THERAPEUTIC GUIDELINES

ANTIRETROVIRAL (ARV) TREATMENT OF ADULT HIV INFECTION

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Prepared by:
The Committee for Drug Evaluation and Therapy,
British Columbia Centre for Excellence in HIV/AIDS (BC-CfE)

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SECTION 1: THERAPEUTIC GUIDELINES FOR ANTIRETROVIRAL TREATMENT OF ADULT HIV INFECTION

Foreword

These guidelines were developed by the British Columbia Centre for Excellence in HIV/AIDS (BC-CfE) and the Committee for Drug Evaluation and Therapy (CDET) for HIV care providers and provide recommendations for the treatment of adult HIV infection in BC. The BC-CfE encourages providers to exercise clinical judgment on a case by case basis and individualize care where appropriate.

This document includes the following sections:

Guideline for Antiretroviral Therapy Regimens for Initial Therapy and for Switching ART in Virologically Stable Suppressed Adults

The section lists regular BC-CfE Drug Treatment Program formulary options for initial ART in adults with HIV infection as of Summer of 2020, taking into consideration the CDET's Scientific Review and recommendations as well as cost considerations. Click **here** to see this section. In the event where ART regimen switch is being considered in virologically suppressed individuals with no known resistance mutations or intolerance to specific agents, these ART options should also be considered.

Prescribers requesting alternative ART are expected to provide justification and appropriate supportive documentation with the prescription request. Consistent with Pharmacare practices, the BC-CfE encourages the use of generics, including voluntary de-simplification of ART regimens, where appropriate.

A complete list of BC-CfE Drug Formulary medications can be found at **here**[a].

BC-CfE Eligibility Criteria for Emtricitabine-Tenofovir Alafenamide (FTC/TAF; Descovy®)

This section summarizes clinical criteria for BC-CfE Drug Treatment Program eligibility for FTC/TAF 200-25 mg and FTC/TAF 200-10 mg tablets. Justification and supportive documentation should accompany the HIV Drug Treatment Program Prescription Request Form for FTC/TAF.

Scientific Review and Recommendations for the Therapeutic Guidelines

This section includes the BC-CfE Committee for Drug Evaluation and Therapy (CDET) review of the available evidence and scientific recommendations regarding the use of antiretroviral therapy (ART) in adults with HIV-1 infection.

- When to start
- What to start with (For BC-CfE formulary options, please refer to Guideline for ART Regimens for Initial Therapy)
- Assessment and monitoring
- Changing antiretroviral therapy
- Adverse drug reactions of antiretroviral therapy

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[a] Linked address: **http://www.cfenet.ubc.ca/publications/centre-documents/hivaids-drugs-available-through-bc-cfe**

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Guideline for Antiretroviral Therapy (ART) Regimens for Initial Therapy and for Switching ART in Virologically Stable Suppressed Adults

The following represents the BC-CfE ART regular formulary options for initial therapy, as of the Summer 2020. The formulary takes into consideration both the recommendations of the CDET's Scientific Review of the available evidence and cost considerations, including the real bulk purchase costs to the BC-CfE program. Prescribers are reminded that the generic version of ART drugs will be preferentially used, where possible. As an additional cost-containment measure, eligible participants may be offered voluntary de-simplification (e.g. from a single tablet regimen to a 2-tablet once daily regimen of the same drugs) if deemed clinically appropriate.

The ART regimens listed below for initial therapy are available as regular drug formulary benefits through the BC-CfE Drug Treatment Program. The regimens are presented in hierarchical order based on cost-benefit considerations. Prescribers are encouraged to consider the various ART regimens for initial therapy in the hierarchical order as presented under Options (Regular drug formulary benefit), recognizing that the cost range between regimens at the top of the list (most favourable cost-benefit) and those at the bottom of the list is greater than 5-fold. The cost gap is even greater for regimens not listed below (least favourable cost-benefit). Prescribers who may wish to use regimens other than those listed below will be expected to justify their choice with appropriate supportive documentation accompanying the BC-CfE prescription request form.

ART Regimens for Initial Therapy – Listed in hierarchical order based on cost-benefit

REGIMEN DRUG CLASS	OPTIONS (REGULAR DRUG FORMULARY BENEFIT)	PILLS/ DAY	FOOD REQUIREMENT	COST-BENEFIT
PI	*Atazanavir* + ritonavir + *abacavir/lamivudine*[a,b]	3	Y	+++
PI	*Atazanavir* + ritonavir + *emtricitabine/tenofovir DF*	3	Y	+++
PI	*Darunavir* + ritonavir + *abacavir/lamivudine*[a,b]	3	Y	+++
PI	*Darunavir* + ritonavir + *emtricitabine/tenofovir DF*	3	Y	+++
NNRTI	*Efavirenz/emtricitabine/tenofovir DF*	1	N	+++
InSTI	Dolutegravir/lamivudine[c,d]	1	N	++
InSTI	Dolutegravir + *abacavir/lamivudine*[a]	2	N	++
InSTI	Dolutegravir + *emtricitabine/tenofovir DF*	2	N	++
InSTI	Bictegravir/emtricitabine/tenofovir alafenamide	1	N	+

Drugs in *bold italics* are generic products
[a] abacavir use contraindicated if HLA-B*57:01 allele positive
[b] regimen acceptable if baseline HIV plasma viral load <100,000 copies/mL
[c] acceptable as initial regimen if baseline pVL <500,000 c/mL, CD4 count >200 cells/mm^3, no resistance to dolutegravir or lamivudine, not pregnant, *and* absence of hepatitis B (HBV) chronic infection
[d] acceptable as switch option if no resistance to dolutegravir or lamivudine, no previous virologic failure to NRTIs or INSTIs, virologically suppressed >6 months, not pregnant, *and* absence of HBV chronic infection

In the event where ART regimen switch is being considered in virologically suppressed individuals with no history of ARV drug resistance mutations or allergy/intolerance to specific agents, the above ART regimen options should be considered. When considering regimen change in cases of virologic failure, seeking expert advice is recommended.

A complete list of drugs available through the BC-CfE Drug Treatment Program can be found at
http://www.cfenet.ubc.ca/publications/centre-documents/hivaids-drugs-available-through-bc-cfe

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BC-CfE Eligibility Criteria for emtricitabine/tenofovir alafenamide

All new prescriptions for emtricitabine/tenofovir alafenamide (FTC/TAF; Descovy®) require submission of an HIV Drug Treatment Program Prescription Request form. When requesting Descovy®, the prescriber should provide justification for its use on the prescription form and include appropriate documentation (i.e. laboratory or DXA scan results).

The **specific criteria** are (must meet **both** criteria A **and** B):

A. *Cannot take abacavir*, due to HLA-B*5701 positivity, documented abacavir resistance, or documented significant abacavir intolerance; or abacavir contraindicated because of established cardiovascular disease or high estimated risk of cardiovascular disease in accordance with the Canadian Cardiovascular Society guidelines (**http://www.ccs.ca/eguidelines/Content/Topics/Dyslipidemia/_landing_page_dyslipidemia.htm**)

OR

Hepatitis B co-infection

AND

B. One or more of the following conditions, currently or in the past, *while receiving tenofovir disoproxil fumarate (TDF)*:

- Estimated glomerular filtration rate (eGFR) >30 and <60 mL/min for >3 months (TAF is not licensed for individuals with eGFR <30 mL/min)
- eGFR 60-70 mL/min but declining
- eGFR 60-89 mL/min plus proteinuria (urine albumin to creatinine ratio [UACR]>3 mg/mmol)
- Persistent moderate to severe hypophosphatemia (serum phosphate <0.64 mmol/L)
- Persistent significant proteinuria (UACR >30 mg/mmol)
- Documented osteoporosis (at least one T-score <-2.5 at the hip or spine on DXA scan)
- In premenopausal individuals and men <50 years of age, a Z-score ≤-2.0
- High (>10%) 10-year risk of major osteoporotic fracture as determined by FRAX score (**https://www.sheffield.ac.uk/FRAX/tool.aspx?country=19**)
- Fragility fracture (atraumatic fracture or fracture resulting from minimal trauma)
- Documented osteomalacia (laboratory and/or imaging)

WHAT'S NEW IN THE GUIDELINES

Added March 31, 2020:

Coadministration of Biktarvy® with darunavir/cobicistat, darunavir/ritonavir, doravirine, or rilpivirine is off-label, but may be considered an option in selected patients who require treatment with a multi-class antiretroviral regimen, and for whom more well-established regimens are not appropriate. Close monitoring of viral load, renal function, and potentially bone health is advised due to limited clinical data supporting the safety or efficacy of these regimens.

Added June 2020:

Dolutegravir-lamivudine (DTG-3TC) is an acceptable option for first line therapy for ARV naive individuals, and for treatment switches in virologically suppressed individuals, when certain conditions are met.

DTG-3TC is not recommended in patients with hepatitis B virus (HBV) coinfection or those with any known or suspected viral resistance to dolutegravir or lamivudine. DTG-3TC should be avoided in individuals who are pregnant and within 12 weeks post-conception; who are of childbearing potential and planning to become pregnant; or who are of childbearing potential, sexually active, and not using effective contraception.

The Guideline for Antiretroviral Therapy (ART) Regimens for Initial Therapy and for Switching ART in Virologically Stable Suppressed Adults has been updated with consideration to the updated Scientific Review and Recommendations for the Therapeutic Guidelines, as well as changes to the BC-CfE drug formulary.

Revised March 2023:

The following recommendation has been removed:

> Dolutegravir should be avoided in individuals who are pregnant and within 12 weeks post-conception; who are of childbearing potential and planning to become pregnant; or who are of childbearing potential, sexually active, and not using effective contraception.

Updated data have shown rates of neural tube defects that are not significantly different from those with non-dolutegravir regimens.

Two-drug regimens (regardless of components) are still not recommended during pregnancy.

THERAPEUTIC GUIDELINES FOR ANTIRETROVIRAL TREATMENT OF ADULT HIV INFECTION

SCIENTIFIC REVIEW AND RECOMMENDATIONS

INITIAL RELEASE: DECEMBER 2019
LAST UPDATED: JUNE 2020

Prepared by:
The Committee for Drug Evaluation and Therapy,
British Columbia Centre for Excellence in HIV/AIDS

SECTION 2: SCIENTIFIC REVIEW AND RECOMMENDATIONS FOR THE THERAPEUTIC GUIDELINES

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INTRODUCTION

Aim of the Scientific Review

This section provides a Scientific Review of the evidence available in the literature as of December 2019, and last updated in June 2020. It provides updated recommendations for the care of people living with HIV. These recommendations focus on the use of antiretroviral therapy in adults with established HIV-1 infection, including when to start treatment, selecting initial regimens, changing regimens, monitoring, and an overview of ARV adverse drug reactions. Some agents or formulations mentioned herein may not be currently available on the BC-CfE formulary. For a list of available medications click **here**[a]

Process

Mandated by the Ministry of Health, the BC Centre for Excellence in HIV/AIDS (BC-CfE) issues guidelines for the management and treatment of HIV and AIDS with the support of its Committee for Drug Evaluation and Therapy (CDET). *Therapeutic Guidelines: Antiretroviral (ARV) Treatment of Adult HIV Infection* is developed in two phases: Phase 1—Scientific Review, and Phase II—Economic Impact Analysis.

The Scientific Review involves the following process:

1. A Scientific Review working group is created, led by one of the co-chairs of the CDET and with the participation of other CDET members representing various areas of expertise.

2. At least one member of the working group conducts a literature review for a specific section, prepares a research synthesis, and drafts a series of recommendations.

3. Through an iterative process, recommendations are classified by strength of the evidence (using the SORT methodology; please see below for more details).

4. After two to three rounds of review by the working group, an ad hoc group of experts is asked to review and validate the preliminary recommendations, focusing on areas that require higher level of expertise (e.g. laboratory, opportunistic infections, women and pregnant individuals, etc.).

5. Recommendations are then compared to other guidelines and differences are flagged for further review.

6. Two iterative review processes are undertaken by members of the CDET and, where and when appropriate, feedback is incorporated into the document by the lead writer of each section.

7. The various recommendations, with supporting evidence and research analysis, are compiled into one document by a medical writer and presented to the CDET for further review.

8. A final version of the Scientific Review and recommendations is submitted to the Executive Director and Physician in Chief at the BC Centre for Excellence in HIV/AIDS.

