BRITISH COLUMBIA
CENTRE *for* EXCELLENCE
in HIV/AIDS

THERAPEUTIC GUIDELINES

ANTIRETROVIRAL (ARV) TREATMENT OF ADULT HIV INFECTION

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The BC-CfE 2013 Therapeutic Guidelines remain generally consistent with the IAS-USA Guidelines, as has been the case since 1996. The current Guidelines are therefore consistent but not identical to those published by M. Thompson et al. in 2012 (Thompson MA, Aberg JA, Hoy JF, et al. Antiretroviral Treatment of Adult HIV Infection: 2012 Recommendations of the International Antiviral Society–USA Panel. JAMA 2012; 308(4):387–402). 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 2013 Guidelines as outlined here.

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I SUMMARY

Treatment is recommended for all HIV infected individuals, except for elite controllers (HIV-1-RNA below the level of quantification without antiretroviral therapy [ART]) and long-term non-progressors (those with stable CD4 cell counts above 500/μL and HIV-1-RNA below 1000 copies/mL while not on ART). The strength of the recommendations (based on the quality of the evidence) increases with decreasing CD4 count and under specific circumstances, such as increasing age, chronic hepatitis C or B infection, established cardiovascular disease or high cardiovascular risk, or HIV associated nephropathy.

ART today represents a lifelong 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); plus either the non-nucleoside RTI (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, etravirine, or nevirapine; the PIs darunavir/r or lopinavir/r; the integrase strand-transfer inhibitors raltegravir or elvitegravir/cobicistat; or the CCR5 attachment inhibitor 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 consistent 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 200 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-1 RNA level should be monitored frequently after the start of ART: every month until plasma HIV-1-RNA 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/μL and the viral load is consistently <40 copies/mL for at least 1 year, the monitoring interval can be increased to every six months. 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 >200 copies/mL), HLA-B*5701 screening prior to initiation of abacavir, and tropism assay prior to initiation of maraviroc. 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.

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 >200 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 be broadly classified as due to virologic, toxicity, tolerance, pharmacological or adherence reasons. Seeking expert advice is strongly encouraged in the assessment and management of treatment failure.

II INTRODUCTION

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

The 2013 BC Centre for Excellence in HIV/AIDS (BC-CfE) Antiretroviral Therapy Guidelines represents an update of the January 2011 edition, and aims to capitalize on improved therapeutic options that have become available over the last two years. 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.[6] 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 2013 Guidelines as outlined here.

III WHEN TO START

As recommended in the 2011 Guidelines, ART should continue to be offered to all HIV infected individuals regardless of their CD4 cell count, except for elite controllers (HIV-1-RNA below the level of quantification without ART) and long-term non-progressors (those with stable CD4 cell counts above 500/μL and HIV-1-RNA below 1000 copies/mL while not on 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, age over 50 years, chronic hepatitis C or B infection, established cardiovascular disease or high cardiovascular risk, or HIV associated nephropathy).

The recommendation to initiate ART under these circumstances is supported by observational cohort data and data from a randomized controlled trials (RCTs) showing that immediate use of ART at CD4 cell counts of above 350/μL is associated with clinical benefit to the individual. In the HIV Prevention Trials Network (HPTN) study 052, a secondary marked reduction (over 96%) in the likelihood of sexual transmission of HIV was also demonstrated.[3] A similar benefit was previously documented within cohorts of injection drug users.[7] [8]

There is no CD4 count threshold above which starting therapy is contraindicated. However, it is noteworthy that the strength of the evidence in support of starting ART increases as the CD4 count decreases, and when certain concurrent conditions are present. Also, while ART is not indicated for elite controllers or long-term non-progressors at this time, such individuals should be monitored at no less than semiannual intervals because they are still at risk of disease progression.

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. Special efforts should be taken to ensure that the patient has adequate adherence education and support.[9] These issues should be regularly evaluated and proactively optimized.

A Recent Evidence

In the HIV-CAUSAL collaboration, there was a significant and steady decrease in AIDS-free survival as the CD4 count threshold for initiation of therapy decreased, with an estimated 38% increase in the hazard of AIDS or death when ART was initiated at a CD4 cell count <350/μL compared with <500/μL.[10] The CASCADE seroconversion cohort, involving over 9000 participants with known duration of HIV infection, confirmed the benefits of starting ART below 500 CD4 cells/μL.[11]

The COHERE study, involving 75,336 individuals, examined the prognostic value of the CD4 count after ART-driven virologic suppression. In this study, higher CD4 counts were associated with progressive decreases in risk of new AIDS events, all cause mortality, and non-AIDS mortality across all CD4 strata up to 500 cells/μL, and a slightly reduced risk of disease progression above 500 cells/μL.[12] Similar results were reported within a sub-Saharan cohort.[13] In the ATHENA cohort,[14] older age, lower CD4 cell nadir, and lower plasma HIV-1 RNA at the start of ART were independent predictors of a poor immunologic recovery and increased morbidity and mortality. Furthermore, the HPTN 052 study of 1763 HIV serodiscordant couples with CD4 cell counts between 350/μL and 550/μL showed that immediate ART initiation resulted in a 41% reduction in the combined endpoint of disease progression and death.[3]

