



British Columbia  
Centre for Excellence  
in HIV/AIDS

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

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Prepared by J Montaner and the BC Centre for Excellence in HIV/AIDS  
Therapeutic Guidelines Committee

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# I. WHEN TO START

## **1.1 Background**

Deciding to start ART requires weighing the benefits of treatment on morbidity and mortality against its risks, including toxicity, resistance, drug interactions, and the costs and inconvenience of lifelong treatment. Sustained viral suppression restores and preserves immunologic function, decreasing opportunistic diseases and mortality. The patient must be ready and willing to adhere to lifelong therapy. Advances in ART continue to shift the therapeutic risk-benefit balance to earlier treatment. Improvements in potency, toxicity and tolerability, and pill burden allow for durable viral suppression for most patients.

The risks associated with ART have decreased, whereas concerns regarding the risks of long-standing untreated viremia have increased. Uncontrolled HIV replication and immune activation lead to a chronic inflammatory state, resulting in end-organ damage and co-morbid conditions not previously thought to be associated with HIV infection. Several studies have shown that the life span of those with HIV infection still falls short of that of the general population, even at high CD4 cell counts.<sup>3-6</sup> This life span decrease is related to serious, non-AIDS events attributed to chronic immune activation and the potentially permanent immune damage associated with prolonged immune depletion. In several data sets,<sup>3-8</sup> non-AIDS events were associated with elevated levels of viral replication and markers of immune activation and coagulation (including D-dimer, interleukin 6, or high-sensitivity C-reactive protein). Mortality from non-AIDS events now exceeds that of AIDS-defining opportunistic diseases in individuals receiving effective ART.<sup>9-11</sup>

The strength of evidence supporting initiation of therapy increases as CD4 cell

count decreases. In a cohort of 17,517 asymptomatic HIV-infected persons, initiating ART at a CD4 cell count greater than 500/ $\mu$ L decreased mortality by 94%, and initiating it at a CD4 cell count between 351 and 500/ $\mu$ L decreased mortality by 69%, although the numbers of deaths were low in both groups. The majority of deaths were from non-AIDS conditions.<sup>10</sup> In an analysis of 62,760 persons in 12 cohorts, reduction in death was 23% and 45% for those beginning therapy with a CD4 cell count greater than 500/ $\mu$ L and 350 to 500/ $\mu$ L, respectively.<sup>12</sup> Data from prospective observational cohorts and clinical trials demonstrate worse outcomes among patients who begin receiving ART at CD4 cell counts less than 350/ $\mu$ L or who have symptomatic HIV disease.<sup>1</sup> Among 24,444 patients from 18 cohorts, there was no additional benefit from initiating therapy at CD4 cell counts of 451 to 550/ $\mu$ L compared with 351 to 450/ $\mu$ L. However, this analysis included only persons who began receiving ART at less than 550/ $\mu$ L.<sup>13</sup>

## **1.2 Present Recommendations**

Indicators of rapid progression of disease, such as **high HIV-1 RNA** and **rapid CD4 cell count decline**, are recognized as reasons to initiate ART regardless of CD4 cell count.<sup>1</sup> **Older age** (older than 50 years old) is also associated with higher risk of AIDS and non-AIDS-related deaths. **Pregnant women** should be offered treatment at least by the second trimester and therapy continued after birth [see Pregnancy Section].<sup>5,10,14-18</sup>

## **1.3 Special Considerations**

Hepatitis screening should be done at baseline in all HIV infected patients. This will be repeated as clinically indicated during follow up, if the initial test was negative.

### **1.3.1 Hepatitis B Infection**

HIV increases the risk of liver-related mortality in those with hepatitis B virus (HBV).<sup>19</sup> Hepatitis B infection should not be treated with lamivudine or emtricitabine alone. If tenofovir is contraindicated, entecavir should be added.<sup>20</sup> The durability of entecavir is compromised by previous HBV treatment failure with regimens including emtricitabine or lamivudine.<sup>21</sup> Flares of hepatocellular inflammation may occur when therapy with agents active against HBV is discontinued or when HBV resistance to lamivudine or emtricitabine emerges in patients receiving these agents without tenofovir or entecavir.<sup>22,23</sup> If ART must be interrupted, patients should be closely monitored for HBV reactivation (ie: increase in liver enzymes and hepatitis B DNA levels).<sup>24</sup>

### **1.3.2 Hepatitis C Infection**

Patients with HIV–hepatitis C virus (HCV) co-infection progress to end-stage liver disease more rapidly than do HCV mono-infected patients.<sup>25</sup> Clearance of HCV is associated with regression of liver fibrosis and a reduced risk of ART-related hepatotoxicity.<sup>26</sup> In one study, abacavir with ribavirin was associated with a reduced rate of sustained HCV virologic response.<sup>27</sup> Zidovudine, didanosine, and stavudine have overlapping hematologic and hepatic toxicities with current HCV therapy.<sup>25</sup> As a result, ART regimens may need to be adjusted accordingly. This should be done in consultation with an experienced HCV/HIV healthcare provider. Additionally, it should be noted that patients with HCV co-infection are at increased risk of hepatotoxicity and, therefore, liver profile should be closely monitored. Current HCV therapy has a higher probability of sustained HCV virologic response with HCV genotype 2 or 3; therefore, for patients with a high CD4 cell count and no imperative to begin ART, HCV treatment before ART may

avoid cumulative drug toxicity and drug interactions.<sup>28</sup>

### **1.3.3 Renal Disease**

Renal disease ranges from HIV-associated nephropathy, to HIV-associated immune complex kidney disease, to thrombotic microangiopathy. In 5 cross-sectional cohort studies, 5.5% of patients had stages 3 to 5 chronic kidney disease (estimated glomerular filtration rate [eGFR] <60 mL/min for more than 3 months). Older patients, black ethnicity, persons with lower CD4 nadirs, and those with diabetes or hypertension have a higher risk of developing chronic kidney disease.<sup>29,30</sup> Albuminuria and eGFR less than 60 mL/min per 1.73 m<sup>2</sup> are independently associated with an increased risk of cardiovascular events.<sup>31</sup> Tenofovir is associated with a decrease in GFR and tubular dysfunction; both indinavir (about 4% of patients)<sup>32</sup> and atazanavir<sup>33</sup> (uncommonly) are associated with nephrolithiasis. All nRTIs except abacavir may require dose adjustments according to the GFR.