9. Depending on budgetary and fiscal constraints, the Executive Director may request that an Economic Impact Analysis (Phase 2) be considered. Phase 2 will be initiated by the CDET.

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[a]Text for link: **http://www.cfenet.ubc.ca/publications/centre-documents/hivaids-drugs-available-through-bc-cfe**

Methodology

Recommendations in the Scientific Review are graded using the Strength of Recommendation Taxonomy (SORT) grading system (See **Table 1**). In this system, patient-oriented and disease-oriented outcomes are considered in regard to diagnosis, treatment/prevention/screening, and prognosis, with algorithms to establish the quality of each study and to establish the strength of the recommendation. Quality of evidence criteria vary by action, and only key recommendations require a grade for strength of recommendation. The taxonomy includes grades A, B, or C for the strength of recommendation for a body of evidence, and levels I, II, or III to distinguish the quality of evidence of individual studies. Ratings are usually based on the highest quality of evidence available.

TABLE 1:   Strength of Recommendation Taxonomy (SORT)

PART 1: STRENGTH OF RECOMMENDATION

GRADE	DEFINITION
A	Recommendation based on consistent and good quality patient-oriented evidence.
B	Recommendation based on inconsistent or limited quality patient-oriented evidence.
C	Recommendation based on consensus, usual practice, opinion, disease-oriented evidence, and case series for studies of diagnosis, treatment, prevention, or screening.

PART 2: STUDY QUALITY

LEVEL	TYPE OF STUDY		
	DIAGNOSIS	TREATMENT / PREVENTION / SCREENING	PROGNOSIS
I: Good quality, patient-oriented evidence	→Validated clinical decision rule →Systematic Review (SR)/meta-analysis of high quality studies →High quality diagnostic cohort study	→SR/meta-analysis of randomized controlled trials (RCTs) with consistent findings →High quality RCT →All or none study	→SR/meta-analysis of good quality cohort studies →Prospective cohort study with good follow-up
II: Limited quality patient-oriented evidence	→Unvalidated clinical decision rule →SR/meta-analysis of lower quality studies or studies with inconsistent findings →Lower quality diagnostic cohort study or diagnostic case-control study	→SR/meta-analysis of lower quality clinical trials or of studies with inconsistent findings. →Lower quality clinical trial →Cohort study →Case-control study	→SR/meta-analysis of lower quality cohort studies or with inconsistent results →Retrospective cohort study or prospective cohort study with poor follow-up →Case-control study →Case series
III: Other evidence	→Consensus guidelines, extrapolations from bench research, usual practice, opinion, disease-oriented evidence (intermediate or physiologic outcomes only), and case series for studies of diagnosis, treatment, prevention or screening.		

Adapted from Ebell MH, Siwek J, Weiss BD, Woolf SH, Susman J, Ewigman B, et al. Strength of recommendation taxonomy (SORT): a patient-centered approach to grading evidence in the medical literature. Am Fam Physician. 2004 Feb 1;69(3):548–56.

List of Tables

I WHEN TO START

A. RECOMMENDATIONS

1. We recommend starting antiretroviral therapy (ART) as soon as possible after diagnosis of HIV (A-I). The suggested time frame is within 2 weeks after diagnosis and when the patient is ready to start the therapy (C-III).

2. Once ART is started, we strongly recommend against subsequent interruptions to treatment (A-I).

3. As a secondary benefit, ART is strongly recommended for individuals with HIV to help prevent HIV transmission (A-I).

4. In chronic HIV infection, we strongly recommend offering ART to patients regardless of the CD4 cell count (A-I).

5. We recommend offering ART immediately to all individuals who are diagnosed in the early or acute stage of HIV infection, regardless of symptoms or CD4 cell count (A-II).

6. In patients who develop an opportunistic infection (OI), in most instances we recommend offering ART to the patient early (within 2 weeks) after starting active OI treatment (A-II). Exceptions include tuberculosis with CD4 cell count >50 cells/µL and central nervous system infections due to cryptococcus or tuberculosis. Toxoplasmosis may also be an exception to early initiation of ART.

B. DISCUSSION OF EVIDENCE

i. Early Initiation of ART

We recommend starting ART as soon as possible after diagnosis of HIV (A-I). The suggested time frame is within 2 weeks after diagnosis and when the patient is ready to start the therapy (C-III).

There is no CD4 cell count threshold above which starting therapy is contraindicated and no demonstrated harm of early ART initiation. Ongoing observational cohorts continue to accumulate data confirming that the benefits of HIV treatment are maximized when it is started earlier in the course of the disease:

- A combined analysis of 6699 ART-treated individuals in the Multicenter AIDS Cohort Study (MACS) and the Women's Interagency HIV Study (WIHS) showed that those who started treatment early (at CD4 cell count >350/µL) were less likely to die of AIDS-related causes and more likely to die at an older age than those who started treatment late (at CD4 cell count <200 cells/µL) (22% vs. 51% from AIDS-related causes, respectively; and median 72 years vs. 66 years of age, respectively) [1].
- An analysis of 8185 participants in the BC-CfE Drug Treatment Program, demonstrated a significant decline in mortality, from 6.4% in 2001-2002 to 3.6% in 2011-2012, in concert with the expansion of HAART in the province [2]. In an adjusted model, every 100-cell higher pre-ART CD4 cell count lowered the risk of death by 16% (adjusted hazard ratio 0.84, 95% CI, 0.78 to 0. 91).

Studies show that starting ART early can have short- and long-term benefits for patient outcomes:

- An observational study followed 86 patients who initiated ART within 30 days of diagnosis, with 45 patients (52%) starting ART between 1 to 4 weeks of their first clinic intake and 41 patients (48%) starting within one week (of the patients in the latter group, 22 began ART on the same day of their first clinic visit). Those who started ART on the same day were more likely to have achieved viral suppression as early as week-12. This study also suggested that early ART initiation within 30 days of diagnosis is associated with rapid viral suppression [3].

- A meta-analysis conducted by Ford and colleagues found that immediate ART initiation, including starting ART on the same day as HIV diagnosis, can lead to improved clinical outcomes by increasing the number of people starting and remaining on ART. Rapid ART start may be especially important for people with very low CD4 cell counts, for whom the risk of death is high [4].

The World Health Organization (WHO) guidelines call for same day treatment initiation [5]; however, this may not be applicable in high resourced settings [6]. In British Columbia, unpublished data from BC-CfE shows that the time interval from HIV diagnosis to treatment has decreased by 15 months from 2006 to 2013. Time to initiation of ART in 2006 was 17 months, which dropped down to just 2 months in 2013 after the implementation of STOP HIV/AIDS program at the provincial level (verbal communication with Dr. VD Lima, December 2019).

It is important to confirm that the patient is ready to commit to a life-long therapy which requires a very high level of adherence to ensure treatment efficacy. This confirmation from the patient is particularly important in view of the potential negative consequences of incomplete adherence in the setting of HIV (specifically, the emergence of drug-resistant virus, which is permanently archived in the individual) [7]. For this reason, **once ART is started, we strongly recommend against subsequent interruptions to treatment (A-I)**. Special efforts should be taken to ensure that the patient has adequate adherence education and support [8]. These issues should be regularly evaluated and proactively optimized. (See also **Chapter III: ART Assessment and Monitoring**.)

Immediate ART has also been shown to decrease the likelihood of sexual transmission of HIV by 96% in the HPTN 052 randomized controlled trial [9], as well as decreasing HIV transmission within cohorts of people who inject drugs [10,11]. Therefore, **as a secondary benefit, ART is strongly recommended for individuals with HIV to help prevent HIV transmission (A-I).** (See **HIV-serodiscordant couples** below.)

ii.   ART Initiation and CD4 Cell Count

In chronic HIV infection, we strongly recommend offering ART to patients regardless of their CD4 cell count (A-I).

The above recommendation is supported by data from three randomized controlled trials showing that early use of ART is associated with clinical benefits to the individual.

1. The HIV Prevention Trials Network (HPTN) 052 study of 1763 HIV serodiscordant couples with CD4 cell counts between 350 cells/μL and 550 cells/μL showed that early ART initiation resulted in a 41% reduction in the combined endpoint of disease progression and death [9].

2. In the Temprano randomized controlled trial (ANRS 12136) in Côte d'Ivoire, 2056 HIV-infected adults (78% women) with CD4 cell count nadir <800 cells/μL (median CD4 cell count nadir 465 cells/μL) received ART either immediately or when indicated according to WHO guidelines at the time (i.e. when CD4 cell count <200 cells/μL from 2008-2009, CD4 cell count <350 cells/μL from 2010-2012, and CD4 cell count <500 cells/μL from 2013-2015) [12]. The risk of severe morbidity (defined as AIDS-defining illness, non-AIDS defining malignancy, or non-AIDS-defining invasive bacterial disease) was 44% lower in the group randomized to receive immediate ART. The same degree of benefit was observed when the analysis was restricted to patients entering the study with CD4 cell count >500 cells/μL.

3. More recently, the large, international INSIGHT START trial demonstrated the benefit of initiating ART immediately in patients with CD4 cell count >500 cells/μL as compared to deferring ART initiation until the CD4 cell count had declined to 350 cells/μL [13]. The primary composite endpoint was any serious AIDS-related event, serious non-AIDS-related event (i.e. cardiovascular disease, end-stage renal disease, decompensated liver disease, or non-AIDS defining cancer), or death from any cause. After a mean of 3 years of follow-up, the primary endpoint occurred in 1.8% of the patients randomized to immediate ART initiation (42 events/2326 patients) as compared to 4.1% of the patients randomized to deferred ART initiation (96 events/2359 patients), for a hazard ratio of 0.43 (95% CI, 0.30 to 0.62, p<0.001). In view of the overwhelming clinical benefit demonstrated for early ART initiation among patients with CD4 cell counts >500 cells/μL, a decision was made to stop the study in May 2015 and offer all participants immediate ART.

There is some evidence to consider treatment for elite controllers (i.e. patients with HIV-1 RNA below the level of quantification without ART) [14,15], but at this time ART is not recommended for this group [16]. Such individuals should be clinically monitored (including CD4 cell count cell and plasma viral load counts) at no less than semiannual intervals because they are still at risk of disease progression [17,18].

iii. Special Considerations

1. Acute HIV Infection

We recommend offering ART immediately to all individuals who are diagnosed in the early or acute stage of HIV infection, regardless of symptoms or CD4 cell count (A-II). For more information on Management of Acute HIV Infections, please to refer the [BC-CfE Therapeutic Guidelines on Acute HIV Infection](#).

2. Pregnancy

ART should not be discontinued post-partum given both the potential benefits for the woman's health and the risks associated with HIV transmission during breastfeeding and with treatment interruption. Treatment of HIV-positive individuals who are pregnant or planning to become pregnant should be done under expert guidance [19]. In British Columbia, practitioners may contact the Women and Family HIV Centre (Oak Tree Clinic) at the BC Women's and Hospital and Health Centre for advice. (See also [Chapter II: What to Start With](#)).

The BC-CfE, in conjunction with the Women and Family HIV Centre (Oak Tree Clinic) at the BC Women's Hospital and Health Centre, has developed [recommendations for ART in pregnancy](#) [19]. ART is indicated for all pregnancies for the individual's health and to prevent HIV transmission to the infant. Individuals on ART at

conception should remain on therapy if the treatment is effective and tolerated, but the regimen should be reviewed for specific teratogenicity and toxicity in pregnancy. Those not on ART should be started on fully suppressive therapy as soon as possible to reduce the risk of HIV transmission. Teratogenicity concerns and the potential for non-adherence due to morning sickness should be considered in selection and timing of antiretrovirals. Nausea and vomiting are common during pregnancy and ideally should be aggressively managed prior to initiating antiretrovirals (50-80% of pregnant individuals experience nausea and 50% experience vomiting and retching) [20]. Overall, adherence to antiretrovirals appears to be improved rather than reduced during pregnancy [19,21].