A registry of more than 20,000 HIV-infected and 215,000 -uninfected persons observed that most cancers were either no longer elevated or were greatly decreased in HIV-infected persons with CD4 cell counts

≥500/μL compared with HIV uninfected persons.[15] Finally, several cross-sectional studies examining the effect of CD4 count nadir on surrogate markers of cardiovascular risk suggested benefit for early ART.[16] [17] [18]

B Treatment as Prevention

The concentration of HIV in both blood and seminal plasma correlates with the probability of transmission of HIV to a sexual partner.[19] Reducing levels of HIV with ART decreases the probability of transmission, as confirmed by the HPTN 052 study.[3] This study found ART to be over 96% effective in reducing HIV transmission from an HIV-infected person to his or her HIV-uninfected partner. Reduction of transmission has also been shown in high-risk men who have sex with men (MSM), [20] although viral suppression in plasma does not guarantee suppression in semen, especially in the presence of inflammation.[21] Additionally, other sexually transmitted infections (STIs) such as hepatitis C virus (HCV)[22] [23] and syphilis[24] continue to be reported, especially in MSM, underscoring the importance of continued promotion of safer sex practices, including continued condom use.

Several communities with high ART coverage have observed reduced "community viral loads" and subsequent lower rates of new HIV diagnoses.[25] [26] [27] 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. 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 recent 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).[28]

C Special Considerations

1. **Pregnancy**. ART is indicated for all pregnant women for the mother's health and to prevent vertical 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[29] and adherence appears to be improved rather than reduced during pregnancy.[30] [31] The Antiretroviral Pregnancy Registry of more than 15,000 HIV exposures reported from January 1989 through July 2011 notes no increase in the rates of congenital birth defects with exposure to ART, including to efavirenz, even in the first trimester.[32] 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.[33] Furthermore, ART should not be discontinued post-partum given both the potential benefits for the mother's health and the risks associated with HIV transmission during breastfeeding and with treatment interruption. The US Department of Health and Human Services (DHHS) has recently updated the recommendations for use of antiretroviral agents in pregnancy. [34] Treatment of HIV positive women who are pregnant or planning to become preg-

nant should be done under expert guidance.[35] In BC, contact the Oak Tree Clinic at BC Women's and Hospital and Health Centre (604-875-2212; toll free 1-888-711-3030)

2. **Opportunistic infections (OIs).** Initiation of ART early after starting active OI treatment has been generally associated with improved survival.[36 37] However, regardless of the OI in question, the potential for drug interactions must be considered. Furthermore, recent data have raised concerns about the timing of ART initiation in the context of cryptococcal meningitis. In a randomized controlled trial (RCT), 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.[38] Immune reconstitution inflammatory syndrome (IRIS) occurred in patients in both groups, but the increased mortality was not attributable solely to IRIS. Whether these results can be generalized is unclear as patients in this study, conducted in Zimbabwe, received antifungal therapy with fluconazole alone.

   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/μL, and for this subgroup the optimal time of ART initiation was within the first 2 weeks of TB treatment.[39 40 41] 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.[42] There were few deaths related to IRIS in these trials, but there were also few patients enrolled with TB meningitis. In a randomized trial in 253 patients with HIV and TB meningitis, initiation of ART within 2 weeks of TB treatment compared with 8 weeks of treatment was not associated with a survival benefit and patients in the immediate ART arm had significantly more severe adverse events. Of note, patients in this study were severely ill and therefore these results may not be generalizable.[43]

3. **Hepatitis B virus (HBV).** HIV increases the risk of liver-related morbidity and mortality in persons also infected with HBV.[44] Furthermore, the ability to treat both infections with the same medications provides a compelling argument for the concomitant treatment of all HIV and HBV co-infected persons. Failing treatments may expose the individual to an increased risk for the development of HBV resistance to dually active agents, including tenofovir, emtricitabine and lamivudine.

4. **Hepatitis C virus (HCV).** HIV increases the risk of liver-related morbidity and mortality in persons also infected with HCV.[44] In some, but not all studies, treatment of HIV reduces progression of HCV-related liver disease and ART improves HCV treatment response.[45 46 47] If the CD4 cell count is above 500 cells/μL, ART initiation may be deferred until HCV treatment is completed, especially if there are potential drug interactions or overlapping toxicities between the two regimens.

5. **Other considerations.** As in previous BC-CfE guidelines, age older than 50 years, HIV-associated nephropathy, and established cardiovascular disease or high cardiovascular risk are indications to start ART regardless of CD4 count.