### **1.3.4 Increased Cardiovascular Risk**

Uncontrolled HIV infection is associated with increased cardiovascular risk.<sup>34</sup> In a multivariate analysis involving 70,357 (487 HIV-infected and 69,870 HIV-uninfected) subjects, elevated high-sensitivity C-reactive protein and HIV were independently associated with acute myocardial infarction. With both risk factors, acute myocardial infarction risk increased greater than 4-fold.<sup>35</sup> There were strong associations between overall mortality or cardiovascular disease and specific biomarkers. Although ART reduces the level of these biomarkers, they can remain elevated compared with those of HIV-uninfected individuals. The clinical utility of these biomarkers for initiation or monitoring therapy is unknown.

Modifiable cardiovascular risk factors should be aggressively addressed in all persons with HIV infection.

### **1.3.5. Active Opportunistic Infections**

In a randomized controlled trial of when to initiate ART for patients with active opportunistic infections (excluding tuberculosis [TB]), early initiation (median, 12 days after presentation) reduced death or AIDS progression by 50% compared with beginning ART after the completion of opportunistic infection treatment.<sup>36</sup> A South African randomized controlled trial including patients with TB and HIV demonstrated that initiating ART within 2 months of beginning tuberculosis treatment decreased mortality by 56% compared with initiating ART after completion of TB treatment.<sup>37</sup> Immune reconstitution inflammatory syndromes (IRIS) occurred more often with early therapy, but no changes in ART were needed and no deaths were related to immune reconstitution inflammatory syndromes. Consideration must be given to the potential for drug interactions among therapies for opportunistic infections and ART.<sup>38,39</sup>

### **1.3.6 Primary HIV Infection**

Patients who present with symptomatic primary HIV infection may progress more rapidly than those who present without symptoms.<sup>40,41</sup> Antiretroviral therapy reduces the extremely high viral loads in primary infection and may reduce transmission.<sup>42,43</sup> For patients presenting with asymptomatic primary infection, there are insufficient data for a recommendation on whether to treat immediately or defer; however, an analysis of 3019 seroconverters showed a 78% reduction in mortality when ART was initiated rather than delayed.<sup>12</sup>



### **1.3.7 ARV Therapy and HIV Transmission (“Treatment as Prevention”)**

Antiretroviral therapy reduces HIV transmission.<sup>44</sup> Widespread use of ART during pregnancy has nearly eliminated mother-to-child transmission in the developed world.<sup>45,46</sup> A meta-analysis concluded that ART also decreases the risk of HIV transmission to uninfected partners in HIV-serodiscordant heterosexual couples,<sup>43</sup> and a cohort study of 3,381 heterosexual serodiscordant couples showed a 92% reduction in transmission when ART was used by the infected partner.<sup>47</sup> Another cohort study showed a strong association between increased ART coverage, decreased community plasma viral load, and decreased HIV incidence among injection drug users.<sup>48</sup> Some mathematical models suggest that more aggressive ART coverage could reduce the incidence of new HIV infections.<sup>49-51</sup> More recently, a decrease in HIV transmission as a result of expanded ART coverage has been shown in a population based study.<sup>52</sup>

### **1.4 Summary of Recommendations**

- Patient readiness for treatment is a key consideration when deciding when to initiate ART.
- There is no CD4 cell count threshold at which initiating antiretroviral therapy is contraindicated.
- Initiation of therapy is recommended (**TABLE 1**) for symptomatic patients with established disease, regardless of CD4 cell count, and for asymptomatic individuals with CD4 cell counts less than or equal to 500/ $\mu$ L.
- Therapy is recommended regardless of CD4 cell count in the following

settings: increased risk of disease progression associated with a rapid decline in CD4 cell count (ie:  $>100/\mu\text{L}$  per year)<sup>1</sup> or a plasma HIV-1 RNA level greater than 100,000 copies/mL<sup>1</sup>; older than 50 years; pregnancy (at least by the second trimester); or chronic HBV or HCV co-infection, although for patients with HCV genotype 2 or 3 and high CD4 cell counts, an attempt to eradicate HCV may be undertaken before ART is initiated; HIV-associated kidney disease, (avoiding drugs with potential adverse effects on the kidney (tenofovir, indinavir, atazanavir), if possible);<sup>53</sup> high cardiovascular risk, (modifiable risk factors for cardiovascular disease should be aggressively managed); opportunistic infections, including tuberculosis, with attention to drug interactions and the potential for immune reconstitution inflammatory syndromes; and symptomatic primary HIV infection to prevent rapid progression, to preserve immune function, and to limit ongoing transmission.<sup>42</sup> Once initiated, ART should be continued.

- Therapy should be considered where there is a heightened risk of HIV transmission (ie: HIV-serodiscordant couples), without supplanting traditional prevention approaches. Risk reduction counseling should be a routine part of care at each patient-clinician interaction.<sup>54</sup>
- Treatment should be considered for asymptomatic individuals with CD4 cell counts greater than  $500/\mu\text{L}$ .

**TABLE 1: WHEN TO START ARV THERAPY**

<b>Clinical Setting</b>	<b>Recommendation</b>
<b>Symptomatic, established disease</b>	<b>Start ARV regardless of CD4 count</b>
<b>Asymptomatic</b>	<b>Start ARV</b>
<b>CD4 count <math>\leq</math> 500/<math>\mu</math>L.</b>	<b>Start ARV if:</b>
<b>CD4 count <math>&gt;</math> 500/<math>\mu</math>L</b>	<ul style="list-style-type: none"><li>• Increased risk of disease progression     i.e.: CD4 decline <math>&gt;</math>100 cells/year or     a plasma HIV-1 RNA <math>\geq</math> 100,000 c/mL</li><li>• Older than 50 years</li><li>• Chronic HBV</li><li>• HCV co-infection</li><li>• HIV-associated kidney disease</li><li>• High cardiovascular risk</li><li>• Active opportunistic infections, including TB</li><li>• Symptomatic primary HIV infection</li><li>• Pregnancy</li><li>• Risk of HIV transmission     i.e.: HIV-serodiscordant couples</li></ul>
<b>CD4 count <math>&gt;</math> 500/<math>\mu</math>L, no other risk</b>	<b>Consider ARV</b>

## II. WHAT TO START

### **2.1 Background**

Selecting an initial regimen has longstanding consequences, particularly as it relates to future therapy options in the event of treatment failure. The initial regimen should be individualized according to resistance testing results and predicted antiviral efficacy, toxicity and tolerability, pill burden, dosing frequency, drug-drug interactions, co-morbidities, and patient and practitioner preference. In the absence of overriding considerations, cost should also be considered. Differential CNS penetration by antiretroviral drugs has been reported; however, the clinical implications of these findings are not yet clear. At this time, CNS penetration by antiretroviral drugs is not considered a criteria for the selection of the initial antiretroviral regimen.