3. Opportunistic infections (OIs)

In patients who develop an opportunistic infection (OI), in most instances we recommend offering ART to the patient early (within 2 weeks) after starting active OI treatment (A-II). Exceptions include tuberculosis with CD4 cell count >50 cells/µL and central nervous system infections due to cryptococcosis, tuberculosis, or toxoplasmosis. Initiating ART early after starting active OI treatment has been generally associated with improved survival [22,23]. However, regardless of the OI in question, the potential for drug interactions must be considered (see http://www.hiv-druginteractions.org or https://hivclinic.ca/drug-information/).

a. Cryptococcal meningitis

Based on the data published to date, which includes a meta-analysis of 4 randomized clinical trials, starting ART early (before 4 weeks) in the setting of cryptococcal meningitis is not recommended (particularly in patients with <5 white cells/mm³ in their cerebrospinal fluid). Patients starting ART should have received appropriate induction anti-fungal therapy (amphotericin B plus 5-flucytosine) and have become culture-negative with respect to cerebrospinal fluid. Optimizing outcomes also depend upon frequent monitoring for possible anti-fungal drug-related adverse effects, appropriate management of high intracranial pressure, and careful management of other underlying conditions. The 6- to 12-month mortality rates following a diagnosis of HIV-related cryptococcal meningitis in high- and low-resource settings range from 20% to at least 50%, respectively.

Published data raise concerns about the timing of ART initiation in the context of cryptococcal meningitis. A randomized controlled trial of 54 patients compared outcomes of starting ART within 72 hours after diagnosis of cryptococcal meningitis or delayed until completing the 10-week anti-fungal treatment. The risk of death was 2.85 times higher in the early ART group [24]. Immune reconstitution inflammatory syndrome (IRIS) occurred in patients in both groups, but the increased mortality was not attributable solely to IRIS. Of note, this study was conducted in Zimbabwe at a time when patients with cryptococcal meningitis were receiving initial treatment with fluconazole, which has been associated with a slower rate of clearance of cerebrospinal fluid infection and higher mortality compared to amphotericin B plus 5-flucytosine [25].

Contrary results have been reported in other trials. In another small randomized controlled trial, 27 patients in Botswana with cryptococcal meningitis receiving induction therapy with amphotericin B were randomized to early (within 7 days) or late (after 28 days) ART; IRIS occurred in 54% (7/13) and none (0/14) of the patients, respectively [26]. There was no increase in mortality associated with early ART (2/13, 15%) compared to late ART (5/14, 36%; p=0.39). The largest randomized controlled trial to address the optimal timing of ART in cryptococcal meningitis was conducted in Uganda and South Africa [27]. This study included 177 HIV patients who received induction therapy with amphotericin B plus fluconazole and randomized to receive early (1 to 2 weeks after

cryptococcal meningitis diagnosis) or deferred (5 weeks after diagnosis) ART. A similar proportion of patients in each group were recognized to develop IRIS (20% and 13%, respectively; p=0.32). However, the 26-week mortality was significantly higher with early vs. deferred ART (45% vs. 30%; hazard ratio for death 1.73, 95% CI, 1.06 to 2.82, p=0.03). One randomized controlled trial comparing early versus later ART initiation in high-resource setting included various OIs, but predominantly *Pneumocystis jiroveci* pneumonia (only 12% with cryptococcal meningitis) [22]. A meta-analysis of these four randomized controlled trials demonstrated a higher mortality risk ratio of 1.42 (95% CI, 1.02 to 1.97) in those starting ART early (<4 weeks) compared to later (≥4 weeks) [28].

In contrast to the above-mentioned meta-analysis, two prospective observational studies of cryptococcal meningitis (one in low-middle [25] and the other in high-resource settings [29]) showed no significant difference in mortality between patients initiating early versus late ART. The first study consisted of a cohort of pooled data from nine clinical trials (501 patients) and showed no significant difference in mortality after one year between the early (within 31 days) and late (after 31 days) ART initiation groups (p=0.3) [25]. The second study included 235 patients followed in 28 different European and North American cohorts and also showed no significant difference in mortality between those starting ART early (<2 weeks) versus late (2 to 8 weeks) [29]. There was a trend towards higher mortality among those individuals who did not begin ART until after 8 weeks. It is notable that there was also no advantage to early ART initiation (<2 weeks) demonstrated in either of these studies.

The randomized controlled trials which have examined the mortality risk associated with early versus late ART initiation in cryptococcal meningitis have been almost exclusively conducted in low-middle resource settings, where first line anti-fungal therapy (amphotericin B plus 5-flucytosine) is generally not available [24,26,27]. It has been suspected that early ART initiation during suboptimal anti-fungal induction therapy occurs at a time when there is still a high fungal burden in the cerebrospinal fluid which may give way to a greater risk of IRIS-related mortality. Although this may in part explain the findings of the above meta-analysis, the absence of adequately powered randomized controlled trials of early versus late ART in high-resourced settings should caution against adopting early ART in the context of cryptococcal meningitis in such countries. Furthermore, the study reported by Ingle and colleagues [29] does not demonstrate an advantage to ART initiation at <2 weeks versus at 2 to 8 weeks.

In summary, ART should be initiated between 4 to 6 weeks after starting induction therapy with amphotericin B (or liposomal amphotericin B) plus 5-flucytosine.

b. Tuberculosis (TB)

The optimal time to start ART in the context of tuberculosis (TB) meningitis is uncertain. However, in this setting ART should probably be started within the first 2 to 8 weeks of HIV diagnosis in these settings and the condition should be managed in consultation with experts.

Three randomized trials evaluating when to start ART during TB treatment [30-32] 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 cell count <50 cells/μL, and for this subgroup the optimal time of ART initiation was within the first 2 weeks of TB treatment. Individuals presenting with higher CD4 cell 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 cell 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 [33].

Persons with CD4 cell counts >50 cells/µL should initiate ART between 2 to 8 weeks after starting TB treatment. The optimal timing of ART for patients with TB meningitis is less certain, but ART appears to be best postponed until after the first 2 weeks of anti-tuberculous therapy. In a randomized controlled trial conducted in Vietnam, 253 participants with HIV and TB meningitis received standard anti-tuberculous therapy plus either immediate or deferred (2 months later) ART [34]. There was no survival benefit, but a higher rate of grade 4 adverse events (102 vs. 87; p=0.04) in the immediate ART group.

c. *Pneumocystis jiroveci* pneumonia (PCP)

ART should be initiated within 2 weeks of starting treatment of *Pneumocystis jiroveci* pneumonia (PCP).

The ACTG study A5164 was a randomized clinical trial which demonstrated that early ART (within 14 days of starting acute OI therapy, median 12 days) was associated with fewer AIDS progression/deaths (odds ratio 0.51, 95% CI, 0.27 to 0.94) compared to deferred ART (started after acute OI treatment was completed, median 45 days) after 48 weeks of follow-up [22]. Among the 282 evaluable patients in the study, PCP was the most common OI (63%).

4. HIV-serodiscordant couples

Reducing levels of HIV with ART decreases the probability of transmission, as the concentration of HIV in both blood and seminal plasma correlates with the probability of transmission of HIV to a sexual partner [35]. This has been confirmed by the HPTN 052 study, which showed ART to be more than 96% effective in reducing HIV transmission from an HIV-infected person to his or her HIV-uninfected partner [9]. Results from the PARTNER Study showed that there were no documented cases of within-couple HIV transmission (upper 95% confidence limit, 0.30/100 couple-years of follow-up) among serodifferent heterosexual and MSM couples (548 heterosexual and 340 MSM) in which the HIV-positive partner was using suppressive ART and who reported condomless sex, during median follow-up of 1.3 years per couple [36].

C. REFERENCES

1. Wada N, Jacobson LP, Cohen M, et al. Cause-specific mortality among HIV-infected individuals, by CD4+ cell count at HAART initiation, compared with HIV-uninfected individuals. AIDS 2014; 28:257-65.

2. Cheung C, Ding E, Sereda P, Yip B, Lourenco L, Barrios R, Montaner JSG, Hogg RS, Lima V, Moore D. Reductions in all-cause and cause-specific mortality among HIV-infected individuals receiving antiretroviral therapy in British Columbia, Canada: 2001-2012. HIV Medicine 2016 Oct; 17(9):694-701.

3. Hoenigl M, Chaillon A, Moore DJ, Morris SR, Mehta SR, Gianella S, Amico KR, Little SJ. Rapid HIV viral load suppression in those initiating antiretroviral therapy at first visit after HIV diagnosis. Scientific reports. 2016 Sep 6; 6:32947.

4. Ford N, Migone C, Calmy A, Kerschberger B, Kanters S, Nsanzimana S, Mills EJ, Meintjes G, Vitoria M, Doherty M, Shubber Z. Benefits and risks of rapid initiation of antiretroviral therapy. AIDS (London, England). 2018 Jan 2; 32(1):17.

5. World Health Organization. Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy, July 2017.

6. Pilcher CD, Ospina-Norvell C, Dasgupta A, Jones D, Hartogensis W, Torres S, Calderon F, Demicco E, Geng E, Gandhi M, Havlir DV. The effect of same-day observed initiation of antiretroviral therapy on HIV viral load and treatment outcomes in a US public health setting. Journal of acquired immune deficiency syndromes (1999). 2017 Jan 1; 74(1):44.

7. Tam LW, Chui CK, Brumme CJ, Bangsberg DR, Montaner JS, Hogg RS, Harrigan PR. The relationship between resistance and adherence in drug-naive individuals initiating HAART is specific to individual drug classes. Journal of acquired immune deficiency syndromes (1999). 2008 Nov 1; 49(3):266.

8. Boufassa F, Lechenadec J, Meyer L, et al; ANRS CO18 HIV Controllers Cohort; Cascade Collaboration in Eurocoord; SCOPE Cohort; International HIV Controllers Study. Blunted response to combination antiretroviral therapy in HIV elite controllers: an international HIV controller collaboration. PLoS One. 2014; 9(1):e85516.

9. Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med. 2011; 365:493-505.

10. Wood E, Hogg RS, Dias Lima V, et al. Highly active antiretroviral therapy and survival in HIV-infected injection drug users. JAMA 2008; 300(5): 550-554.

11. Wood E, Kerr T, Marshall BDL, et al. Longitudinal community plasma HIV-1 RNA concentrations and incidence of HIV-1 among injecting drug users: prospective cohort study. Br Med J. 2009; 338: b1649.

12. The TEMPANO ANRS 12136 Study Group. A trial of early antiretrovirals and isoniazid preventive therapy in Africa. New Engl J Med 2015; 373:808-22.

13. The INSIGHT START Study Group, Initiation of antiviral therapy in early asymptomatic HIV infection. New Engl J Med 2015; doi: 10.1056/NEJMoa1506816.

14. Mocroft A, Furrer HJ, Miro JM, et al. The incidence of AIDS-defining illness at a current CD4count >200 cells/µl in the post- combination antiviral therapy era. Clin Infect Dis 2013; 57:1038-47.

15. Chun T-W, Shawn Justement J, Murray D, et al. Effect of antiretroviral therapy on HIV reservoirs in elite controllers. J Infect Dis. 2013; 208(9):1443-1447.

16. Kim CJ, Kovacs C, Chun T-W, et al. Antiretroviral therapy in HIV-infected elite controllers: impact on gut immunology, microbial translocation, and biomarkers of serious non-AIDS conditions. J Acquir Immune Defic Syndr 2014; 67(5):514-8.

17. Karris MY, Haubrich RH. Antiretroviral therapy in elite controllers: justified or premature? J Infect Dis. 2015:211:1689-91.

18. Hatano H, Yukl SA, Ferre AL, et al. Prospective antiretroviral treatment of asymptomatic, HIV-1 infected controllers. PLoS Pathog. 2013; 9(10): e1003691.

19. British Columbia Guidelines for the care of HIV-positive pregnant individuals and interventions to reduce perinatal transmission and Dolutegravir prescribing guidelines for pregnancy and women of reproductive potential. Available at: http://www.bcwomens.ca/Professional-Resources-site/Documents/Oak%20Tree/BCHIVinpregnancyguidelinesFINALAug72014.pdf

20. Matthews A, Haas DM, O'Mathúna DP, Dowswell T. Interventions for nausea and vomiting in early pregnancy. Cochrane Database of Systematic Reviews 2015, Issue 9. Art. No.: CD007575. DOI: 10.1002/14651858.CD007575.pub4.

21. Lee NM, Saha S. Nausea and vomiting of pregnancy. Gastroenterol Clin North Am. 2011; 40:309-334.

22. Zolopa A, Andersen J, Powderly W, et al. Early antiretroviral therapy reduces AIDS progression/death in individuals with acute opportunistic infections: a multicenter randomized strategy trial. PLoS One 2009; 4:e5575.