6. **Acute HIV Infection**. ART initiation continues to be recommended for people with symptomatic acute HIV infection. ART initiation is now also recommended for those with asymptomatic acute HIV infection, based on physiopathological studies. Some recent studies have shown that early treatment is associated with reduced lymphoid tissue pathology, conserved lymphocyte function,[48] decreased cell-associated HIV-1 DNA,[49] and a transient reduction of viral set point after treatment interruption.[50] RCTs 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.[51] [52] Individuals with acute infection have higher levels of HIV-1 RNA in blood and sexual fluids, increasing the risk of transmission per sexual contact.[53]

D Recommendations regarding when to start ART

- Patient readiness for treatment should be carefully considered and optimized. Special efforts should be taken to ensure that the patient has adequate adherence education and support.
- ART should be offered 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 strongly recommended for:
    - Symptomatic HIV infection, including AIDS-defining opportunistic infections or cancers
        - ART should be started as soon as possible, preferably within the first 2 weeks of diagnosis, in patients with OIs other than cryptococcal and TB meningitis. The optimal timing in the setting of cryptococcal and TB meningitis is unclear, but ART should be started within the first 8 weeks in consultation with experts.
        - ART is recommended in all HIV-infected persons with TB and should be started within 2 weeks of TB treatment when the CD4 count is below 50 cells/μL and by 8 to 12 weeks for those with higher CD4 counts.
    - Asymptomatic infection, at a CD4 cell count of 500/μL and below
    - The HIV-infected member of a serodiscordant couple, regardless of symptoms or CD4 count, to prevent transmission to the HIV-uninfected partner
    - CD4 cell count above 500/μL, if any of these conditions is present:
        - Pregnancy
        - Chronic HBV co-infection
        - Chronic HCV co-infection (ART may be deferred until after HCV treatment)
        - Age older than 50 years
        - Cardiovascular disease or high cardiovascular risk
        - HIV-associated nephropathy

IV WHAT TO START

A Introduction

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 lifelong 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, lifelong, 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.[54] [55] [56] The cost of ART represents an increasingly important concern. As they become available, generic drugs are likely to play a more prominent role in the treatment of HIV infection.

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) or a CCR5 chemokine receptor antagonist may be considered. For each component of a regimen, specific situations can dictate different recommended and alternative agents (Tables 1 and 2).

There is no evidence that drug efficacy differs among different subtypes of HIV-1.[57] 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.[58] 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.

TABLE 1: ART REGIMEN OPTIONS FOR TREATMENT-NAIVE ADULTS

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

	Recommended[1]	Alternative 3rd Agent[1] [2]
Non-nucleoside reverse transcriptase inhibitor (NNRTI)	Efavirenz/emtricitabine/tenofovir (EFV/FTC/TDF) Efavirenz/lamivudine/tenofovir (EFV/3TC/TDF) Efavirenz/lamivudine/abacavir (EFV/3TC/ABC)* * if HLAB*5701 negative and preferably baseline plasma viral load (pVL) <100,000 copies/mL	Nevirapine (NVP)* Rilpivirine (RPV)† Etravirine (ETV) BID * men with CD4<400 cells/mm^3, women with CD4<250 cells/mm^3 † if baseline pVL <100,000 copies/mL
Boosted protease inhibitor (PI)	Atazanavir/ritonavir (ATV/r) + either emtricitabine/tenofovir (FTC/TDF) or lamivudine/tenofovir (3TC/TDF) or lamivudine /abacavir (3TC/ABC)* * if HLAB*5701 negative and preferably baseline pVL <100,000 copies/mL	Darunavir/ritonavir (DRV/r) Lopinavir/ritonavir (LPV/r)
Integrase Inhibitors		Raltegravir (RAL) BID Elvitegravir (EVG)/cobicistat* Dolutegravir (DTG)† * only available as FDC with emtricitabine/tenofovir † pending regulatory approval
CCR5 Antagonist		Maraviroc (MVC) BID* * if CCR5 tropic virus identified on tropism testing

[1] Administered once daily unless specified to be given twice daily (BID)
[2] With either emtricitabine/tenofovir, lamivudine/tenofovir, or lamivudine/abacavir
FDC, fixed-dose combination

TABLE 2: ANTIRETROVIRAL DRUG DOSING, ADMINISTRATION, AND KEY DRUG INTERACTIONS

	Generic name, abbreviation	Brand Name	Usual dose in first line	Dosing/ Administration Issues	Key Drug Interactions
Nucleoside/ tide Reverse Transcriptase Inhibitor (NRTI)	abacavir (ABC)	Ziagen	600 mg QD	Avoid if HLA-B*5701 positive	
	lamivudine (3TC)	3TC	300 mg QD		
	tenofovir (TDF)	Viread	300 mg QD		didanosine; caution nephrotoxic drugs
NRTI combination products	tenofovir-emtricitabine (TDF/FTC)	Truvada	1 tablet QD		didanosine; caution nephrotoxic drugs
	abacavir-lamivudine (ABC/3TC)	Kivexa	1 tablet QD	Avoid if HLA-B*5701 positive	
Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI)	efavirenz (EFV)	Sustiva	600 mg QD	Take at bedtime, preferably on an empty stomach to minimize side effects	CYP450 metabolized drugs*
	etravirine (ETV)	Intelence	200 mg BID	Take with food	CYP450 metabolized drugs*
	nevirapine (NVP)	Viramune	400mg QD	Lead in dose (200mg daily) × 14 days	CYP450 metabolized drugs*
	rilpivirine (RPV)	Edurant	25 mg QD	Take with a meal (500–600 kcal)	CYP450 metabolized drugs*; proton pump inhibitors
Boosted Protease Inhibitor (PI)	atazanavir (ATV)	Reyataz	300 mg/r 100 mg QD	Take with food (340 kcal)	CYP450 metabolized drugs*; proton pump inhibitors
	darunavir (DRV)	Prezista	800 mg/r 100 mg QD	Take with food	CYP450 metabolized drugs*
	lopinavir/ritonavir (LPV/r)	Kaletra	800mg/200mg QD or 400mg/100mg BID		CYP450 metabolized drugs*
	ritonavir (RTV, r)	Norvir	—	Take with food	CYP450 metabolized drugs*
Integrase Inhibitor	raltegravir (RAL)	Isentress	400 mg BID		
CCR5 Inhibitor	maraviroc (MVC)	Celsentri	300 mg BID		CYP450 metabolized drugs*
Multi-class combination products	efavirenz-tenofovir-emtricitabine (EFV/TDF/FTC)	Atripla	1 tablet QD	Take at bedtime, preferably on an empty stomach to minimize side effects	CYP450 metabolized drugs*; didanosine; caution nephrotoxic drugs
	rilpivirine-tenofovir-emtricitabine (RPV/TDF/FTC)	Complera	1 tablet QD	Take with a meal (500–600 kcal)	CYP450 metabolized drugs*; didanosine; proton pump inhibitors; caution nephrotoxic drugs
	elvitegravir-cobicistat-tenofovir-emtricitabine (EVG/COBI/TDF/FTC)	Stribild	1 tablet QD	Take with food	CYP450 metabolized drugs*; didanosine; caution nephrotoxic drugs

