery, severe illness, or serious drug toxicity. For planned short treatment interruption, the different half-lives of the individual components of the ART regimen should be considered, as this may dictate the need for a staggered cessation of treatment or a drug replacement strategy prior to full discontinuation, to prevent the emergence of drug resistance.<sup>190</sup>

#### E. Management of Immunologic Failure

Lower CD4 cell counts at ART initiation are associated with suboptimal immunologic responses despite adequate viral suppression. In the longest study conducted to date, the percentage of patients with suppressed viremia who reached a CD4 count >500 cells/μL through 6 years of treatment was 42% in those starting treatment with a CD4 count <200 cells/μL, 66% in those starting with a CD4 count 200 to 350 cells/μL, and 85% in those starting with a CD4 count >350 cells/μL.<sup>191,192,193</sup>

Other factors that have been associated with poor CD4 recovery include<sup>194</sup>:

- Older age
- Coinfection e.g. HCV
- Certain antiretrovirals (e.g. zidovudine, tenofovir DF + didanosine) and other medications
- Persistent immune activation
- Loss of regenerative potential of the immune system
- Concomitant medical conditions

Higher risk of morbidity (due to AIDS and serious non-AIDS events) and mortality are reported in those with poor immunologic recovery despite virologic suppression.<sup>195</sup> A number of strategies to improve CD4 count responses have been evaluated, including switching of nRTIs or class of drugs<sup>196</sup> and treatment intensification, with no consistent success.<sup>197,198,199</sup>

Currently, there is no immune-based therapy that has shown a clinical benefit in this situation.<sup>200</sup>

## F. Switching for ART Regimens for Toxicity or Improved Tolerability and Adherence

In virologically suppressed patients, switching regimens to reduce short- or long-term toxicity, to improve tolerability and adherence, or to address or minimize drug interactions, can be done by switching one or more agents in the regimen. Single-agent switches for acute or chronic toxicity are possible in patients with virologic suppression, as long as regimen potency is maintained. Switching from a boosted protease inhibitor (PI/r) to raltegravir has shown conflicting results,<sup>201,202</sup> primarily related to the activity of the background regimen. It is therefore recommended that the continued integrity of the ART backbone be taken into consideration when switching drugs in virologically suppressed patients, and this is particularly critical if the genetic barrier of the new regimen is lower than that of the preceding one. The latter is the case when going from a PI/r to an NNRTI or raltegravir or maraviroc, while preserving the nRTIs in the existing regimen.

In virologically suppressed patients with efavirenz intolerance or toxicity, nevirapine or rilpivirine substitution has proven safe and effective.<sup>100,203</sup> Of note, there was no increased risk of nevirapine-induced hepatotoxicity or rash, even in the presence of high CD4 counts at the time of the switch from efavirenz to nevirapine.<sup>204,205</sup> The rilpivirine switch can be accomplished with rilpivirine/tenofovir DF/emtricitabine FDC. In this scenario, efavirenz can also be replaced with a PI/r or InSTI or maraviroc, if the tropism assay is favourable. However, there are fewer supporting data for switching to a maraviroc-based regimen in virologically suppressed individuals. An experimental assay is available at the BC-CfE virology laboratory to determine tropism in individuals with undetectable plasma viral load. For information on tropism testing, see: <http://www.cfenet.ubc.ca/clinical-activities/lab-tests/ccr5-tropism>; to order the test in BC, requisition form available at: <http://cfenet.ubc.ca/research/laboratory-program/laboratory-test-order-forms>

Preemptive or reactive changes for short- and long-term toxic effects such as metabolic

abnormalities,<sup>206</sup> and prevention of or management of lipodystrophy, cardiovascular risk,<sup>207</sup> and renal impairment, have been used successfully with maintenance of virologic suppression.

## G. ART Simplification

A number of strategies have been explored for regimen simplification in virologically suppressed patients. Reduction in pill burden using FDCs or decreasing regimen dosing to improve or maintain adherence has been used successfully, and a meta-analysis has confirmed better adherence for once-daily versus twice-daily dosing regimens.<sup>208,209</sup> Of note, however, raltegravir once-daily dosing was inferior to twice-daily dosing in a study of simplification from ritonavir-boosted PI- based regimens.<sup>210</sup> Once-daily dosing of darunavir/ritonavir is effective in treatment-experienced patients with either no prior exposure to PIs or no darunavir- associated resistance mutations.<sup>211</sup>

The induction/maintenance strategy of initiating therapy with two NRTIs and a PI/r until virologic suppression is achieved, with subsequent continuation with PI/r alone has been evaluated for lopinavir/ritonavir and darunavir/ritonavir. A darunavir/ritonavir monotherapy maintenance strategy reported good efficacy, but concern about poor central nervous system (CNS) penetration persists with reports of discordant plasma and cerebrospinal fluid (CSF) viral loads.<sup>212</sup> This also was observed in a randomized trial of lopinavir/ritonavir monotherapy maintenance.<sup>213</sup> Therefore, the use of PI/r monotherapy is strongly discouraged due to higher rates of virologic failure.