23. Geng EH, Kahn JS, Chang OC, et al. The effect of AIDS Clinical Trials Group Protocol 5164 on the time from Pneumocystis jirovecii pneumonia diagnosis to antiretroviral initiation in routine clinical practice: a case study of diffusion, dissemination, and implementation. Clin Infect Dis. 2011; 53:1008-1014.

24. Makadzange AT, Ndhlovu CE, Takarinda K, et al. Early versus delayed initiation of antiretroviral therapy for concurrent HIV infection and cryptococcal meningitis in Sub-Saharan Africa. Clin Infect Dis. 2010; 50:1532-1538.

25. Jarvis NJ, Bicanic T, Loyse A, et al. Determinants of mortality in a combined cohort of 501 patients with HIV-associated cryptococcal meningitis: implications for improving outcomes. Clin Infect Dis 2014; 58:736-45.

26. Bisson GP, Molefi M, Bellamy S, et al. Early versus delayed antiretroviral therapy and cerebrospinal fluid fungal clearance in adults with HIV and cryptococcal meningitis. Clin Infect Dis 2013; 56:1165-73.

27. Boulware DR, Meya DB, Muzoora C, et al. Timing of antiretroviral therapy after diagnosis of cryptococcal meningitis. N Engl J Med 2014; 370:2487-98.

28. Eshun-Wilson I, Okwen MP, Richardson M, Bicanic T. Early versus delayed antiretroviral treatment in HIV-positive people with cryptococcal meningitis. Cochrane Database Syst Rev. 2018 24; 7:CD009012.

29. Ingle SM, Miro JM, Furrer H, et al. Impact of ART on Mortality in Cryptococcal Meningitis Patients: High-Income Settings. Paper presented at Conference on Retroviruses and Opportunistic Infections; Seattle; 2015 February 23-26.

30. Abdool Karim SS, Naidoo K, Grobler A, et al. Integration of antiretroviral therapy with tuberculosis treatment. N Engl J Med. 2011; 365:1492-1501.

31. Blanc FX, Sok T, Laureillard D, et al. Earlier versus later start of antiretroviral therapy in HIV-infected adults with tuberculosis. N Engl J Med. 2011; 365:1471-1481.

32. Havlir DV, Kendall MA, Ive P, et al. Timing of antiretroviral therapy for HIV-1 infection and tuberculosis. N Engl J Med. 2011; 365:1482-1491.

33. Meintjes G, Wilkinson R, Morroni C, et al. Randomized placebo-controlled trial of prednisone for paradoxical tuberculosis- associated immune reconstitution inflammatory syndrome. AIDS 2010; 24:2381-2390.

34. Torok ME, Nguyen TB, Tran THC, et al Timing of initiation of antiretroviral therapy in human immunodeficiency virus (HIV)-associated tuberculous meningitis. Clin Infect Dis 2011; 52:1374.

35. Hughes JP, Baeten JM, Lingappa JR, et al. Determinants of per-coital-act HIV-1 infectivity among African HIV-1-serodiscordant couples. J Infect Dis. 2012; 205:358-365.

36. Rodger AJ, Cambiano V, Bruun T, et al. Sexual Activity Without Condoms and Risk of HIV Transmission in Serodifferent Couples When the HIV-Positive Partner Is Using Suppressive Antiretroviral Therapy. *JAMA*.2016; 316(2):171–181. doi:10.1001/jama.2016.5148.

II WHAT TO START WITH

A. RECOMMENDATIONS

1. For adults with chronic HIV-1 infection, we strongly recommend a standard antiretroviral therapy (ART) which comprises a backbone of two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) and a third agent from another drug class (an integrase strand transfer inhibitor [INSTI], protease inhibitor [PI], or non-nucleoside reverse transcriptase inhibitor [NNRTI]) (A-I).

2. Dolutegravir-lamivudine (DTG-3TC) is an acceptable option for first line therapy for ARV naïve individuals (A-1) when the following conditions are met: not pregnant; absence of hepatitis B chronic infection; HIV drug resistance test must be performed and show no evidence of resistance to DTG or 3TC; baseline viral load is <500,000 copies/mL; and baseline CD4 count is >200 cells/mm³.

3. We recommend selecting the initial antiretroviral (ARV) regimen based on the results of genotypic resistance testing as well as individual patient factors which include co-existing conditions, concomitant medications, psychosocial factors, and, in the case of an individual with child-bearing potential, plans for conception and use/type of contraception. (A-II). If resistance test results are not available, we suggest a robust regimen able to overcome common resistance mutations (C-III).

4. Where possible, clinicians should prescribe an ARV regimen with a high barrier to resistance and without the need of a boosting agent (B-III).

5. It is strongly recommended that pregnant individuals receive ART for their own health and to reduce HIV transmission to the infant (A-I). For an HIV-positive individual in British Columbia who is pregnant or planning a pregnancy, we suggest consulting with the Women and Family HIV Centre (Oak Tree Clinic) at the BC Women's Hospital and Health Centre (see resource list in appendix), as ARV selection in the context of pregnancy requires expert guidance (C-III).

6. For triple ARV therapy, we strongly recommend abacavir/lamivudine, emtricitabine/tenofovir disoproxil fumarate (DF), or emtricitabine/tenofovir alafenamide (TAF) as NRTI backbones for ART initiation (A-I).

7. We strongly recommend against prescribing abacavir to those who test positive for the HLA-B*5701 allele or for whom no test result is available (A-I). See **Chapter III: ART Assessment and Monitoring** for more about the HLA-B*5701 test.

8. Abacavir should be used with caution in persons with a high risk of cardiovascular disease (B-II).

9. We strongly recommend against prescribing tenofovir DF for individuals with established chronic kidney disease (CKD) (estimated glomerular filtration rate [eGFR] <60 mL/min) or at high risk of CKD (A-I). For individuals at high risk of CKD, abacavir and TAF are recommended alternatives (the latter only if eGFR >30 mL/min) (A-II).

10. We strongly recommend against prescribing tenofovir DF for individuals with established osteoporosis (A-I). For those at high risk for osteoporosis (e.g. post-menopausal individuals), abacavir and TAF are preferred alternatives (B-III).

11. Regimens including either tenofovir DF or TAF, with either emtricitabine or lamivudine, are strongly recommended in patients who are co-infected with HIV and hepatitis B (A-I).

12. For triple ARV therapy, we strongly recommend an INSTI as the third agent for initial ART (A-I). Among the INSTIs, bictegravir or dolutegravir is recommended (A-I).

B. DISCUSSION OF EVIDENCE

i. General Principles

For adults with chronic HIV-1 infection, we strongly recommend a standard antiretroviral therapy (ART) which comprises a backbone of two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) and a third agent from another drug class (an integrase strand transfer inhibitor [INSTI], protease inhibitor [PI], or non-nucleoside reverse transcriptase inhibitor [NNRTI]) (A-I). In numerous randomized controlled trials, ART comprising two NRTIs and a third agent have demonstrated superior efficacy in achieving virologic suppression and increasing CD4 cell counts as compared to two-drug regimens [1-4]. In clinical trials using modern three-drug regimens, >80% of patients achieved virologic suppression to below 40 copies/mL by 48 weeks (with the majority reaching this target at or before 24 weeks) [5-11].

A number of factors need to be considered in selecting an ARV regimen, including characteristics of the regimen, the virus, and the individual patient (see **Table 3**). General recommendations can be made based on the available data for each ARV regimen (see **Table 2**), but alternative regimens may be appropriate in certain clinical situations. With the availability of generic ARV medications, the cost of medications is also an increasingly important consideration.

TABLE 2: **General Recommendations for ARV Regimen Selection**

GENERAL RECOMMENDATIONS	COMMENTS
We recommend selecting the initial ARV regimen based on the results of genotypic resistance testing as well as individual patient factors which include co-existing conditions, concomitant medications, psychosocial factors, and, in the case of an individual with child-bearing potential, plans for conception and use/type of contraception (see Table 3) (A-II).	Transmitted drug resistance rates in British Columbia are approximately 17% (2015 estimate), mainly involving NNRTIs (11%), while transmitted resistance is uncommon to PIs (2.5%) and NRTIs (0.4% to lamivudine/emtricitabine and 4.5% to others), and resistance to INSTIs is likely to be rare [12; Chanson Brumme, personal communication].
If genotypic resistance test results are not available, a robust regimen able to overcome common resistance mutations is suggested (C-III).	In cases where it is necessary or desirable to start ART before the resistance test results are available, the recommended initial regimen is emtricitabine/tenofovir disoproxil fumarate (DF) plus either a boosted protease inhibitor (atazanavir/ritonavir, darunavir/cobicistat, or darunavir/ritonavir) or dolutegravir (if there is a potential for significant drug-drug interactions with a boosting agent). The regimen can be adjusted if necessary once results of resistance and HLA-B*5701 tests become available.

GENERAL RECOMMENDATIONS	COMMENTS
Where possible, clinicians should prescribe an ARV regimen with a high barrier to resistance and without the need of a boosting agent (B-III).	HIV can develop resistance to some ARV agents more readily than to others. Boosted PIs and newer INSTIs (bictegravir, dolutegravir) have a higher barrier to resistance than older INSTIs (raltegravir, elvitegravir) and NNRTIs (efavirenz, rilpivirine). Pharmacokinetic boosting agents (ritonavir, cobicistat) are associated with increased potential for drug-drug interactions and gastrointestinal intolerance.

TABLE 3:   Factors to Consider when Selecting an ARV Regimen

FACTOR	CHARACTERISTICS	
Regimen	Regimen efficacy Genetic barrier to resistance Tolerability and short-term adverse events Potential for drug-drug interactions	Toxicity and long-term safety Pill burden and dosing frequency Food requirements
Virus	Resistance test results	
Individual	HIV infection →Baseline CD4 cell count and HIV viral load HLA-B*5701 test result Co-existing conditions →Bone disease (osteoporosis) →Cardiovascular disease →Chronic kidney disease →Hepatitis B co-infection →Hepatitis C co-infection	→Liver disease with severe hepatic impairment →Opportunistic infections and cancers[b] →Pregnancy/child-bearing potential[c] →Psychiatric illness, depression →Substance use disorder Concomitant medications Psychosocial factors →Food security →Potential barriers to adherence

It is strongly recommended that pregnant individuals receive ART for their own health and to reduce HIV transmission to the infant (A-I) (see Chapter I: When to Start; British Columbia guidelines for the care of HIV-positive pregnant individuals and interventions to reduce perinatal transmission). As data are constantly being updated regarding ARV safety during pregnancy, **ARV selection in the context of pregnancy requires expert guidance. For an HIV-positive individual in British Columbia who is pregnant or planning a pregnancy, we suggest consulting with the Women and Family HIV Centre (Oak Tree Clinic) at the BC Women's Hospital and Health Centre (C-III).**

ii.   NRTI Backbones

We strongly recommend abacavir/lamivudine, emtricitabine/tenofovir disoproxil fumarate (DF), or emtricitabine/tenofovir alafenamide (TAF) as NRTI backbones for ART initiation (see Table 4) (A-I). All NRTI in the table are available as fixed-dose combinations for once-daily dosing. None have specific food requirements.

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[b] Selection of an ARV regimen in the presence of an opportunistic infection should be done with the expert guidance of an Infectious Disease specialist.

[c] Patients of childbearing age should be asked about their pregnancy desires prior to initiation of ART. Pregnancy plans may influence the decisions on which ARV regimen to initiate. In general, newer ARV agents should be avoided in this setting due to limited data regarding their safety in pregnancy.