CYP450, Cytochrome P450
QD, once daily
BID, twice daily
*Consult with St Paul's Hospital Ambulatory Pharmacy (toll-free) 1-888-511-6222

B Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (nRTIs)

1. Recommended nRTIs

Tenofovir disoproxil fumarate (TDF) and *emtricitabine* (FTC) are available together in a once-daily FDC with no food restrictions. Tenofovir 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.[59] [60] [61] [62] Renal function (serum creatinine, estimated glomerular filtration rate [eGFR], phosphorus, urinalysis, urine albumin and/or protein to creatinine ratio) should be assessed before use and monitored over time.[63] TDF should be avoided, if at all possible, in the case of renal impairment (eGFR below 50 mL/min). If TDF 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,[64] with the guidance of the St. Paul's Hospital Pharmacy (1-888-511-6222). TDF has been associated with decreases in bone mineral density in the spine and hip and increased risk of osteoporotic fractures.[65] [66] FTC is clinically similar to lamivudine (3TC); however, it has been associated with rashes and gastrointestinal intolerance, particularly among women.[67] If FTC is not tolerated, *lamivudine* (3TC) can be given with TDF as separate entities. 3TC is extremely well tolerated.

Abacavir (ABC) and 3TC 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 ABC and this drug should not be prescribed to a patient who is positive for HLA-B*5701. This strategy markedly reduces the risk of potentially life-threatening hypersensitivity reactions to ABC. In one RCT, initial regimens containing the ABC/3TC backbone had lower rates of viral suppression than regimens containing TDF/FTC in persons with baseline HIV-1 RNA levels above 100,000 copies/mL.[44] This remains controversial as this effect was not confirmed in a second randomized trial.[68] The current recommendation is to avoid starting ABC-based regimens in patients with viral load above 100,000 copies/mL; however, ABC may be used in this situation with close monitoring, if it is judged to be the most suitable option In some non-randomized observational cohort studies, recent use of ABC has been associated with a higher risk for acute myocardial infarction or other cardiovascular events.[69] [70] However, other cohort studies and randomized controlled trials have not confirmed this association.[71] [72] [73] Furthermore, three large meta-analyses of RCT data, one of which was conducted by the United States Food and Drug Administration (FDA), failed to find any evidence of an association between ABC use and increased risk of cardiovascular events,[74] [75] [76] and a plausible biological mechanism for such an association has yet to be demonstrated. Given the uncertainty of the association, use of ABC 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 (ZDV) and 3TC 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 ABC or TDF, and in some cases during pregnancy. Stavudine (d4T) and didanosine (ddI) are generally no longer acceptable alternatives because of tolerability and safety concerns.

C Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Nevirapine (NVP), *efavirenz* (EFV), and *rilpivirine* (RPV) are each available as a single pill for once-daily use; the two latter drugs are available in FDCs with TDF and FTC. *Etravirine* is usually reserved for later treatment as it has a higher pill burden.

1. Recommended NNRTIs

Efavirenz (EFV) is used once daily, preferably without food, at bedtime. Central nervous system side effects include sleep disturbance, abnormal dreams, and less commonly, depressed mood.[77] [78] EFV can cause a rash, which usually, but not always, decreases despite continued treatment.

2. Alternative NNRTIs

Nevirapine (NVP) is available in a 400 mg once-daily formulation. NVP requires a two-week lead-in of 200 mg once daily.[79] Rash is more common and may be more severe than with EFV. 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/μL and men with baseline CD4 counts above 400/μL; therefore, NVP is not recommended in these situations.