Current evidence supports the combination of 2 nRTIs and a potent third agent from another class (**TABLE 2a**). Fixed-dose formulations and once-daily regimens are generally preferred for initial therapy. **TABLE 2b** presents a summary of key features for selected frequently used agents in treatment-naive patients.

**TABLE 2a: Recommended Components of the Initial Antiretroviral Regimen**

- **Dual nucleoside or nucleotide reverse transcriptase inhibitor (nRTI) Component**
  - **Recommended**
    - Tenofovir (TDF)/emtricitabine (FTC)
    - **Alternative**
      - Abacavir (ABC)/lamivudine (3TC)
- **Key Third Agent**
  - **Recommended**
  - **within non-nucleoside reverse transcriptase inhibitor (NNRTI) Class**
    - Efavirenz
  - **within protease inhibitor (PI) Class**
    - Atazanavir (ATV)/ritonavir (r)
    - **Alternatives**
    - **within New Drug Classes**
      - Raltegravir (RAL) - Integrase Inhibitor
      - Maraviroc (MVC) - CCR5 antagonist
    - **within PI Class**
      - Lopinavir (LPV)/r
      - Darunavir (DRV)/r
      - Fosamprenavir/r
    - **within NNRTI Class**
      - Nevirapine (NVP)

**TABLE 2b: Key Considerations for Selected Frequently Used Agents in Treatment-Naive Patients**

<b>TDF/FTC</b>	Available as fixed-dose combination (FDC) as Truvada Available as FDC with efavirenz as Atripla Once daily Low genetic barrier to resistance May be associated with: Renal dysfunction Hypophosphatemia, may decrease bone mineral density Both drugs are active against hepatitis B virus.
<b>ABC/ 3TC</b>	Available as FDC as Kivexa Once daily Possibly slightly decreased efficacy if baseline HIV-1 RNA >100,000 c/mL Low genetic barrier Need HLA-B*5701 to screen for risk of ABC-HSR hypersensitivity May be associated with increased cardiovascular risk (ABC) 3TC needs another HB active agent if active hepatitis B present
<b>Efavirenz</b>	Preferred choice within the NNRTI class Available as FDC with TDF/FTC as Atripla Low genetic barrier Not recommended if there is Significant psychiatric illness First trimester of pregnancy Intention to become pregnant
<b>ATV/r</b>	Preferred choice within the PI/r class Once daily Leaves salvage options available within the PI/r class for future regimens Less lipogenic potential than lopinavir/r

Hyperbilirubinemia make ATV/r undesirable in some settings  
 Some acid-reducing agents may compromise bioavailability  
 Not recommended if there is  
     Risk of nephrolithiasis  
     Concomitant ongoing use of corticosteroids  
         inhaled  
         injections (i.e.: even single dose intra-ocular or articular)  
         topical in high doses

<b>Raltegravir</b>	<p>Only integrase strand transfer inhibitor (INSTI) agent approved          Twice daily          Low drug interaction potential          Rapid decline in HIV-1 RNA slope after initiation              Of unknown clinical significance          Low genetic barrier          Limited experience in treatment-naive patients and              availability of other options in most naive patients, and high efficacy in              treatment experienced patients, and in the setting of multidrug resistant              virus make RAL a less desirable option in treatment naive patients</p>
<b>Maraviroc</b>	<p>Only chemokine receptor 5 (CCR5) antagonist approved          Targets host protein (viral co-receptor)          Need to perform viral tropism assay before use          Limited clinical experience in treatment-naive patients          Strategically, may be more useful in treatment experienced patients or when              primary (transmitted) drug resistance is present but viral population              remains exclusively CCR5 tropic</p>
<b>Darunavir/r</b>	<p>May be used once daily in treatment-naive patients          High genetic barrier          Limited experience in treatment-naive patients and              availability of other options in most naive patients, and high efficacy in              treatment experienced patients, and in the setting of multidrug resistant              virus make DRV/r a less desirable option in treatment naive patients</p>
<b>Lopinavir/r</b>	<p>Extensive clinical experience          Only PI co-formulated with ritonavir (heat stable)          Can be given once daily in naive patients          Hyperlipidemia and gastrointestinal adverse effects influence choice          May be useful when ATV/r not tolerated          LPV/r failures typically retain sensitivity to DRV/r</p>
<b>Fosamprenavir/r</b>	<p>Can be given once daily in naive patients          Hyperlipidemia and gastrointestinal adverse effects influence choice          May be an option when ATV/r or LPV/r not tolerated</p>