TABLE 4: NRTI Backbones

NRTI	RECOMMENDATIONS	COMMENTS
Abacavir 600 mg – lamivudine (3TC) 300 mg* once daily	**Do not use if patient tests positive for the HLA-B*5701 allele or if HLA- B*5701 status is unknown (A-I).** [d] Use of fixed-dose tablet not recommended in renal impairment (creatinine clearance <50 mL/min) or hepatic impairment due to potential need for dose adjustment. Use separate preparations[e]. Seek guidance from an HIV-experienced pharmacist. **Should be used with caution in persons with a high risk of cardiovascular disease (B-II).**	Abacavir does not have activity against hepatitis B virus. Lamivudine has activity against hepatitis B virus. Available as generic formulation. Also available as a single-tablet regimen with dolutegravir.
Emtricitabine (FTC) 200 mg-tenofovir disoproxil fumarate (DF) 300 mg* once daily	Potential renal and bone toxicity. [f] **We strongly recommend against prescribing tenofovir DF for individuals with established chronic kidney disease (CKD) (eGFR <60 mL/min) or at high risk of CKD (A-I).** Dose interval adjustment required if creatinine clearance 30-49 mL/min. [f] Not recommended if creatinine clearance <30 mL/min. [f] For patients with end-stage renal disease on dialysis, seek guidance from an HIV-experienced pharmacist. **We strongly recommend against prescribing tenofovir DF for individuals with established osteoporosis (A-I).**	FTC and tenofovir DF have activity against hepatitis B virus. Available as generic formulation. Also available as single-tablet regimens with efavirenz*, elvitegravir/cobicistat,[g] or rilpivirine.
Emtricitabine (FTC) 200 mg-tenofovir alafenamide (TAF) 10 mg or 25 mg once daily	Not recommended if creatinine clearance <30 mL/min. [h] TAF dose 10 mg if regimen includes ritonavir or cobicistat, and 25 mg if no boosting agent (both doses available as fixed-dose combination). [h]	FTC and TAF have activity against hepatitis B virus. Not available as generic formulation. Also available as single-tablet regimens with bictegravir or elvitegravir/cobicistat.

*available as generic formulations

1. Abacavir

Abacavir is associated with a hypersensitivity reaction in patients who are positive for the HLA-B*5701 allele (approximately 6% prevalence in British Columbia) [13]. (See **Chapter III: ART Assessment and Monitoring** for more about the HLA-B*5701 test). Abacavir is available in fixed-dose combination with lamivudine, and with lamivudine and dolutegravir as a single-tablet regimen.

Randomized controlled trials comparing abacavir/lamivudine to emtricitabine/tenofovir DF in ARV-naïve patients showed these two backbones to be equally efficacious overall. Among patients with baseline viral load ≥100,000 copies/mL, emtricitabine/tenofovir DF showed significantly greater virologic efficacy (14% virologic

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[d] See **Chapter III: Assessment and Monitoring** for more about the HLA-B*5701 test.

[e] Kivexa® Product Monograph. ViiV Healthcare, Laval, Quebec. 2018 December 20.

[f] Truvada® Product Monograph. Gilead Sciences, Inc. Mississauga, Ontario. 2018 July 5.

[g] Elvitegravir/cobicistat/emtricitabine/tenofovir DF should not be initiated in patients with creatinine clearance <70 mL/min. [Stribild® Product Monograph. Gilead Sciences, Inc. Mississauga, Ontario. 2018 September 17.]

[h] Descovy® Product Monograph. Gilead Sciences, Inc. Mississauga, Ontario. 2018 June 25.

failure with abacavir/lamivudine vs. 7% with emtricitabine/tenofovir DF after a median of 60 weeks) when the third agent in the regimen was efavirenz or atazanavir/ritonavir [14,15]. There was no difference in virologic efficacy at higher viral loads when the third agent was lopinavir/ritonavir or dolutegravir [7,16,17]. Limited data are available for the use of abacavir/lamivudine with either raltegravir or boosted darunavir [18-20]. If abacavir/lamivudine is used in patients with baseline viral load >100,000 copies/mL, the third agent in the regimen should be dolutegravir.

Abacavir has been associated with an increased risk of myocardial infarction (MI) in some observational cohort studies. Meta-analyses of randomized controlled trials have not shown any association but have a limited statistical power [21]. Data from a large North American cohort study showed that recent use of abacavir (within 6 months) was associated with a significantly increased risk of both Type 1 and Type 2 MI (adjusted hazard ratio for the combined MI outcome was 1.84, 95% CI, 1.17 to 2.91) after adjusting for other known risk factors for coronary artery disease [22]. Although the association remains controversial, abacavir should be used with caution in persons with a high risk of cardiovascular disease (e.g. 10-year risk >20%), where an increased relative MI risk would result in a significant absolute risk.[i]

2.   Tenofovir

Tenofovir disoproxil fumarate (DF) and tenofovir alafenamide (TAF) are prodrugs of tenofovir and its active intracellular moiety tenofovir diphosphate. Both are available in fixed-dose combination with emtricitabine and in a number of single tablet regimens (see **Table 4**). Emtricitabine-tenofovir DF has been available in Canada since 2004 and for many years has been the most widely prescribed NRTI backbone in British Columbia. Since July 2018 it has been available in a generic formulation. Emtricitabine-tenofovir DF has demonstrated virologic efficacy in many clinical trials and in clinical practice with all currently available third drugs [7-11] (except bictegravir, which has only been studied with TAF).

Tenofovir DF is usually well-tolerated but can be associated with proximal renal tubular toxicity and CKD, particularly among patients with underlying CKD risk factors and/or who are taking concomitant nephrotoxic medications [24-26]. Presence of other CKD risk factors (e.g. diabetes, hypertension) may increase the likelihood of nephrotoxicity with tenofovir DF [27,28]; therefore, **for individuals at high risk of CKD, abacavir or TAF are recommended alternatives (the latter only if eGFR >30 mL/min) (A-II).** Tenofovir DF has also been associated with greater loss of bone mineral density and more frequent fractures compared to ARV regimens not containing tenofovir DF [29,30]. **For individuals with osteoporosis or at high risk for osteoporosis (e.g. post-menopausal individuals), abacavir and TAF are preferred alternatives (B-III).**

More recently, in 2016, the fixed-dose combination emtricitabine/TAF was approved by Health Canada and is available in two doses: 200 mg/10 mg (to be given in regimens including ritonavir or cobicistat) and 200 mg/25 mg (in regimens without a booster). In a head-to-head comparison of TAF and tenofovir DF, using pooled data from two randomized double-blind trials among 1733 ARV-naïve patients, the virologic efficacy of elvitegravir/cobicistat/emtricitabine/TAF (E/C/F/TAF) was non-inferior to that of

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[i] Several prediction models are available to estimate the risk of cardiovascular disease in adults living with HIV. Risk categories (high, intermediate, and low) estimated using the Framingham equation correlated well with observed cumulative incidence of MI among HIV-infected patients in NA-ACCORD [22]. However, the Framingham risk score has not been validated in HIV-infected populations and may overestimate their cardiovascular disease risk. The HIV-specific risk prediction model based on the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) prospective cohort study is an alternative risk calculator for estimating cardiovascular disease risk in this population [23].

elvitegravir/cobicistat/emtricitabine/tenofovir DF (E/C/F/TDF) at 48 and 96 weeks, and superior at 144 weeks (viral load <50 copies/mL in 84.2% vs. 80.0%; difference 4.2%, 95% CI, 0.6% to 7.8%) [31]. Less proteinuria and smaller declines in bone mineral density were seen with E/C/F/TAF than with E/C/F/TDF.

A meta-analysis of randomized controlled trials [32] comparing TAF and tenofovir DF indicated that:

- In patients taking a regimen including a boosting agent (e.g. elvitegravir/cobicistat, darunavir/cobicistat, ritonavir-boosted PIs), TAF had 2% higher rates of viral load <50 copies/mL than tenofovir DF (95% CI, 0% to +4%, p=0.05).
- In patients taking an unboosted regimen (e.g. rilpivirine, efavirenz, dolutegravir, raltegravir), there was no difference in viral suppression rates between TAF and tenofovir DF (difference 0%, 95% CI, -2% to +2%, p=0.90).

With regard to safety parameters, the same meta-analysis showed:

- No significant differences between TAF and tenofovir DF in clinical adverse events.
- The risk of discontinuation for renal adverse events was 1% lower for boosted TAF than for boosted tenofovir DF (95% CI, -1% to 0%, p=0.002).
- No difference in the risk of discontinuation for renal adverse events for unboosted TAF and unboosted tenofovir DF (difference 0%, 95% CI, 0%).
- Smaller decreases in bone mineral density at the hip and spine with TAF than with tenofovir DF, in both boosted and unboosted regimens.
- The risk of bone fractures was 1% lower for boosted TAF compared with boosted tenofovir DF (95% CI, -2% to 0%, p=0.04).
- No difference in the risk of fractures between unboosted TAF and unboosted tenofovir DF (difference 0%, 95% CI, 0% to +1%).

The authors concluded that "TDF boosted with ritonavir or cobicistat was associated with higher risks of bone and renal adverse events, and lower HIV RNA suppression rates, compared with TAF. By contrast, when ritonavir and cobicistat were not used, there were no efficacy differences between TAF and TDF, and marginal differences in safety" [32]. The clinical significance of the differences in bone mineral density is unclear.

3. Lamivudine and Emtricitabine

Lamivudine (3TC) and emtricitabine (FTC) are chemically related and have similar activity. Both are usually very well-tolerated, but emtricitabine may be associated with more gastrointestinal tolerability issues and rash in some individuals [33,34]. The choice between these two agents is usually influenced by the co-formulation (**Table 4**). Lamivudine is available as a single entity and co-formulated with abacavir (both of which are available in generic forms), and co-formulated with tenofovir DF and doravirine in a single-tablet regimen. Emtricitabine is available in co-formulations with tenofovir DF and TAF.

d. Hepatitis B

Tenofovir DF, TAF, emtricitabine, and lamivudine have activity against hepatitis B virus, while abacavir does not. **Regimens including either tenofovir DF or TAF, with either emtricitabine or lamivudine, are strongly recommended in patients who are co-infected with HIV and hepatitis B (A-I).**

iii.   Third agent

Third agent options include a drug from one of three ARV drug classes: integrase strand transfer inhibitors (INSTIs), protease inhibitors (PIs), or non-nucleoside reverse transcriptase inhibitors (NNRTIs).

Table 5 shows options for the third agents in first-line ARV regimens. Some are also available with an NRTI backbone as a single-tablet regimen. **We strongly recommend an INSTI as the third agent for initial ART (A-I). Among the INSTIs, bictegravir or dolutegravir is recommended (A-I).**

TABLE 5:   **Third Agents (in alphabetical order within each class)**

DRUG AND STRENGTH	NUMBER OF PILLS IN INITIAL THERAPY	AVAILABLE AS SINGLE-TABLET REGIMEN WITH	FOOD REQUIREMENT
INTEGRASE STRAND TRANSFER INHIBITORS (INSTIs)			
Bictegravir 50 mg fixed-dose combination with emtricitabine and TAF	1 tablet once daily	Emtricitabine 200 mg – TAF 25 mg	None
Dolutegravir 50 mg	1 tablet once daily	Abacavir 600 mg – lamivudine 300 mg	None
Elvitegravir 150 mg-cobicistat 150 mg fixed-dose combination with emtricitabine and tenofovir DF or TAF	1 tablet once daily	Emtricitabine 200 mg - tenofovir DF 300 mg, or Emtricitabine 200 mg – TAF 10 mg	Take with food or a snack (minimum 250 kcal)
Raltegravir (standard) 400 mg tablet Raltegravir HD 600 mg tablet	1 standard tab twice daily or 2 HD tabs once daily	None	None
PROTEASE INHIBITORS (PIs)			
Atazanavir 300 mg* + ritonavir 100 mg	1 capsule + 1 tablet once daily	None	Take with food (minimum 350 kcal)
Darunavir 800 mg + ritonavir 100 mg	1 + 1 tablet once daily	None	Take with food or a snack (minimum 250 kcal)
NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTIs)			
Doravirine 100 mg	1 tablet once daily	Lamivudine 300 mg – tenofovir DF 300 mg	None
Efavirenz 600 mg*	1 tablet once daily	Emtricitabine 200 mg - tenofovir DF 300 mg*	Fewer CNS side effects if taken without food
Rilpivirine 25 mg	1 tablet once daily	Emtricitabine 200 mg - tenofovir DF 300 mg	Take with food (minimum 390 kcal)

DF, disoproxil fumarate; TAF, tenofovir alafenamide; kcal, kilocalories; CNS, central nervous system

a. Integrase strand transfer inhibitors (INSTIs)

INSTIs have shown non-inferior, and in some cases superior, virologic efficacy in randomized controlled trials in comparison to third-drug options from other classes (**Table 5**) [7,9,10,17,35-38]. No direct comparisons are available between an INSTI and either rilpivirine or doravirine. No agent has shown superior virologic efficacy in comparison to an INSTI [39]. INSTIs have shown more rapid suppression of viral load compared to other classes: $\geq$80% of study participants receiving INSTI-based regimens had viral load <50 copies/mL by 8 to 12 weeks, compared to 24 weeks among those receiving PI- or NNRTI-based regimens [5-11]. This represents a potential benefit in the context of acute infection and for Treatment as Prevention.