Rilpivirine (RPV) is administered once daily. In 2 studies, efficacy of RPV was non-inferior to that of EFV; however, rates of virologic failure were higher with RPV and rates of adverse events were higher with EFV.[80] [81] Virologic failure was more common with RPV than with EFV in patients with HIV-1 RNA above 100,000 copies/mL at baseline; RPV should be avoided in this population. RPV has substantial food interactions and should be taken with at least a 500–600 calorie meal. Concomitant use of proton-pump inhibitors is contraindicated. RPV inhibits tubular transport of creatinine, resulting in an increase in serum creatinine during the first 2 weeks of use, without affecting renal function.[81] [82] In clinical trials, doses of RPV higher than the currently recommended dose were associated with QTc interval prolongation.[83]

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.

D 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. A new, virologically inactive booster, cobicistat, has recently become available.[84] As a class, PIs may be associated with mild to moderate nausea, diarrhea, and dyslipidemia and other metabolic disorders. All PIs may be associated with cardiac conduction abnormalities, particularly PR interval prolongation.[85] Some ritonavir-boosted PIs (saquinavir and lopinavir) have been associated with QTc interval prolongation.[86] [87] 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). A pre-HAART baseline electrocardiogram (ECG) should be considered, and the ECG should be monitored if concomitant use of other PR- or QTc-prolonging drugs cannot be avoided.

1. Recommended PIs

Ritonavir-boosted atazanavir (ATV/r) 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. ATV/r 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 ATV dose in selected cases. Expert advice should be sought to optimally use and interpret TDM. ATV is available for use without boosting, but its potency is reduced and therefore unboosted ATV is not

recommended for initial treatment. ATV/r may be associated with nephrolithiasis [88] and renal dysfunction, independent of TDF.[60 62] ATV/r is the only PI/r shown to have similar efficacy to EFV-based therapy in a large randomized trial.[89]

2. Alternative PIs

Alternative ritonavir-boosted PIs include *darunavir (DRV/r)* and *lopinavir (LPV/r)*.

DRV/r is used once daily in initial regimens and should be taken with a meal to improve bioavailability. DRV contains a sulfonamide moiety and may produce hypersensitivity reactions, especially in people with a known sulfonamide allergy.

LPV is only available as a FDC with ritonavir. Fewer individuals randomized to LPV/r in combination with TDF/FTC maintained their HIV-1 RNA below 50 copies/mL at 48 and 96 weeks as compared to those randomized to DRV/r or ATV/r.[90] LPV/r 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. LPV/r has been associated in cohort studies with increased risk of renal dysfunction[60 62] and cardiovascular events.[69 71]

Other alternatives, which are recommended less often, include *fosamprenavir* (FPV) or *saquinavir* (SQV), both boosted with ritonavir. These may be used once daily, taken with a meal, in initial therapy. FPV contains a sulfonamide moiety and may cause rash, and is associated with gastrointestinal symptoms similar to LPV/r. Also like LPV/r, FPV/r has been associated with CVD risk in cohort studies.[71] In one randomized trial, once-daily SQV/r was non-inferior to ATV/r and had comparably mild adverse effects.[91] However, due to high pill burden and other issues, SQV/r is seldom recommended now.

E Integrase Strand Transfer Inhibitors (InSTIs)

InSTIs are the newest class of potent antiretroviral drugs used with a dual nRTI backbone. Similar to the NNRTIs, current InSTIs may have a relatively low genetic barrier to resistance when compared to the PI/r class.

1. Recommended InSTIs

Raltegravir (RAL) should be used twice daily as once-daily dosing diminishes efficacy.[92] RAL does not require concomitant food consumption. It is well tolerated with minimal metabolic impact or other long-term toxicities. It has few drug interactions with concomitant medications, including chemotherapeutic agents and newer agents used to treat HCV.[11]

2. Alternative InSTIs

Elvitegravir (ELV) is a new InSTI recently approved in Canada. It must be boosted to achieve sufficient potency and thus is co-formulated with the new boosting agent *cobicistat* and with the nRTIs TDF and FTC.[93] This FDC 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.[94] How to best manage creatinine increases in the context of co-administered TDF has not yet been fully defined. Like ritonavir, cobicistat is associated with gastrointestinal side effects. At this time, ELV and cobicistat are not available as separate entities (outside the FDC with TDF/FTC) through the BCCfE Drug Treatment Program.

Dolutegravir (DTG) is an investigational InSTI pending regulatory approval in Canada. It is administered once daily without the need for a pharmacologic booster, and has demonstrated non-inferior efficacy

and similar safety to raltegravir in clinical trials.[95] Dolutegravir has a similar effect on serum creatinine to that of cobicistat and rilpivirine.

F CCR5 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. The phenotypic assay that measures tropism is expensive and time-consuming, but genotypic tropism testing is faster and readily available.[96] *Maraviroc* is the only currently approved CCR5 attachment inhibitor. It is used twice daily and has no food restrictions.