### ***2.1.1 Nucleoside and Nucleotide Reverse Transcriptase Inhibitors (nRTIs)***

Tenofovir has activity against both HIV-1 and HBV and a long intracellular half-life. Potent viral suppression and CD4 cell count increases occur when tenofovir and emtricitabine are used with a third agent. Alternative nRTIs are preferred over dose-adjusted tenofovir for patients with renal dysfunction.<sup>55</sup> Tenofovir concentration can be increased by some protease inhibitors (PIs), particularly

ritonavir, and studies have suggested a greater risk of renal dysfunction when tenofovir is used in PI-based regimens.<sup>56-58</sup> Tenofovir is available in fixed-dose, once-daily formulations with emtricitabine and with emtricitabine plus efavirenz. HLA-B\*5701 testing identifies persons at high risk for abacavir hypersensitivity (HSR).<sup>59,60</sup> In the AIDS Clinical Trials Group study A5202, inferior virologic responses were observed with abacavir plus lamivudine compared with tenofovir plus emtricitabine in subjects with baseline HIV-RNA levels greater than 100,000 copies/mL. Abacavir plus lamivudine also was associated with more lipid abnormalities.<sup>61,62</sup> The Data Collection on Adverse Events of Anti-HIV Drugs study, a large multinational observational cohort, found that recent, current, or cumulative use of abacavir predicted an increased risk of myocardial infarction, an association not observed with tenofovir.<sup>63,64</sup> This risk was accentuated in participants who had pre-existing cardiovascular risk factors. In contrast, in a pooled analysis of 52 clinical trials involving more than 9500 participants who received abacavir, no increased risk of myocardial infarction was found.<sup>65</sup> Thus, no consensus has yet been reached regarding this possible association or its putative mechanism.<sup>66</sup> Until further data is available, avoid abacavir in patients with history of cardiovascular disease.

Lamivudine and emtricitabine are each well tolerated. They both can select for the M184V mutation, which confers high-level resistance to both drugs but enhances the activity of tenofovir. Both are active against HBV but should only be used in combination with a second HBV-active drug, typically tenofovir, when treating HIV-HBV coinfecting patients. The role of zidovudine in initial regimens is limited by tolerability issues, as well as increased risk for lipodystrophy and hyperlipidemia compared with tenofovir.<sup>1</sup> Stavudine and didanosine are not recommended for initial therapy because of increased toxicity of each.<sup>1</sup>

Combination regimens including 3 or 4 nRTIs alone are not recommended because of suboptimal virologic activity and increased toxicity.<sup>1,67</sup>

### **2.1.2 Non-Nucleoside Reverse Transcriptase Inhibitors**

Several studies have shown consistently high and sustained rates of viral suppression with efavirenz in the initial regimen.<sup>1,68</sup> Efavirenz has been shown to be virologically superior to ritonavir-boosted lopinavir (lopinavir/r)<sup>69,70</sup> and comparable to atazanavir/r<sup>61,62</sup> and raltegravir.<sup>71</sup> Lopinavir/r has shown better CD4 cell count responses and less drug resistance after virologic failure than efavirenz in three clinical trials.<sup>69,72,73</sup> Efavirenz is associated with rash and central nervous system adverse effects and should not be used during the first trimester of pregnancy or in women of childbearing age trying to conceive or not using effective and consistent contraception.<sup>17</sup> Efavirenz is an inducer of cytochrome P450, and potential drug interactions are an important consideration. Baseline genotypic testing is important when considering non-nucleoside reverse transcriptase inhibitor (NNRTI) use. Primary NNRTI resistance rates vary from approximately 8.1% in the United States to 2.3% in Europe.<sup>74-76</sup>

Nevirapine was non-inferior to atazanavir/r (each combined with tenofovir plus emtricitabine) in a randomized controlled trial restricted to women and men with CD4 cell counts less than 250/ $\mu$ L and 400/ $\mu$ L, respectively.<sup>77</sup> Nevirapine was similar virologically to lopinavir/r (again, each with tenofovir/emtricitabine) in a randomized trial of 500 African women with CD4 cell counts less than 200/ $\mu$ L.<sup>78</sup> However, drug discontinuation because of adverse events was higher among nevirapine recipients.<sup>79,80</sup> Serious hepatic events have been described within the first several weeks of initiation of nevirapine-based therapy but are less frequent



if nevirapine is restricted to pretreatment CD4 cell counts less than 250/ $\mu$ L (women) or less than 400/ $\mu$ L (men).<sup>81</sup> Patients who experienced CD4 cell count increases to levels above these thresholds with undetectable viremia as a result of previous ART can be safely switched to nevirapine therapy.<sup>82</sup> The efficacy in initial therapy of etravirine, a newer NNRTI, has not yet been fully evaluated.

### **2.1.3 Protease Inhibitors**

Atazanavir should be used in combination with low dose ritonavir, as atazanavir/r has substantially greater virologic activity than unboosted atazanavir when combined with 2 nRTIs as initial therapy.<sup>83</sup> Once-daily atazanavir/r and twice-daily lopinavir/r, both combined with tenofovir plus emtricitabine, have similar virologic and CD4 cell count responses.<sup>84,85</sup> The hyperbilirubinemia, scleral icterus, or frank jaundice associated with atazanavir exposure is not accompanied by hepatic transaminase elevations but is more frequent with ritonavir boosting. Nephrolithiasis has occurred uncommonly with atazanavir, with or without ritonavir,<sup>33</sup> and the eGFR may decrease when atazanavir is combined with tenofovir.<sup>86</sup> Unboosted atazanavir, is generally reserved for special cases under therapeutic drug monitoring, this is a particular consideration if tenofovir is co-administered as there is a concern that tenofovir lowers atazanavir exposure.<sup>87</sup> Atazanavir requires acidic gastric pH for dissolution. Thus, concomitant use of drugs that increase gastric pH, such as antacids, H2 antagonists, and particularly proton-pump inhibitors, may impair absorption of atazanavir and compromise its activity; hence, therapeutic drug monitoring may be particularly useful in this setting.<sup>88</sup>

Darunavir/r once daily was virologically superior to lopinavir/r at 96 weeks. This was evidenced earlier among subjects with baseline HIV-1-RNA levels greater

than 100,000 copies/mL.<sup>89</sup> Grade 2 to 4 adverse events, primarily diarrhea, were more frequent in the lopinavir/r arm.<sup>90</sup> However, darunavir/r is not generally recommended for initial therapy because it is particularly useful for patients with resistant HIV infection.

When compared with efavirenz, lopinavir/r demonstrates lower virologic efficacy but better CD4 response and fewer emergent resistance mutations.<sup>69,72,73</sup> For initial therapy, once-daily and twice-daily lopinavir/r in combination with tenofovir plus emtricitabine achieved comparable rates of plasma HIV-1-RNA levels less than 50 copies/mL at 48 weeks,<sup>91</sup> with similar rates of moderate to severe drug-related diarrhea, insulin resistance and hyperlipidemia.