Within the INSTI class, most agents have shown virologic non-inferiority with none being superior to any other in direct comparisons. However, a systematic review and network meta-analysis including studies published up to July 2015, before the availability of bictegravir, showed "a clear hierarchy within the INSTI class, with dolutegravir being the most efficacious, followed by raltegravir, and then elvitegravir" [39].

1. <u>Bictegravir</u>

Bictegravir has demonstrated non-inferior efficacy to dolutegravir over 96 weeks in randomized controlled trials [5,6, 44,45] and has a similarly high barrier to resistance. The tolerability profile of bictegravir appears to be generally similar to that of dolutegravir. The bictegravir/FTC/TAF fixed-dose combination was approved by Health Canada in July 2018.

b. <u>Dolutegravir</u>

Dolutegravir was approved by Health Canada in October 2013 and 3-year clinical trial data have been published (SINGLE, showing superiority of dolutegravir + abacavir/lamivudine compared to efavirenz/tenofovir DF/emtricitabine) [17]. Raltegravir and dolutegravir are usually well-tolerated and have similar side effect profiles [43]. Dolutegravir has a higher genetic barrier to resistance and lower pill burden than raltegravir (one vs. two pills daily) and is available with an NRTI backbone as a single-tablet regimen, while raltegravir is not.

c. <u>Elvitegravir</u>

Elvitegravir co-formulated with cobicistat, emtricitabine, and tenofovir DF has demonstrated non-inferior efficacy to efavirenz/emtricitabine/tenofovir DF [11] and to atazanavir/ritonavir + emtricitabine/tenofovir DF [46,47]. However, elvitegravir is a less attractive INSTI option as it requires cobicistat as a boosting agent, with the associated potential for drug-drug interactions. Elvitegravir/cobicistat has a similar resistance profile to raltegravir, and is associated with more gastrointestinal side effects, fatigue, and malaise than dolutegravir or raltegravir [43].

Among INSTIs, the longest clinical experience is available with <u>raltegravir</u>, which was approved by Health Canada in 2007; there are published 5-year clinical trial data (including STARTMRK, showing superiority of raltegravir 400 mg twice daily compared to efavirenz at 4 and 5 years) [35,40]. A once-daily raltegravir formulation (Isentress™ HD), administered as two 600 mg tablets, was approved by Health Canada in June 2017. The virologic efficacy of raltegravir 1200 mg (HD formulation) once daily was shown to be non-inferior to that of raltegravir 400 mg (standard formulation) twice daily at 48 and 96 weeks in a randomized controlled trial among

ARV-naïve adults [41,42].

4. Protease inhibitors (PIs)

In ARV-naïve patients, both <u>darunavir</u> and <u>atazanavir</u> can be given once daily, and both require pharmacokinetic boosting with either ritonavir or cobicistat to achieve effective plasma levels. In comparative trials with a 2-NRTI backbone, darunavir 800 mg/ritonavir 100 mg once daily and atazanavir 300 mg/ritonavir 100 mg once daily have shown similar rates of virologic suppression among ARV-naïve patients [39,48-50]. Due to the necessity of co-administration with a boosting agent, both PIs have the potential for drug-drug interactions and gastrointestinal intolerance. A notable difference between the two PIs is that atazanavir is associated with ≥Grade III hyperbilirubinemia (total bilirubin ≥2.5x the upper limit of normal) in close to 50% of patients [51-53], while darunavir is not. This is usually benign unconjugated hyperbilirubinemia and is reversible when atazanavir is discontinued. Unlike darunavir, atazanavir is available in a generic formulation.

Darunavir is available as a single entity requiring ritonavir boosting or in fixed-dose combination with cobicistat (darunavir 800 mg/cobicistat 150 mg). Trough darunavir levels are 30% lower when given with cobicistat 150 mg than with ritonavir 100 mg [51,54]. Cobicistat is not recommended for use as a boosting agent in pregnancy due to substantially lower drug exposures during pregnancy that may reduce treatment effectiveness [55-57].

Virologic suppression rates seen in ARV-naïve patients with darunavir/cobicistat + two NRTIs are similar to those seen with darunavir/ritonavir + two NRTIs [58,59], although head-to-head comparative studies have not been done.

Similar to the integrase inhibitors bictegravir and dolutegravir, boosted PIs have a relatively high barrier to resistance, making them an appropriate choice for patients with adherence challenges or primary resistance to NRTIs or NNRTIs.

5. Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

1. <u>Efavirenz</u>

Efavirenz in combination with two NRTIs was the standard first-line ART worldwide for many years. Efavirenz was approved by Health Canada in 2003. In 2007, efavirenz/emtricitabine/tenofovir DF became the first approved single tablet regimen for the treatment of HIV and remained the only one for many years. Both efavirenz and the single tablet regimen are now available as generics.

In randomized controlled trials, efavirenz has demonstrated similar virologic efficacy to atazanavir/ritonavir, darunavir/ritonavir, elvitegravir/cobicistat, rilpivirine, and doravirine [39,60]. However, raltegravir and dolutegravir have shown superior efficacy in direct comparisons to efavirenz [7,17,35] (see **Table 4**) and in network meta-analysis [39]. Efavirenz has a lower barrier to resistance compared to boosted PIs, bictegravir, dolutegravir, and doravirine. Efavirenz has a higher rate of adverse effects than raltegravir, dolutegravir, rilpivirine, or doravirine [7,10,17,35,60-64]. Central nervous system (CNS) adverse effects (such as sleep disturbances, somnolence, dizziness, impaired concentration, anxiety, and depression) occur in approximately 50% of efavirenz-treated patients [65]. Efavirenz has been associated with increased suicide risk in some studies [66]. In a meta-analysis of the United States AIDS Clinical Trials Group (ACTG) randomized controlled trials among ARV-naïve participants, those receiving efavirenz had a two-fold increased hazard of suicidality as compared to those receiving non-efavirenz based regimens [67].

d. Rilpivirine

Compared to efavirenz in randomized controlled trials, rilpivirine is virologically non-inferior overall and better tolerated, with less rash and fewer CNS adverse events [62-65]. However, rilpivirine has lower virologic efficacy than efavirenz in patients with high viral load and is approved only for patients with baseline viral load ≤100,000 copies/mL [68,69]. Furthermore, since rates of virologic failure were higher in clinical trials among participants with baseline CD4 cell counts <200 cells/mm³ [61,63], rilpivirine-based regimens are recommended only for ARV-naïve patients with baseline CD4 cell counts >200 cells/mm³. Rilpivirine requires stomach acid for absorption, so must be administered with a meal [68,69]. Dosing without food or with concomitant proton pump inhibitors can substantially lower rilpivirine plasma concentrations and increase the risk of virologic failure and emergence of NRTI- and NNRTI-resistant mutations. Rilpivirine is available alone and as a single-tablet regimen with emtricitabine/tenofovir DF.

e. Doravirine

Health Canada approved the newest NNRTI, doravirine, in October 2018 and a single-tablet regimen comprising doravirine/lamivudine/tenofovir DF in November 2018. 48-week results of two randomized controlled trials have been published, one showing non-inferior virologic efficacy of doravirine/lamivudine/tenofovir DF compared to efavirenz/emtricitabine/tenofovir DF [60], and another showing non-inferior virologic efficacy of doravirine + two NRTIs compared to darunavir/ritonavir + two NRTIs [70]. For the latter study, 96-week results show superior efficacy of doravirine: 73.1% of doravirine recipients and 66.0% of darunavir/ritonavir recipients had viral load <50 copies/mL (treatment difference 7.1%, 95% CI, 0.5 to 13.7) [71]. In these studies, doravirine was associated with fewer CNS adverse events than efavirenz (e.g. dizziness 9% vs. 37%; abnormal dreams 5% vs. 12%) [60] and less diarrhea than darunavir/ritonavir (14% vs. 22%) [70,71], but clinical experience with this agent is limited. Doravirine has a distinct resistance profile and a higher barrier to resistance than efavirenz or rilpivirine, suggesting doravirine should remain active against HIV strains harbouring primary NNRTI resistance [60,70]. No study results are available comparing doravirine to an INSTI. There is no data on doravirine in pregnancy.

f. Two-drug ARV regimens

Two-drug regimens are not generally recommended for initial therapy at this time, due to lack of sufficient long-term efficacy data (B-II), with the exception of dolutegravir (DTG)-lamivudine (3TC). **DTG-3TC is an acceptable option for first line therapy for ARV naïve individual (A-I) when the following conditions are met:**

- **Absence of hepatitis B chronic infection.**

- **HIV drug resistance test must be performed and show no evidence of resistance to DTG or 3TC.**

- **Baseline viral load is <500,000 copies/mL, and baseline CD4 count is >200 cells/mm³.**

- **Not pregnant.**

A number of two-drug ARV regimens have been investigated as initial therapy for treatment-naïve individuals [72], but only the fixed-dose combination dolutegravir-lamivudine (DTG-3TC) has been approved by Health Canada for this indication [73]. In the two identically designed double-blind Phase 3 GEMINI studies, treatment-naïve adults were randomized to receive either once-daily dolutegravir and lamivudine (DTG + 3TC) (N = 716) or a once-daily standard three-drug regimen of dolutegravir and emtricitabine-tenofovir DF (DTG +

FTC-TDF) (N = 717). In both trials, the two-drug regimen was non-inferior to the three-drug regimen in terms of virologic efficacy at weeks 48 [74] and 96 [75]. No treatment-emergent resistance was observed among participants who met confirmed virologic withdrawal criteria in either arm. Drug-related adverse events were observed less frequently with DTG + 3TC (9.6%) than with DTG + FTC-TDF (25.0%) [75]. A screening viral load (VL) >500,000 copies/mL was an exclusion criterion for the GEMINI studies, but a small number of participants (N=28, 2%) had a VL >500,000 copies/mL at the baseline visit [74, 75]. Among these, the proportion with VL<50 copies/mL at week 96 favoured the three-drug regimen: 80% (12/15) with DTG + TDF-FTC vs. 69% (9/13) with DTG + 3TC. Among GEMINI participants with baseline VL >100,000 copies/mL, results did not differ by treatment arm: 86% (132/153) with three drugs vs. 84% (117/140) with two drugs had VL<50 copies/mL at 96 weeks [75]. A relatively small number (N=118, 8%) of participants in the GEMINI studies had a CD4 count $\leq$200 cells/mm^3 at baseline [74, 75]. Among them, the proportion with VL<50 copies/mL at week 96 again favoured the three-drug regimen: 87% (48/55) with DTG + TDF-FTC vs. 68% (43/63) with DTG-3TC [78]. DTG-3TC is not sufficient treatment for hepatitis B virus (HBV), and is not recommended for patients with any known or suspected viral resistance to dolutegravir or lamivudine [73].

Dolutegravir-rilpivirine is available as a fixed-dose combination and is approved by Health Canada only for maintenance therapy in patients who are already virologically suppressed; it is not recommended for initial treatment [76]. Other two-drug regimens are under investigation for the treatment of ARV-naïve patients.

C. REFERENCES

1. Gullick RM, Mellors JM, Havlir D, et al. Treatment with indinavir, zidovudine, and lamivudine in adults with human immunodeficiency virus infection and prior antiretroviral therapy. N Engl J Med. 1997; 337:734–9.

2. Montaner JSG, Reiss P, Cooper D, et al. A randomized, double-blind trial comparing combinations of nevirapine, didanosine, and zidovudine for HIV-infected patients: The INCAS Trial. J Amer Med Assoc. 1998; 279: 930-7.

3. Staszewski S, Morales-Ramirez J, Tashima KT, et al. Efavirenz plus zidovudine and lamivudine, efavirenz plus indinavir, and indinavir plus zidovudine and lamivudine in the treatment of HIV-1 infection in adults. N Engl J Med. 1999; 341(25):1865-73.

4. Gartland M, Gerstoft J, Goebel F, et al. AVANTI 2. Randomized, double-blind trial to evaluate the efficacy and safety of zidovudine plus lamivudine versus zidovudine plus lamivudine plus indinavir in HIV-infected antiretroviral-naive patients. AIDS 2000; 14(4):367-74.

5. Sax P, Pozniak A, Montes ML, et al. Coformulated bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir with emtricitabine and tenofovir alafenamide, for initial treatment of HIV-1 infection (GS-US-380-1490): a randomized, double-blind, multicentre, phase 3, non-inferiority trial. Lancet 2017;390: 2073-82.