G Special Considerations

1. **Pregnancy**. 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. No substantial risk of maternal or fetal harm attributed to ART has been reported in the Antiretroviral Pregnancy Registry,[32] including for EFV (classified as Category D) during the first trimester. However, in BC, EFV is still not recommended to be given to women of childbearing potential or during the first trimester of pregnancy, based on primate teratogenicity data and anecdotal reports of neural tube defects in humans.[33] Management of HIV positive women who are pregnant or planning to become pregnant should be conducted under expert guidance.[35] In BC, contact the Oak Tree Clinic at BC Women's and Hospital and Health Centre (604-875-2212; toll free 1-888-711-3030).
2. **Co-morbid diseases**. 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.
3. **Cardiovascular disease (CVD).** As noted above, data linking abacavir (ABC) with an increased risk of CVD are inconsistent and no explanatory mechanism has been identified. LPV/r[69 71] and FPV/r[71] have been associated with CVD risk in cohort studies; treatment with either of these two boosted PIs has been associated with a proatherogenic lipid profile,[97] making this association biologically plausible. The same cohort analyses have not found associations between CVD risk and use of TDF, EFV, NVP, or ATV/r.[69 70 98] Sufficient cohort data to analyze CVD risks associated with DRV/r, RAL, RPV, or ELV are not yet available.

   In summary, use of LPV/r and FPV/r should be avoided if possible in patients at high risk for CVD. Given the uncertainty of the association, use of ABC 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). A pre-HAART baseline electrocardiogram (ECG) should be considered, and the ECG should be monitored if concomitant use of one or more additional PR- or QTc-prolonging drugs cannot be avoided.
4. **Renal disease.** In patients with reduced renal function, prolonged use of TDF is associated with cumulative nephrotoxicity,[60 61 62] and should be avoided. ATV/r and LPV/r have each been associ-

ated in cohort studies with loss of renal function, either in the setting of concomitant tenofovir[59] or independent of it.[60 62] The clinical significance of this finding remains to be elucidated.

5. **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 TDF and LPV/r have been found to be independent risk factors for fractures in some recent studies.[66 99] 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 TDF-containing regimens.[65 100] Notably, in postmenopausal women, both HIV infection and TDF use are independently associated with higher rates of bone loss.[101] Given their increased risk of fragility fractures it may be prudent to consider avoiding TDF as part of initial therapy in postmenopausal women and others with established or high risk for osteoporosis.
6. **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 EFV plus nRTIs. Data are conflicting about the effect of rifampin co-administration on EFV concentrations. Early studies reported a 26% reduction in EFV exposure,[102] but more recent studies in patients with HIV and TB co-infection have not shown a clinically significant effect of rifampin on EFV exposure.[103 104 105 106] Although the prescribing information for EFV indicates the dose should be increased to 800 mg daily for patients weighing more than 50 kg who are being treated with rifampin, the current FDC with 600 mg of EFV is associated with good HIV and TB outcomes regardless of weight.[107] If EFV cannot be used, rifabutin-based TB therapy with a PI/r plus two nRTIs is recommended. Rifabutin reportedly has little effect on ATV/r[108] or LPV/r,[109] results in only modest increases in DRV/r,[110] and has no clinically meaningful effect on RAL.[111] However, serum concentrations of rifabutin and its major metabolite are markedly increased by all PIs/r, 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 PI/r regimen[112 113] and lower than expected concentrations of rifabutin. Additional clinical trials are underway, but in the interim rifabutin 150 mg daily is suggested when used with a PI/r regimen, and patients should be closely monitored. RAL concentrations are decreased when co-administered with rifampin; if a RAL-based ART regimen is used, the RAL dose should be increased to 800 mg twice daily or rifabutin should be substituted for rifampin, but neither approach has been evaluated in patients with HIV and TB co-infection. The recent recommendation for use of a 3-month once weekly regimen of isoniazid with rifapentine for treatment of latent TB infection is not recommended for HIV-infected patients receiving ART.[114]
7. **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. RAL combined with TDF/FTC 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.[115 116]
8. **HBV.** The optimal ART regimen for HIV and HBV co-infected persons should include TDF and FTC (or 3TC) 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 TDF. Entecavir has been used safely in co-infected patients, but has impaired activity against 3TC-resistant HBV, and can select for M184V in HIV reverse transcriptase.[117] [118] [119] In persons without 3TC-resistant HBV, entecavir is an alternative to TDF if used with a fully suppressive ART regimen. Regimens containing 3TC or FTC 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.[120] [121]

9. **HCV.** Peginterferon alfa and ribavirin have been routinely used for the treatment of HCV in HIV co-infected persons. Ribavirin cannot be used with didanosine (ddI) or with stavudine (d4T) and has overlapping toxicity with ZDV. It is not clear whether ribavirin is less effective when used with ABC than with TDF. The HCV PIs telaprevir and boceprevir are each being studied for the treatment of genotype 1 chronic HCV in the setting of HIV co-infection.[122] [123] Drug–drug interactions between telaprevir or boceprevir and antiretroviral drugs, particularly HIV PIs, may alter the optimal choice of ART when their use is anticipated. Data from clinical trials continue to evolve, but at this time the combination of TDF/FTC and RAL appears reasonable in this setting. Prior virologic failure and previous evidence of NRTI resistance mutations may limit switches to RAL from a boosted PI regimen due to increased risk of virologic failure in this setting. Updated drug interaction information can be accessed at www.hep-druginteractions.org.[124]
10. **Malignancy**. The concomitant use of anticancer drugs and ART is associated with overlapping toxicities and the potential for substantial drug interactions. RAL-based regimens may be considered in this setting due to their favourable drug interaction profile.[125] [126]