Twice-daily fosamprenavir/r and lopinavir/r, both administered with abacavir plus lamivudine, had comparable rates of virologic suppression and adverse events at 48 and 144 weeks.<sup>92</sup> Once-daily vs twice-daily fosamprenavir/r did not differ in rates of virologic suppression.<sup>93</sup>

Saquinavir/r was compared with lopinavir/r, both with tenofovir plus emtricitabine, resulting in rates of viral suppression at 48 weeks of about 65% for each regimen; however, the statistical power of this study was limited by small sample size and short length of follow-up.<sup>94</sup> Triglyceride levels were higher in the lopinavir/r arm. A formal warning has been issued regarding a potential risk for QT-interval prolongation with saquinavir/r, however, this may well be a class effect.<sup>95</sup>

Hepatic transaminase elevations can occur with any of the above PI regimens,<sup>96</sup> especially in patients with underlying liver disease. Cumulative exposure to indinavir/r, lopinavir/r, and fosamprenavir/r (but not saquinavir/r) has also been

associated with an increased risk of cardiovascular events.<sup>63,64,97</sup> These drugs are therefore best avoided in patients with elevated cardiovascular risk, if there are other safer options available. Data concerning cardiovascular risk associated with atazanavir/r or darunavir/r are pending.

#### **2.1.4 Integrase Strand Transfer Inhibitors**

Raltegravir and efavirenz, each combined with tenofovir and emtricitabine, showed similar high virologic efficacy during 192 weeks.<sup>71,98,99</sup> Raltegravir is well tolerated and has a favorable lipid and drug interaction profile; however, it is generally dosed twice daily and has a relatively low genetic barrier for selection of resistance mutations.<sup>100</sup> However, raltegravir is not generally recommended for initial therapy because it is particularly useful for patients with resistant HIV infection.

#### **2.1.5 Entry Inhibitors**

The chemokine receptor 5 (CCR5) inhibitor, maraviroc, was compared with efavirenz, both in combination with zidovudine plus lamivudine, in 633 subjects with CCR5-tropic virus and no evidence of resistance to the study drugs.<sup>101</sup> At 48 weeks, HIV-1 RNA less than 50 copies/ mL was achieved in 65% and 69% of maraviroc and efavirenz recipients, respectively. The results did not meet pre-specified criteria for non-inferiority for maraviroc. Through 48 weeks, more participants discontinued maraviroc because of lack of efficacy (11.9% and 4.2%, respectively), whereas fewer participants discontinued maraviroc because of toxicity (4.2% and 13.6%, respectively). Follow-up results at 96 weeks demonstrated durable responses in both groups.<sup>102</sup> Re-analysis of the results with a more sensitive tropism assay or with a novel genotype-based approach suggested that the differences between treatment arms could be attributed to

misclassification of tropism in some patients by the older assay.<sup>101,103-105</sup> If only subjects with R5 virus at entry, as judged by the new tropism or genotype-based assays were considered, maraviroc showed similar efficacy to efavirenz. Maraviroc has not been evaluated extensively with other nRTI backbones in initial therapy. Maraviroc based therapy is substantially more expensive than efavirenz or atazanavir/r based therapy in treatment naive individuals.

## **2.2 Summary of Recommendations**

- Fixed-dose combinations are recommended whenever possible as they decrease pill burden and are generally more convenient. Tenofovir plus emtricitabine is the recommended nRTI combination for initial therapy.
- If tenofovir plus emtricitabine cannot be used, abacavir plus lamivudine may be used as an alternative when HLA B\*5701 testing results are negative. HLA B\*5701 testing is best done at once, during baseline evaluations, in all infected individuals. However, it is important to keep in mind that abacavir may have lower efficacy at high viral loads and it may be associated with increased cardiovascular risk, and only 3TC will be active for hepatitis B co-infected patients.
- Zidovudine plus lamivudine should be reserved for instances in which neither tenofovir nor abacavir can be used.
- Three or 4 nRTIs alone are not recommended for initial therapy.
- Efavirenz or atazanavir/r, are recommended as the third component of an initial regimen.

- Either darunavir/r or raltegravir can be considered as possible alternatives as the third component of an initial regimen in selected cases, if efavirenz or atazanavir/r cannot be used. However, more evidence is available for efavirenz and atazanavir/r than for darunavir/r or raltegravir. Cost also favours efavirenz and atazanavir/r in this setting. Finally, it should be kept in mind that darunavir/r or raltegravir are particularly useful for patients with extensive resistant HIV infection. As a result, the use of darunavir/r or raltegravir as alternative third component of an initial regimen is generally not encouraged.

Lopinavir/r, fosamprenavir/r, and maraviroc are alternative third-component choices. Neither saquinavir/r nor unboosted PIs, including unboosted atazanavir, are recommended for initial therapy. Nevirapine should be used as an alternative initial therapy only if pretreatment CD4 cell count is less than 250/ $\mu$ L in women or less than 400/ $\mu$ L in men. Considerations for initial therapy in patients with specific conditions are summarized in **Table 3**.

**Table 3. Initial Antiretroviral Therapy (ART) and Considerations in Patients with Specific Conditions<sup>a</sup>**

Condition	Regimen Components		Considerations
	Possible Backbone Drugs	Third Agent	
High atherosclerotic cardiovascular risk	Emtricitabine, lamivudine, tenofovir	Efavirenz, nevirapine, atazanavir/r, raltegravir	Initiation of ART, regardless of CD4 cell count, is recommended. <sup>34</sup> Avoid abacavir, fosamprenavir/r, indinavir/r, lopinavir/r because of possible increased cardiovascular risk. <sup>63,97</sup>
Chronic kidney disease	Abacavir, <sup>b</sup> emtricitabine, lamivudine Avoid tenofovir (glomerular and	Efavirenz, raltegravir, nevirapine, maraviroc, PI/r Avoid atazanavir and indinavir	Initiate ART regardless of CD4 cell count. Avoid potentially nephrotoxic drugs. <sup>53</sup> If potentially nephrotoxic drugs must be used, monitor renal