Among currently available PIs, only atazanavir has the potential for unboosting, i.e. switching to atazanavir 400mg daily without ritonavir, offering a potential option for virologically suppressed patients experiencing ritonavir-related intolerance or toxicity (e.g. hyperbilirubinemia) on atazanavir/ritonavir. This strategy has been successfully implemented in a number of clinical trials with abacavir/lamivudine backbones<sup>214,215</sup>. Because of a negative drug-drug interaction between tenofovir DF and atazanavir, unboosting should be undertaken with caution in patients taking atazanavir with a tenofovir DF-based backbone. In this setting, consideration should be given to adjusting the backbone to abacavir/lamivudine, if possible<sup>216</sup>.

There are limited data to support switching to unboosted atazanavir while maintaining the tenofovir DF backbone<sup>217</sup>; this strategy should be implemented with TDM guidance under the advice of an experienced HIV-treating physician.

## VIII USE OF ART FOR PREVENTION OF HIV INFECTION

### A. Introduction

A comprehensive HIV prevention package includes strategic use of ART as well as behavioural and structural approaches, as recently reviewed elsewhere<sup>218</sup>.

### B. Treatment as Prevention<sup>®</sup>

Treatment as Prevention<sup>®</sup> (TasP<sup>®</sup>) refers to the use of ART in the infected person and the

secondary preventive benefit derived from it. Reducing levels of HIV with ART decreases the probability of transmission, a fact confirmed by the HPTN 052 randomized controlled trial,<sup>3</sup> and supported by preliminary results of the PARTNER Study<sup>45</sup>.

Several communities with high ART coverage have observed reduced “community viral loads” and subsequent lower rates of new HIV diagnoses.<sup>61, 219, 220</sup> In the absence of a cure or a vaccine, the use of HIV treatment as prevention addresses an important public health objective. Of note, the evidence that HIV treatment is a highly effective preventive strategy converges with a growing body of evidence favouring the expansion of ART coverage based on individual benefit considerations. As such, a powerful synergy has emerged between the recommendations for the treatment of the individual and the public health goal of preventing new HIV infections.

In response to the mounting evidence for the multiple benefits of expanding ART programs worldwide, in 2014 UNAIDS announced their new “90-90-90” targets for 2020, calling for 90% of people living with HIV to know their status, 90% of diagnosed people to be receiving effective ART, and 90% of people receiving ART to be virologically suppressed (<http://www.unaids.org/en/resources/documents/2014/90-90-90>). Estimates show that achieving these ambitious targets would mean that by 2020, 73% of people living with HIV globally would have undetectable plasma viral load, and by 2030 the HIV/AIDS pandemic could be transformed into a low level sporadic endemic.

However, many challenges remain, including limited workforce resources, the need to implement broader testing and to enhance engagement within the full cascade of care, and the need to develop comprehensive strategies to address co-morbidities and social inequities. Finally, there is a critical need to correct the persistent and pervasive stigma, discrimination and criminalization that continue to affect HIV-infected individuals and most at-risk populations. This issue has been compounded by the 2012 decision of the Supreme Court of Canada on the issue of HIV disclosure (<http://scc.lexum.org/decisia-scc-csc/scc-csc/scc-csc/en/item/10008/index.do>).<sup>221</sup>

### C. Post-exposure prophylaxis (PEP)

ART also plays an important role in post-exposure prophylaxis. The BC-CfE offers a fully funded program for accidental, work related and sexual assault cases; the BC-CfE guidelines for post-exposure prophylaxis are available at <http://cfenet.ubc.ca/therapeutic-guidelines/> accidental-exposure. In 2012, the BC-CfE initiated a non-occupational post-exposure prophylaxis (nPEP) pilot program in selected Vancouver sites. Following the completion of the pilot, recommendations will be developed and presented to the Ministry of Health Pharmacare program for consideration.

### D. Pre-exposure Prophylaxis (PrEP)

Evidence is emerging regarding the use of ART as oral pre-exposure prophylaxis (PrEP). This approach has been shown to be effective in 4 large trials using daily tenofovir DF/emtricitabine or tenofovir DF, one in gay and bisexual men and transgender women (iPrEX),<sup>222</sup> one in heterosexual HIV serodiscordant couples (Partners PrEP),<sup>223</sup> one in heterosexual men

and women (TDF2),<sup>224</sup> and one in people who inject drugs (Bangkok TDF Study)<sup>225</sup>. A PrEP trial in high-risk women (FEM-PrEP)<sup>226</sup> and one with an oral daily tenofovir DF arm (VOICE)<sup>227</sup> failed to show benefit. The effectiveness of PrEP has been shown to be directly associated with medication adherence. The high efficacy rate (86%-90%) in Partners PrEP was associated with an estimated 82% adherence level<sup>223</sup> and the FEM PrEP trial that showed no benefit had a very low level of adherence<sup>226</sup>, with iPrEX between these in both effect and adherence<sup>222</sup>. In 2014, the US Centers for Disease Control and Prevention published clinical practice guidelines for management of patients taking TDF/FTC for PrEP.<sup>228</sup> More recently, PrEP studies using tenofovir DF/emtricitabine, taken either continuously (The PROUD Study in the UK) or on a frequent on-demand basis (ANRS Ipergay Trial in France and Canada), demonstrated relative reductions in HIV incidence of 86% among high-risk men who have sex with men<sup>229,230</sup>. At this time, the use of PrEP is considered a medically acceptable option for selected individuals; however, this approach is not currently approved by Health Canada, nor is it funded by the BC-CfE Drug Treatment Program. The BC-CfE has provided recommendations for appropriate use of PrEP which are available on its website (<http://www.cfenet.ubc.ca/hiv-pre-exposure-prophylaxis-prep>).

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