H Recommendations regarding what to start

- Preferred recommended initial regimens comprise a backbone of two nucleoside/-tide 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 and preferably the baseline HIV-1-RNA level is <100,000 copies/mL); plus either the non-nucleoside RTI (NNRTI) efavirenz, or the ritonavir-boosted protease inhibitor (PI/r) atazanavir. Alternative third agents may be used if justified in specific circumstances (see Tables 1 and 2).
- LPV/r and FPV/r should be avoided in patients with CVD or at high risk of CVD. Use of ABC may be considered in this setting, depending on the availability of a suitable alternative.
- TDF should be avoided in patients with impaired renal function (eGFR<50 mL/min). If treatment for hepatitis B (HBV) is required, consult an expert for advice.
- TDF should be used with caution in post-menopausal women others with established or high risk for osteoporosis.
- EFV plus two nRTIs is the recommended initial ART regimen in the setting of rifampin-based 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.
- TDF plus FTC or 3TC should be included as the nRTI background for HIV/HBV co-infected persons. Consideration should be given to the continued used of these agents even if the HIV regimen is altered for whatever reason, including HIV resistance to any or all of TDF, FTC or 3TC. Consult an expert for the treatment of HBV in the setting of impaired renal function (eGFR<50 mL/min).

V MONITORING PATIENTS ON ART

A 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.[127] [128] In general, it is recommended that plasma HIV-1 RNA levels be monitored frequently, typically monthly until suppression of plasma viral load to below 40 copies/mL is confirmed, and every 3–4 months thereafter, as long as treatment is stable and the patient is clinically well and adherent. CD4 counts are typically monitored in tandem with plasma HIV-1 RNA levels. The same monitoring strategy applies when ART is initiated or changed for any reason.

Once the viral load is suppressed for a year and CD4 cell counts are stable at ≥350/μL, plasma HIV-1-RNA levels and CD4 cell counts can be monitored at intervals of up to 6 months in clinically stable, adherent patients.

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. However, it should be noted that a recent study indicated that any level of detectable HIV-1 RNA below the 50 copies/mL threshold (i.e. between 40 and 50 copies/mL) predicted rebound,[129] and that evolution of viral resistance can occur in the setting of low-level viremia, with new resistance mutations detected in 40% of patients with persistent viremia above 100 copies/mL.[130] 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 HIV-1 RNA levels below 200 copies/mL. Also, ART modification or intensification has been shown to have no appreciable impact when plasma HIV-1 RNA is between 1 and 10 copies/mL using research-based assays.[131]

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 often defined as a confirmed detectable HIV-1 RNA of more than 200 copies/mL after virologic suppression or failure to achieve viral load below 40 copies/mL by at least 24 weeks of therapy.[132] An immediate change in the regimen may not be necessary unless new resistance is documented on genotypic testing. Expert advice should be sought for the management of patients with persistently detectable HIV-1 RNA levels below 200 copies/mL.

Levels of transmitted drug resistance remain stable, with prevalence rates of 12% and 14% in Europe, North America, Africa, and Asia.[133] [134] [135] [136] In BC, these levels remain stable and are around 8–10% overall. The most common clinically important transmitted resistance concerns the NNRTIs, at about 4% and slowly increasing. 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- to 5-fold greater risk of virologic failure, which highlights the importance of pre-therapy

resistance testing.[137] [138] For confirmed virologic failure, resistance testing is essential and should, when possible, be performed preferably while the patient is still receiving the failing regimen.

Therapeutic drug monitoring (TDM) 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, with patient consent. Use of the recently approved HCV PIs telaprevir or boceprevir may be optimized using TDM, given the potential for reciprocal drug interactions with HIV treatments. Telapravir has known interactions with HIV PIs; the interactions between boceprevir and certain HIV PI/r can reduce the effectiveness of these drugs when used together. Until specific guidance is available, awareness of the potential for drug interactions with these agents is important. [139] [140] TDM may also prove valuable in the management of pregnant women, and children.

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. Recent initiatives[141] [142] 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.[143] [144]

B Recommendations regarding monitoring of patients on ART

Plasma HIV-1 RNA levels should be monitored frequently: 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.

Once the regimen is well tolerated and stable, and the viral load is suppressed and CD4 cell counts are stable at ≥350/μL for at least a year, HIV-1-RNA and CD4 cell counts can be monitored at intervals of up to 6 months.

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 200 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-naïve patients at baseline and in cases of confirmed virologic rebound.

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. Use of TDM should be considered to guide ART in the setting of concomitant HCV PIs, telaprevir or boceprevir.

ART adherence and engagement in the cascade of care should be monitored as part of individual patient care and programmatic evaluation.

VI TREATMENT-EXPERIENCED PATIENTS

New regimens for ART-experienced patients should include fully active drugs, based on 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. Treatment failures may be broadly classified as due to virologic, toxicity, tolerance, pharmacological or adherence reasons. Seeking expert advice is strongly encouraged in the assessment and management of treatment failure.