	tubular toxicity)	(nephrolithiasis)	function closely. For patients with reduced estimated glomerular filtration rate, dose adjustment for drugs with renal metabolism (emtricitabine, lamivudine, tenofovir, maraviroc) may be needed.
Chronic HBV infection	Emtricitabine, lamivudine, tenofovir. Use 2 HBV-active drugs. Do not use abacavir or abacavir/lamivudine alone for treatment of HBV in coinfecting patients	Efavirenz, raltegravir, PI/r should be monitored for hepatotoxicity. Avoid nevirapine. Maraviroc should be used with caution in patients with liver disease.	ART that includes tenofovir/emtricitabine should be used irrespective of CD4 cell count. <sup>20</sup> Monitor alanine aminotransferase after ART initiation and after withdrawal of suppressive therapy. <sup>22-24</sup> In patients with moderate to severe liver impairment, dose adjustment for drugs metabolized by the liver should be considered. Avoid alcohol use.
Chronic HCV infection requiring therapy	Emtricitabine, lamivudine, tenofovir	Efavirenz, raltegravir, PI/r should be monitored for hepatotoxicity. Avoid nevirapine. Maraviroc should be used with caution in patient with liver disease.	ART should generally be initiated first in all patients with HCV coinfection regardless of CD4 cell count to slow liver disease progression, except possibly in patients with HCV genotype 2 or 3 infection and a high CD4 cell count, for whom current HCV therapy has a higher probability of a sustained virologic response. <sup>26,28</sup> Avoid zidovudine, didanosine, zalcitabine, and stavudine, as well as abacavir. <sup>25,27</sup> Alcohol should be avoided by all coinfecting patients.
Pregnant women	Complete recommendations for the use of antiviral therapy in pregnant women are available at <a href="http://www.aidsinfo.nih.gov/ContentFiles/PerinatalGL.odf">http://www.aidsinfo.nih.gov/ContentFiles/PerinatalGL.odf</a> , and <a href="http://www.european-aidsclinicalociety.org/guidelines.asp">http://www.european-aidsclinicalociety.org/guidelines.asp</a> . <sup>17,18</sup>		ART is recommended to prevent the transmission of the virus to the fetus or infant. Efavirenz should generally be avoided, especially in the first trimester of pregnancy (teratogenic effect).
Opportunistic infections, including tuberculosis	Any, according to the "What to Start" section	Choice of agent will be influenced by drug interactions, especially with rifampin and rifabutin.	ART should be initiated as soon as possible in patients with opportunistic infections, including tuberculosis, with attention to drug interactions and the potential for

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immune reconstitution inflammatory syndromes.<sup>36,37</sup>  
Drug interactions likely to require dose adjustments; consult drug interaction dosing references (<http://www.hiv-druginteractions.org>, and <http://hivinsite.ucsf.edu/insite?page=ar-00-02>).<sup>38,39</sup>

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Abbreviations: ART, antiretroviral therapy; HBV, hepatitis B virus; HCV, hepatitis C virus; PI, protease inhibitor; /r, ritonavir boosted.

<sup>a</sup>Details, cautions, considerations and supporting data are described in the text. Levels of evidence are described in the eBox (available at <http://www.jama.com>).

<sup>b</sup>In HLAB\*5701-negative patients; has been associated with increased risk of myocardial infarction. Lower efficacy in patients with >100,000 copies/mL of HIV RNA at baseline (see text).

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## III. MONITORING

### 3.1 Background

Effective therapy should result in suppression to less than 50 copies/mL (polymerase chain reaction) or 75 copies/ $\mu$ L (branched DNA) by 24 weeks, regardless of previous treatment experience. Frequent HIV-1 RNA monitoring is recommended during the first year of ART to detect failure.<sup>106</sup> Testing of HIV-1 RNA should be repeated 4 weeks after initiation, every 4 to 8 weeks until suppressed, and then every 3 to 4 months for at least the first year. Plasma HIV-1 RNA should be repeated 2 to 4 weeks after it first becomes detectable in a previously suppressed patient, to diagnose viral rebound or failure. Currently, viral failure at the BC-CfE is only to be diagnosed if the plasma HIV-1 RNA is twice consecutively at  $\geq 250$  copies/mL. This is the case because of the performance characteristics of the assay (Roche Taqman assay) currently in use. Resistance testing should be done if viral failure is confirmed. CD4 cell counts should be monitored in tandem with HIV-1 RNA, especially among patients with counts less than 200/ $\mu$ L, to determine the need for continuing opportunistic infection prophylaxis.<sup>107,108</sup> In a EuroSIDA study, patients who maintained stable and fully suppressive ART for 1 year had a low chance of experiencing treatment failure in the ensuing months.<sup>109</sup> Therefore, once viral replication is suppressed and sustained for at least six months, monitoring intervals may be extended up to every 6 months among patients who remain virologically suppressed and have CD4 cell counts greater than 350/ $\mu$ L. More frequent monitoring is required for patients who have changed therapy because of virologic failure.<sup>110</sup>

Changes in assay methodology may result in detectable viral load in individuals with previously undetectable viremia.<sup>111,112</sup> Detection artifacts have also been



attributed to specific plasma processing practices.<sup>113</sup> New assays may soon be available with a lower limit of 20 copies/mL; however, the clinical implications of viremia between 20 and 50 copies/mL are not yet clear. Confirmed viral load rebound on 2 separate tests at least 2 to 4 weeks apart should prompt a careful evaluation of regimen tolerability, drug-drug interactions, and patient adherence. The prevalence of transmitted drug resistance varies in resource-rich societies from 8% to 16%.<sup>75,76,114</sup> Baseline genotypic testing is strongly recommended for all treatment-naive patients at the time of HIV diagnosis and prior to initiating therapy.<sup>81</sup> This will be automatically performed by the Centre's laboratory.

Similarly, genotypic testing is strongly recommended for all confirmed virologic failure (plasma HIV-1 RNA  $\geq$  250 copies/ml), as resistance testing is essential to decide the next therapeutic steps. Resistance testing should be performed while the patient is receiving the failing regimen, whenever possible. Of note, the Centre's Laboratory stores viral load samples on a long-term basis so that resistance tests can be run retrospectively in selected cases. Minority variants not detected by current resistance testing have been associated with an increased risk of virologic failure; however, the assay thresholds that identify patients at greatest risk of experiencing poor outcomes have not been defined.<sup>40,115-119</sup> Tropism testing before use of a CCR5 antagonist is essential because this class has no activity against chemokine receptor 4 or dual-tropic viruses.<sup>101</sup> New tropism or genotype-based assays are strongly recommended to evaluate potential eligibility for CCR5 antagonists.<sup>101,120</sup> The genotype-based tropism assay is preferentially used at the Centre, as this is faster, reliable and less expensive.