6. Gallant J, Lazzarin A, Mills A, et al. Bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir, abacavir, and lamivudine for initial treatment of HIV-1 infection (GS-US-380-1489): a double-blind, multicentre, phase 3, randomised controlled non-inferiority trial. Lancet 2017;390: 2063-72.

7. Walmsley S, Antela A, Clumeck N, et al. Dolutegravir plus abacavir-lamivudine for the treatment of HIV-1 infection. N Engl J Med. 2013; 369: 1807-18.

8. Raffi F, Rachlis A, Stellbrink H-J, et al. Once-daily dolutegravir versus raltegravir in antiretroviral-naive adults with HIV-1 infection: 48 week results from the randomized, double-blind, non-inferiority SPRING-2 study. Lancet 2013; 381:735-43.

9. Clotet B, Feinberg J, Lunzen JV, et al. Once-daily dolutegravir versus darunavir plus ritonavir in antiretroviral-naive adults with HIV-1 infection (FLAMINGO): 48 week results from the randomized open-label phase 3b study. Lancet 2014; 383: 2222-31.

10. Lennox JL, DeJesus E, Lazzorin A, et al. Safety and efficacy of raltegravir-based versus efavirenz-based combination therapy in treatment-naïve patients with HIV-1 infection: a multicenter, double-blind randomized controlled trial. Lancet 2009; 374:796-806.

11. Sax, PE DeJesus E, Mills A, et al. Co-formulated elvitegravir, cobicistat, emtricitabine, and tenofovir versus co-formulated efavirenz, emtricitabine, and tenofovir for initial treatment of HIV-1 infection: a randomized, double-blind, phase 3 trial, analysis of results after 48 weeks. Lancet 2012; 379:2439-48.

12. Rocheleau G, Brumme CJ, Shoveller J, Lima VD, Harrigan PR. Longitudinal trends of HIV drug resistance in a large Canadian cohort, 1996–2016. Clin Microbiol Infect. 2018; 24 (2):185-91.

13. Mallal S, Phillips E, Carosi G, et al. HLA-B*5701 Screening for Hypersensitivity to Abacavir. N Engl J Med. 2008; 358(6):568-79.

14. Post F, Moyle G, Stellbrink H, et al. Randomized Comparison of Renal Effects, Efficacy, and Safety With Once-Daily Abacavir/Lamivudine Versus Tenofovir/Emtricitabine, Administered With Efavirenz, in Antiretroviral-Naive, HIV-1–Infected Adults: 48-Week Results From the ASSERT Study. J Acquir Immune Defic Syndr. 2010; 55(1): 49-57.

15. Sax PE, Tierney C, Collier AC, et al. Abacavir-lamivudine versus tenofovir-emtricitabine for initial HIV-1 therapy. N Engl J Med. 2009; 361 (23):2230-40.

16. Smith KY, Patel P, Fine D, et al. Randomized, double-blind, placebo-matched, multicenter trial of abacavir/lamivudine or tenofovir/emtricitabine with lopinavir/ritonavir for initial HIV treatment. AIDS 2009; 23:1547-56.

17. Walmsley S, Bau mgarten A, Berenguer J, et al. Dolutegravir Plus Abacavir/Lamivudine for the Treatment of HIV-1 Infection in Antiretroviral Therapy-Naive Patients: Week 96 and Week 144 Results From the SINGLE Randomized Clinical Trial. J Acquir Immune Defic Syndr. 2015; 70(5): 515-19.

18. Young B, Vanig T, DeJesus E. et al. 96-Week Results of a Pilot Study of Abacavir/Lamivudine and Raltegravir in Antiretroviral-Naïve HIV-1-Infected Patients: The SHIELD Trial. HIV Clin Trials 2010; 12(4):228-33.

19. Podzamczer D, Imaz A, Perez I, et al. Abacavir/Lamivudine plus darunavir/ritonavir in routine clinical practice: a multicenter experience in antiretroviral therapy-naïve and -experienced patients. J Antimicrob Chemother. 2014; 69:2536-40.

20. Nishijima T, Tsukada K, Teruya K, et al. Efficacy and safety of once-daily ritonavir-boosted darunavir and abacavir/lamivudine for treatment-naïve patients: a pilot study. AIDS 2012; 26:649-51.

21. Llibre JM, Hill A. Abacavir and cardiovascular disease: A critical look at the data. Antivir Res. 2016; 132: 116-21.

22. Elion RA, Althoff KN, Zhang J, et al. Recent abacavir use increases risk of Type 1 and Type 2 myocardial infarctions among adults with HIV. J Acquir Immune Defic Syndr. 2018; 78(1):62-72.

23. Krikke M, Hoogeveen RC, Hoepelman AIM, Visseren FLJ, Arends JE. Cardiovascular risk prediction in HIV-infected patients: comparing the Framingham, atherosclerotic cardiovascular disease risk score (ASCVD), Systematic Coronary Risk Evaluation for the Netherlands (SCORE-NL) and Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) risk prediction models. HIV Med. 2016; 17:289-97.

24. Scherzer R, Estrella M, Li Y, et al. Association of tenofovir exposure with kidney disease risk in HIV infection. AIDS 2012; 26: 867-75.

25. Ryom L, Mocroft A, Kirk O, et al. Association Between Antiretroviral Exposure and Renal Impairment Among HIV-Positive Persons With Normal Baseline Renal Function: the D:A:D Study. J Infect Dis. 2013; 207: 1359-69.

26. Mocroft A, Kirk O, Reiss P, et al. Estimated glomerular filtration rate, chronic kidney disease and antiretroviral drug use in HIV-positive patients. AIDS 2010; 24:1667–78.

27. Morlat P, Vivot A, Vandenhende MA, Dauchy FA, Asselineau J, et al. Role of Traditional Risk Factors and Antiretroviral Drugs in the Incidence of Chronic Kidney Disease, ANRS CO3 Aquitaine Cohort, France, 2004–2012. PLOS ONE 2013; 8(6): e66223. **https://doi.org/10.1371/journal.pone.0066223**

28. Scherzer R, Gandhi M, Estrella MM, et al. A chronic kidney disease risk score to determine tenofovir safety in a prospective cohort of HIV-positive male veterans. AIDS 2014; 28: 1289-95.

29. Bedimo R, Maalouf NM, Zhang S, Drechsler H, Tebas P. Osteoporotic fracture risk associated with cumulative exposure to tenofovir and other antiretroviral agents. AIDS 2012; 26:825–31.

30. McComsey GA, Tebas P, Shane E, et al. Bone Disease in HIV Infection: A Practical Review and Recommendations for HIV Care Providers. Clin Infect Dis. 2010;51(8):937-46.

31. Arribas JR, Thompson M, Sax PE, et al. Randomized, Double-Blind Comparison of Tenofovir Alafenamide (TAF) vs Tenofovir Disoproxil Fumarate (TDF), Each Coformulated With Elvitegravir, Cobicistat, and Emtricitabine (E/C/F) for Initial HIV-1 Treatment: Week 144 Results. J Acquir Immune Defic Syndr. 2017; 75 (2): 211-18.

32. Hill A, Hughes SL, Gotham D, Pozniak AL. Tenofovir alafenamide versus tenofovir disoproxil fumarate: is there a true difference in efficacy and safety? J Virus Erad. 2018; 4: 72–9.

33. Pollock K, Stebbing J, Bower M, Gazzard B, Nelson M. Emtricitabine intolerance in treatment-experienced patients switched from lamivudine: a method of assessing toxicity. Antimicrob Chemoth. 2006; 58(1): 227-8.

34. Borrás-Blasco J, Navarro-Ruiz A, Borrás C, Casterá E. Adverse cutaneous reactions associated with the newest antiretroviral drugs in patients with human immunodeficiency virus infection. J Antimicrob Chemoth. 2008; 62: 879–88.

35. Rockstroh JK, DeJesus E, Lennox JL, et al. Durable Efficacy and Safety of Raltegravir Versus Efavirenz When Combined With Tenofovir/Emtricitabine in Treatment-Naive HIV-1–Infected Patients: Final 5-Year Results From STARTMRK. J Acquir Immune Defic Syndr. 2013; 63 (1):77-85.

36. Molina, JM, Clotet, B, Jan VL, et al. Once-daily dolutegravir is superior to once-daily darunavir/ritonavir in treatment-naïve HIV-1-positive individuals: 96 week results from FLAMINGO. In: Abstracts of the HIV Drug Therapy Glasgow Congress 2014; J Int AIDS Soc. 2014; 17 (4 Suppl 3):19490:1.

37. Orrell C, Hagins DP, Belonosova E, et al. Fixed-dose combination dolutegravir, abacavir, and lamivudine versus ritonavir-boosted atazanavir plus tenofovir disoproxil fumarate and emtricitabine in previously untreated women with HIV-1 infection (ARIA): week 48 results from a randomised, open-label, non-inferiority, phase 3b study. Lancet 2017; 4:536-46.

38. Squires K, Kityo C, Hodder S, et al. Integrase inhibitor versus protease inhibitor based regimen for HIV-1 infected women (WAVES): a randomised, controlled, double-blind, phase 3 study. Lancet 2016; 3:410-20.

39. Kanters S, Vitoria M, Doherty M, et al. Comparative efficacy and safety of first-line antiretroviral therapy for the treatment of HIV infection: a systematic review and network meta-analysis. Lancet HIV 2016; 3: e51020.

40. Gotuzzo E, Markowitz M, Ratanasuwan W, et al. Sustained Efficacy and Safety of Raltegravir After 5 Years of Combination Antiretroviral Therapy as Initial Treatment of HIV-1 Infection: Final Results of a Randomized, Controlled, Phase II Study (Protocol 004). J Acquir Immune Defic Syndr. 2012; 61(1):73-77.

41. Cahn P, Kaplan R, Sax P, et al. Raltegravir 1200 mg Once Daily versus raltegravir 400 mg twice daily, with tenofovir disoproxil fumarate and emtricitabine, for previously untreated HIV-1 infection: a randomized, double-blind, parallel-group, phase 3, non-inferiority trial. Lancet HIV. 2017; 4(11):e486-e494.

42. Cahn P, Sax PE, Squires K, et al. Raltegravir 1200 mg Once Daily vs 400 mg Twice daily, With Emtricitabine and Tenofovir Disoproxil Fumarate, for Previously Untreated HIV-1 Infection: Week 96 Results From ONCEMRK, a Randomized, Double-Blind, Noninferiority Trial. J Acquir Immune Defic Syndr. 2018; 78 (5):589-98.

43. Lepik K, Yip B, Ulloa AC, et al. Adverse drug reactions to integrase strand transfer inhibitors. AIDS 2018; 32:903-12.

44. Stellbrink HJ, Arribas J, Stephens JL, et al. Co-formulated bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir with emtricitabine and tenofovir alafenamide for initial treatment of HIV-1 infection: week 96 results from a randomised, double-blind, multicentre, phase 3, non-inferiority trial. Lancet HIV 2019 May 3; pii: S2352-3018(19)30080-3. doi: 10.1016/S2352-3018(19)30080-3. [Epub ahead of print]

45. Wohl DA, Yazdanpanah Y, Bau mgarten A, et al. Bictegravir combined with emtricitabine and tenofovir alafenamide versus dolutegravir, abacavir, and lamivudine for initial treatment of HIV-1 infection: week 96 results from a randomised, double-blind, multicentre, phase 3, non-inferiority trial. Lancet HIV 2019 May 3; 2019 May 3. pii: S2352-3018(19)30077-3. doi: 10.1016/S2352-3018(19)30077-3. [Epub ahead of print]

46. DeJesus E, Rockstroh J, Henry K, et al. Co-formulated elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate versus ritonavir-boosted atazanavir plus co-formulated emtricibine and tenofovir disoproxil fumarate for initial treatment of HIV-1 infection: a randomized, double-blind, phase 3, non-inferiority trial. Lancet 2012; 379: 2429-38.

47. Rockstroh, JK, DeJesus E, Henry, K, et al. A Randomized, Double-Blind Comparison of Coformulated Elvitegravir/Cobicistat/Emtricitabine/Tenofovir DF vs Ritonavir-Boosted Atazanavir Plus Coformulated Emtricitibine and Tenofovir DF for Initial Treatment of HIV-1 Infection: Analysis of Week 96 Results. J Acquir Immune Defic Syndr. 2013; 62(5):483-6.