A 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 likely to emerge upon failure of these regimens. 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 PI/r-based regimens.** Initial virologic failure of a PI/r-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 3TC or FTC containing PI/r based therapy, as long as the PI and the second agent are fully active. If the nRTI backbone is otherwise compromised, NNRTIs or RAL should be used with caution due to their low genetic barrier to resistance. DRV/r may be preferable in this situation, since is associated with a lower incidence of virologic failure than LPV/r in treatment-experienced patients.[145]
3. **Initial RAL-based regimens.** There are several available treatment options with three fully active drugs from classes not used in an initial RAL-based regimen. Standard genotypic tests do not include the integrase region; however, this is available upon request from the BC-CfE Virology Laboratory. RAL and ELV are almost completely cross-resistant. Prompt discontinuation of these drugs in a failing regimen will increase the potential utility of the investigational drug dolutegravir, as discussed below.

B 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 DRV/r, combined with RAL and potentially ETV, depending on the spectrum of NNRTI mutations detected.[146] Upon request, the BC-CfE Virology Laboratory can reevaluate past resistance tests to include estimates of ETV or RPV 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 3TC or FTC and/or TDF, might be considered even if resistance is present, because residual activity of these compounds has been demonstrated in this setting.[147] Expert advice should be sought in the management of MDR virus. Dolutegravir, an InSTI currently in development, appears to have substantial activity against RAL- and ELV-resistant viruses, but reduced susceptibility has been reported for viruses with the Q148 or G140 mutations.[148 149] With high-level RAL resistance, there is no clinical benefit from continuing RAL.[150]

Treatment interruptions are strongly discouraged as they have been shown to be associated with increased risk of disease progression and death.[151 152] 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.[153]

C Management of Immunologic Failure

There is no consensus definition of immunologic failure, which encompasses patients who are unable to achieve adequately protective CD4 cell count increases despite durable virologic suppression on ART. 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.[154] A number of strategies to improve CD4 count responses have been evaluated, including switching of nRTIs or class of drugs[155] and treatment intensification, with no consistent success.[156 157 158] Currently, there is no immune-based therapy that has shown a clinical benefit in this situation.[159]

D Switching for ART Regimens for Toxicity or Improved Tolerability and Adherence

Switching regimens to reduce toxicity, improve adherence and tolerability, and avoid drug interactions in virologically suppressed patients, 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 enfuvirtide to RAL in virologically suppressed patients with MDR has been successful.[160 161] However, switching from a PI/r to RAL has shown conflicting results,[162 163] 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 RAL or MVC, while preserving the nRTIs in the existing regimen.

In virologically suppressed patients with EFV intolerance or toxicity, NVP or RPV substitution has proven safe and effective.[82 164] Of note, there was no increased risk of NVP-induced hepatotoxicity or rash, even in the presence of high CD4 counts at the time of the switch from EFV to NVP.[165 166] The RPV switch can be accomplished with RPV/TDF/FTC FDC. In this scenario, EFV can also be replaced with a PI/r or InSTI or MVC, if the tropism assay is favourable. Of note, however, there are fewer supporting data for switching to a MVC-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.

Preemptive or reactive changes for short- and long-term toxic effects such as metabolic abnormalities,[167] and prevention of or management of lipodystrophy, cardiovascular risk,[168] and renal impairment, have been used successfully with maintenance of virologic suppression.

E 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.[169] [170] Of note, however, RAL once-daily dosing was inferior to twice-daily dosing in a study of simplification from PI/r based regimens.[171] Once-daily dosing of DRV/r is effective in treatment-experienced patients with either no prior exposure to PIs or no DRV-associated resistance mutations.[172]

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 LPV/r and DRV/r. A DRV/r 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.[173] This also was observed in a randomized trial of LPV/r monotherapy maintenance.[174] Therefore, the use of PI/r monotherapy is strongly discouraged due to higher rates of virologic failure.[174] [175]

F Recommendations regarding treatment experienced patients

- In the setting of confirmed virologic failure (HIV RNA >200 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.
- Intensification of or switching therapy has not been successful in improving suboptimal CD_4 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.
- PI/r monotherapy is associated with an increased risk of virologic failure and is not recommended.

VII EMERGING ISSUES: USE OF ART FOR PREVENTION OF HIV INFECTION

A detailed discussion of the use of ART for the prevention of HIV transmission is beyond the scope of this document. This topic has recently been reviewed in depth elsewhere.[176]

Treatment as Prevention (TasP) refers to the use of ART in the infected person and the secondary preventive benefit derived from it. TasP is now accepted to be over 95% effective in the vertical, sexual and parenteral transmission settings. 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 www.cfenet.ubc.ca/therapeutic-guidelines/accidental-exposure. More recently, the BC-CfE has 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.

New evidence has recently emerged regarding the use of ART as oral pre-exposure prophylaxis (PrEP). This approach has been shown to be effective in 3 large trials using daily TDF/FTC or TDF, one in gay and bisexual men and transgender women (iPrEX),[177] one in heterosexual HIV serodiscordant couples (Partners PrEP),[178] and one in heterosexual men and women (TDF2).[179] A PrEP trial in high-risk women (FEM-PrEP)[180] and one with an oral daily TDF arm (VOICE),[181] 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[178] and the FEM PrEP trial that showed no benefit had a very low level of adherence, with iPrEX between these in both effect and adherence. The CDC has published an interim guidance for management of patients taking TDF/FTC for PrEP.[182] At this time the use of PrEP is considered a medically acceptable option for selected individuals; however, this approach is not currently funded by the BC-CfE.

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