The frequency of monitoring for ART toxicity depends on the known potential

toxicities of specific drugs, concomitant medications and underlying co-morbidities. Monitoring may occur every 2 to 8 weeks after initiation of therapy, decreasing to up to every 6 months after stabilization of HIV disease.<sup>108,121</sup>

Assessment of renal function should occur before initiation and during ART, in particular when tenofovir is used. Tenofovir should not be continued if there is progressive impairment of the renal function (ie: increasing creatinine, decreasing eGFR, progressive albuminuria and increase of albumin creatinine ratio – ACR-, increased phosphorus wasting).

The recommendations and algorithms of the National Osteoporosis Foundation<sup>122</sup> and the World Health Organization fracture risk assessment tool<sup>123,124</sup> are useful for the assessment of risk and prevention of osteoporotic fractures; however, these tools have not been specifically validated in the HIV-infected population. Vitamin D deficiency is common in the setting of HIV infection and may be associated with ART use.<sup>125</sup> Monitoring of vitamin D levels may be of benefit.<sup>125-127</sup>

Hepatic, cardiovascular, and renal complications may be associated with uncontrolled HIV replication. Clinical and laboratory assessment of relevant co-morbid conditions should be performed before initiation of treatment and during follow up.<sup>108,121</sup> Cardiovascular disease risk should be assessed by available tools. The Framingham risk algorithm may be the most appropriate but may underestimate cardiovascular disease risk in the setting of HIV infection.<sup>128</sup> Guidelines for the prevention and management of metabolic complications and non-infectious comorbidities in HIV infection are available.<sup>108,121</sup>

The ultimate effectiveness of therapeutic drug monitoring remains controversial.<sup>129</sup> However, monitoring of PI and NNRTI levels can be useful in pregnant women, children, and patients with renal or liver impairment to minimize over-exposure and adverse effects, manage potential drug-drug interactions, or evaluate virologic failure in the absence of resistance in selected cases. HLA-B\*5701 screening is strongly recommended for all HIV infected individuals at baseline as this identifies patients at risk for abacavir hypersensitivity (HSR).<sup>59</sup>

### **3.2 Summary of Recommendations**

- Plasma HIV-1RNA levels should be monitored frequently when treatment is initiated or changed for virologic failure until they decrease below detection limits and regularly thereafter. Once the viral load is suppressed for a year and CD4 cell counts are stable above 350/ $\mu$ L, viral load and CD4 cell counts can be monitored at intervals of up to 6 months in stable patients.
- Baseline genotypic testing for resistance should be performed in all treatment-naive patients and in cases of confirmed virologic failure.
- For practical purposes virological failure can be arbitrarily defined as a confirmed consecutive plasma HIV-1RNA level over 400 copies/mL.
- HLA-B\*5701 screening should be performed in any patient for whom abacavir is considered, including patients who have been started on abacavir without ill effects in the absence of HLA-B\*5701 screening.
- Assessment of viral tropism is recommended before using maraviroc.

Therapeutic drug monitoring (TDM) is not recommended in routine care; however, selected patients can benefit from this intervention.

- Safety laboratory monitoring including hematological, renal, hepatic, and metabolic profiles should be performed as frequent as every 1 to 2 months at treatment initiation, and every 4 to 6 months when patients are stable, typically after 6 to 12 months.

## IV. WHEN TO CHANGE AND WHAT TO CHANGE

### **4.1 Changing for Virologic Failure**

The virologic goal of treatment for first-and multiple-regimen failure is to achieve a plasma HIV-1 RNA level below the limit of detection of the most sensitive assays available. With the availability of new drugs and regimens, this goal is achievable, even in most patients with multi-regimen failure.<sup>130-132</sup> Reasons for viral rebound after complete suppression, such as poor adherence, drug-to-drug interactions, concurrent infections, and recent vaccinations, should be considered before the regimen is changed. Testing should be repeated following an isolated detectable viral load to exclude measurement error or self-resolving low-level viremia (viral load blip).<sup>1</sup> Similarly, resistance testing must be completed on all plasma HIV-1 RNA  $\geq 250$  copies/ml before a new regimen can be rationally designed. Stage of HIV disease, nadir and current CD4 cell count, co-morbidities, treatment history, current and previous drug resistance tests, and concomitant medications with potential for interactions should be considered when the new regimen is designed. Ideally 3, but at least 2 fully active drugs should be included and drugs from new classes should be considered. Toxicities of stavudine, didanosine, and to a lesser extent zidovudine, make their use problematic, and they should be used only when options are truly limited.

Once failure has been confirmed, an NNRTI-containing regimen should be discontinued promptly to minimize the selection of additional mutations. Initial NNRTI failures traditionally have been treated with 2 active nRTIs plus a PI/r and this remains an adequate approach to date.

For patients on an initial PI/r based regimen, resistance to the PI/r component does not always emerge when regimen failure is confirmed, allowing the same drug(s) or an alternative PI/r to be used in the next regimen.

In the setting of 2 or more drug class failure, 3 active drugs, most often including new classes of agents (integrase strand transfer inhibitors or entry inhibitors), should be used. These individuals usually benefit from a PI/r with activity against resistant strains, such as darunavir/r or tipranavir/r. However, darunavir/r will generally be preferred over lopinavir/r or tipranavir/r because of its superior efficacy, better tolerability and favorable toxicity profile, and problematic drug interactions associated with tipranavir/r.<sup>1</sup> If not previously used, an NNRTI may be included, provided that potential drug interactions are considered. Alternatively, etravirine may be considered if sensitivity to this agent remains. Whenever possible, a new antiretroviral regimen should contain 3 or at least 2 fully active drugs.

Etravirine can be paired with darunavir/r<sup>133</sup> (but not tipranavir/r) and may be of value, depending on the number of NNRTI mutations present. Enfuvirtide or T20 may be an option if no other new class can be used, despite the inconvenience of subcutaneous injection and injection site reactions. Dual-boosted PIs are not recommended.<sup>134</sup> Lamivudine or emtricitabine is sometimes included to maintain the M184V mutation and decrease viral fitness, but there is no new evidence to support this approach, particularly if the regimen contains 3 drugs or at least 2 fully active drugs with a high genetic barrier. Another theoretically beneficial strategy is to use zidovudine to prevent the emergence of the K65R mutation in the presence of thymidine analogue mutations when using tenofovir in patients in whom nRTI-containing regimens are failing. However, no clinical benefit has been shown for this approach.<sup>135</sup> Patients presenting with 2 or more drug class failure should be managed in close collaboration with an experienced practitioner.

## **4.2 Changes for Toxicity, Tolerability, or Convenience**

Single-agent switches are possible when there is a need to address toxicity to a particular agent within a regimen that is otherwise working well, or if there is a need to avoid a particular drug interaction, or improve convenience and adherence, provided the potency of the regimen is maintained and drug interactions are managed. If a switch is done in a patient with background resistance, the integrity of the genetic barrier of the regimen should also be preserved. Such regimen alterations are best done under the guidance of an experienced HIV practitioner. Although some studies have shown maintenance of virologic suppression with PI/r monotherapy as a simplification strategy,<sup>136</sup> other studies have shown higher rates of failure, especially in the central nervous system<sup>137</sup> than with a combination including 2 nRTI plus a PI/r.<sup>138,139</sup> Therefore, PI/r mono-therapy is not recommended. Delaying switches when adverse effects persist may affect adherence and facilitate the emergence of resistance. Close monitoring is advised before and after regimen switches.

## **4.3 Simplification**

It may be desirable to switch to an equally effective regimen with fewer drugs or lower pill burden. Not all switches, even with a drug from a new class, are successful because the activity of the accompanying drugs in the regimen is a key determinant of outcome. For example, continuing lopinavir/r was virologically better than switching to raltegravir in patients with extensive previous 3-class experience and pre-existing nRTI resistance.<sup>140</sup> With raltegravir, it is important to maintain a strong ART backbone, usually a PI/r. Raltegravir was shown to be safe, well tolerated, and virologically similar when substituting enfuvirtide in patients with multi-drug resistant HIV-1.<sup>141,142</sup>

Once-daily darunavir 800 mg/ritonavir 100 mg was non inferior to twice-daily darunavir 600 mg/ritonavir 100 mg in an open-label study in treatment-experienced patients.<sup>143</sup> Dual therapy strategies intended to take advantage of drug interactions, such as the combination of unboosted atazanavir and raltegravir are still experimental and are not recommended for clinical practice. Patients with virologic suppression receiving a boosted or unboosted PI-based regimen, switching to a once-daily regimen containing atazanavir provided better maintenance of virologic suppression, comparable safety, and improved lipids compared with those on continued unmodified therapy.<sup>144</sup> Treatment interruptions should be avoided.<sup>1</sup> Interruptions, such as those for planned surgeries or severe toxicities in patients without options for switching, should consider the different half-lives of the regimen components; drugs should be discontinued in a staggered manner (or a PI/r temporarily substituted) when an NNRTI is a component.<sup>145</sup>

#### **4.4 Summary of Recommendations**

- Viral rebound after complete suppression should be confirmed, and the reasons for the failure understood before treatment failure is diagnosed and the regimen is changed.
- Design of a new regimen should consider previous drug exposure, previous resistance profile, drug interactions, and history of intolerance and toxicity. The virologic goal of treatment for first-and multiple-regimen failure is to achieve sustained plasma HIV-1 RNA undetectability.
- A failing NNRTI-containing regimen should be discontinued promptly to minimize the selection of additional mutations. Initial NNRTI failures are adequately treated with 2 active nRTIs plus a PI/r.



- Patients diagnosed with virologic failure on an initial PI/r based regimen, resistance to the PI/r component does not always emerge when regimen failure is confirmed, allowing the same drug(s) or an alternative PI/r to be used in the next regimen.
- In the setting of 2 or more drug class failure, 3 active drugs, most often including new classes of agents (integrase strand transfer inhibitors or entry inhibitors), should be used. The use of raltegravir, darunavir/r and etravirine in this setting has been highly successful. Preserving these drugs for the treatment of experienced patients is therefore warranted at this time.
- Patients presenting with 2 or more drug class failure should be managed in close collaboration with an experienced practitioner.
- Maraviroc and enfuvirtide remain potentially valuable agents in selected cases of multiple class failure. PI/r monotherapy and treatment interruptions should be avoided. However, if clinically indicated, elective treatment interruptions should consider the different half-lives of the regimen components.
- Single-agent switches to decrease toxicity avoid drug interactions, or improve convenience and adherence is possible, provided the potency of the regimen is maintained and drug interactions are managed. Similarly, it may be desirable to switch to an equally effective regimen with fewer drugs or lower pill burden. However, before undertaking a single drug switch, even with a drug from a new class, it is important to be confident that both potency and genetic barrier of the regimen is preserved,

particularly if there has been a history of virological failure in the distant past.

## V. CONCLUSIONS

Increasing evidence that insidious damage occurs during “asymptomatic” HIV infection coupled with the increasing prominence of non-AIDS events as a major cause of morbidity and mortality in those with ongoing HIV replication and the now established secondary preventive effect of ART provide a powerful rationale in support of early ART initiation. The strategic use of newer drugs can improve tolerability and provide durable and potent viral suppression in initial and subsequent rounds of therapy.

However, far too many HIV-infected persons present for medical care with advanced disease. Universal voluntary HIV testing, comprehensive prevention services, and early linkage to care, treatment and support are key to ensure that advances in ART are fully realized. One of the greatest remaining challenges is that full implementation of these guidelines will require addressing social and structural barriers to diagnosis and care, particularly to the most affected population including: men who have sex with men, drug users, sex trade workers, and Aboriginal individuals. Additionally, it is imperative that the pervasive stigma and discrimination towards infected and at-risk populations be urgently addressed.

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