48. Lennox JL, Landovitz RJ, Ribaudo HJ, et al. A Phase III Comparative Study of the Efficacy and Tolerability of Three Non-Nucleoside Reverse Transcriptase Inhibitor-Sparing Antiretroviral Regimens for Treatment-Naïve HIV-1-Infected Volunteers: A Randomized, Controlled Trial. Ann Intern Med. 2014; 161(7): 461–71.

49. Martinez E, Gonzalez-Cordon A, Ferrer E, et al. Differential Body Composition Effects of Protease Inhibitors Recommended for Initial Treatment of HIV Infection: A Randomized Clinical Trial. Clin Infect Dis. 2015; 60:811-20.

50. Aberg JA, Tebas P, Turner Overton E, et al. Metabolic Effects of Darunavir/Ritonavir Versus Atazanavir/Ritonavir in Treatment-Naive, HIV Type 1-Infected Subjects over 48 Weeks. AIDS Res Hum Retrov. 2012; 28 (10): 1184-95.

51. Laprise C, Baril JG, Dufresne S, Trottier H. Atazanavir and Other Determinants of Hyperbilirubinemia in a Cohort of 1150 HIV-Positive Patients: Results from 9 Years of Follow-Up. AIDS Patient Care STDs. 2013; 27 (7):378-86.

52. Torti C, Lapadula G, Antinori A, et al. Hyperbilirubinemia during Atazanavir Treatment in 2,404 Patients in the Italian Atazanavir Expanded Access Program and MASTER Cohorts. Infection 2009; 37(3):244-9.

53. Johnson M, Grinsztejn B, Rodriguez C, et al. Atazanavir plus ritonavir or saquinavir, and lopinavir/ritonavir in patients experiencing multiple virological failures. AIDS 2005; 19 (7):685-94.

54. Kakuda TN, Opsomer M, Timmers M, et al. Pharmacokinetics of Darunavir in Fixed-Dose Combination with Cobicistat Compared with Coadministration of Darunavir and Ritonavir as Single Agents in Healthy Volunteers. J Clin Pharmacol. 2014; 54 (8):949-57.

55. Boyd SD, Sampson MR, Viswanathan P, Struble KA, Arya V, Sherwat AI. Cobicistat-containing antiretroviral regimens are not recommended during pregnancy: viewpoint. AIDS. 2019 May 1;33(6):1089-1093.

56. Crauwels HM, Osiyemi O, Zorrilla C, Bicer C, Brown K. Reduced exposure to darunavir and cobicistat in HIV-1-infected pregnant individuals receiving a darunavir/cobicistat-based regimen. HIV Med. 2019 May;20(5):337-343.

57. Prezcobix® Product Monograph. Janssen, Inc. Toronto, Ontario. 2019 Apr 9.

58. Tashima K, Crofoot G, Tomaka FL, et al. Cobicistat-boosted darunavir in HIV-1-infected adults: week 48 results of a Phase IIIb, open-label single-arm trial. AIDS Res Ther. 2014; 11(39):1-12.

59. Mills A, Crofoot G, McDonald C, et al. Tenofovir Alafenamide Versus Tenofovir Disoproxil Fumarate in the First Protease Inhibitor–Based Single-Tablet Regimen for Initial HIV-1 Therapy: A Randomized Phase 2 Study. J Acquir Immune Defic Syndr. 2015; 69 (4):439-45.

60. Orkin C, Squires KE, Molina J-M, et al. Doravirine/Lamivudine/Tenofovir Disoproxil Fumarate is Non-inferior to Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate in Treatment-naive Adults With Human Immunodeficiency Virus–1 Infection: Week 48 Results of the DRIVE-AHEAD Trial. Clin Infect Dis. 2019; 68:535-44.

61. Cohen CJ, Molina J-M, Cassetti I, et al. Week 96 efficacy and safety of rilpivirine in treatment-naive, HIV-1 patients in two Phase III randomized trials. AIDS 2013; 27:939–50.

62. Cohen C, Wohl D, Arribas JR, et al. Week 48 results from a randomized clinical trial of rilpivirine/emtricitabine/tenofovir disoproxil fumarate vs. efavirenz/emtricitabine/tenofovir disoproxil fumarate in treatment-naïve HIV-1-infected adults. AIDS 2014; 28:989–97.

63. van Lunzen J, Antinori A, Cohen CJ, et al. Rilpivirine vs. efavirenz-based single-tablet regimens in treatment-naive adults: week 96 efficacy and safety from a randomized phase 3b study. AIDS 2016; 30:251–9.

64. Pozniak AL, Morales-Ramirez J, Katabira E, et al. Efficacy and safety of TMC278 in antiretroviral-naïve HIV-1 patients: week 96 results of a phase IIb randomized trial. AIDS 2010; 24:55–65.

65. Kenedi CA, Goforth HW. A Systematic Review of the Psychiatric Side-Effects of Efavirenz. AIDS Behav. 2011; 15:1803–18.

66. Arenas-Pinto A, Grund B, Sharma S, et al. Risk of suicidal behavior with use of efavirenz: results from the strategic timing of antiretroviral treatment trial. Clin Infect Dis. 2018; 67(3):420-9.

67. Mollan KR, Smurzynski M, Eron JJ, et al. Association between efavirenz as initial therapy for HIV-1 infection and increased risk for suicidal ideation or attempted or completed suicide: an analysis of trial data. Ann Intern Med. 2014; 161(1):1-10.

68. Edurant® Product Monograph. Janssen Inc. Toronto, Ontario. 2018 August 13.

69. Complera® Product Monograph. Gilead Sciences, Inc. Mississauga, Ontario. 2018 May 23.

70. Molina J-M, Squires K, Sax PE, et al. Doravirine versus ritonavir-boosted darunavir in antiretroviral-naive adults with HIV-1 (DRIVE-FORWARD): 48-week results of a randomised, double-blind, phase 3, non-inferiority trial. Lancet HIV 2018; 5:211-20.

71. Molina J-M, Squires K, Sax PE, et al. Doravirine versus ritonavir-boosted darunavir in antiretroviral-naive adults with HIV-1 (DRIVE-FORWARD): 96-week results of a randomised, double-blind, phase 3, non-inferiority trial. Lancet HIV 2020; 7(1):e16-e26.

72. Corado KC, Caplan M, Daar ES. Two-drug regimens for treatment of naïve HIV-1 infection and as maintenance therapy. Drug Design, Development and Therapy 2018; 12:3731-3740.

73. Dovato Product Monograph. ViiV Healthcare, Laval, Quebec. 2019 August 22.

74. Cahn P, Madero JS, Arribas JR, et al. Dolutegravir plus lamivudine versus dolutegravir plus tenofovir disoproxil fumarate and emtricitabine in antiretroviral-naïve adults with HIV-1 infection (GEMINI-1 and GEMINI-2): week 48 results from two multicentre, double-blind, randomised, non-inferiority, phase 3 trials. Lancet 2019; 393 (10167): 143-155. http://dx.doi.org/10.1016/S0140-6736(18)32462-0.

75. Cahn P, Sierra Madero J, Arribas J, et al. Durable efficacy of dolutegravir plus lamivudine in antiretroviral treatment-naïve adults with HIV-1 infection: 96-week results from the GEMINI-1 and GEMINI-2 randomized clinical trials. J Acquir Immune Defic Syndr. 2020:83(3): 310-318. **https://www.ncbi.nlm.nih.gov/pubmed/31834000**.

76. Juluca Product Monograph. ViiV Healthcare, Laval, Quebec. 2018 August 27.

III ART ASSESSMENT AND MONITORING

A. RECOMMENDATIONS

1. We recommend performing HIV genotype drug resistance testing before starting ART to assess for transmitted drug resistance (A-II).

2. Plasma HIV-1 RNA viral load should be assessed before starting ART (or when ART is changed for any reason) and monitored frequently thereafter using the following schedule:

   a. every 4 to 6 weeks until HIV-1 RNA viral load is suppressed (i.e. below 40 copies/mL),

   b. every 3 months until HIV-1 RNA viral load is suppressed for at least 2 years, and then

   c. every 6 months. (B-III)

3. CD4 cell count should be performed in tandem with HIV-1 RNA viral load test every 3 months until HIV-1 RNA virus is suppressed for 2 years (B-III). Thereafter, we recommend reducing the frequency of CD4 cell count monitoring to every 6 months, if the patient maintains consistent medication adherence and viral suppression and their CD4 cell count is over 300 cells/μL for at least 2 years (A-III). In patients with CD4 cell count >500 cells/μL and consistently suppressed HIV-1 RNA viral load while on ART for at least 2 years, CD4 cell count should be performed on an annual basis (B-II).

4. A one-time HLA-B*5701 testing is strongly recommended before initiating ART or prescribing abacavir (A-I).

5. CCR5 tropism testing is strongly recommended each time maraviroc is considered as part of ART (A-I).

6. We recommend age- and risk-appropriate screening for sexually transmitted infections (STIs) at various anatomical sites, anal or cervical dysplasia, tuberculosis, hepatitis A, B and C, medication toxicity, and general health (A-III).

7. In patients who have achieved viral suppression on ART and whose HIV-1 RNA viral load subsequently becomes detectable (>200 copies/mL), we recommend a repeat viral load measurement within 4 weeks and a reassessment of the patient's medication adherence and tolerability (A-III).

8. HIV genotype drug resistance testing is recommended when HIV-1 RNA viral load exceeds 250 copies/mL in patients already receiving ART (A-III).

B. DISCUSSION OF EVIDENCE

Several laboratory tests are recommended for initial evaluation of patients with HIV upon entry into care and before and after initiating or modifying their antiretroviral therapy (ART). These tests help determine appropriate antiretroviral (ARV) regimen, assess virologic and immunologic efficacy of ART, and monitor for laboratory abnormalities that may be associated with ARV drugs. See **Table 6** for a list of recommended laboratory tests to be performed prior to ART initiation, as well as subsequent testing once ART is initiated.

Clinicians need to ask their HIV-positive patients about adherence to ART at regular monitoring visits and provide resources to improve adherence for those patients who have challenges [1,2]. Management by physicians experienced in HIV medicine is increasingly recognized as a critical contributor to improved health outcomes [3,4].

i.   Laboratory Assessments

Before starting ART, recommended laboratory tests include HIV drug genotypic drug resistance testing, HIV-1 RNA viral level, and CD4 cell count. Other baseline tests include: HLA-B*5701 testing, complete blood count, chemistry profile, transaminase levels, creatinine, urinalysis, fasting blood glucose, and serum lipids (see **Table 6** for the complete list of baseline assessments). Within 4 to 6 weeks of starting ART, patients should be assessed for adherence, tolerability, and virologic response to their ART.

1.   Drug Resistance Testing

Transmission of drug-resistant HIV strains is well-documented and is associated with suboptimal virologic response to initial ART [5-7]. In British Columbia, the reported prevalence of primary HIV drug resistance to nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs) increased from 12% in 1996 to 18% in 2014 [6]. In a randomized cohort study where 26% of the participants had virologic failure, the prevalence of baseline NNRTI resistance was 5% and the risk of virologic failure was higher in subjects with baseline NNRTI than in subjects without such resistance (hazard ratio 2.27, 95% CI, 1.15 to 4.49, p=0.018) [7]. These results support resistance testing before starting ART [8]. **We therefore recommend performing HIV drug resistance genotype testing before starting ART to assess for transmitted drug resistance (A-II).** Since 2010, the BC-CfE laboratory performs automatic genotypic drug resistance testing in all first HIV-1 RNA samples in patients who have HIV-1 RNA levels >250 copies/mL.

Standard genotypic drug resistance testing in ARV-naïve persons involves testing for mutations in the reverse transcriptase and protease genes. Although reports of transmission of virus resistant to integrase strand transfer inhibitors (INSTIs) are rare, clinicians are increasingly prescribing this class of ARVs and there is greater potential for the transmission of INSTI-resistant virus [9-11]. Other HIV guidelines currently do not recommend baseline INSTI genotyping; however, since 2016, automated HIV resistance testing of patients' first sample with plasma viral load >250 copies/mL has included testing for resistance to the INSTI class.

In general, ART initiation should not be deferred for genotypic drug resistance testing results, but in the few cases when patients or providers may delay treatment initiation (see **Chapter I: When to Start**), resistance testing should still be performed and repeated prior to starting ART [11,12]. Treatment initiation should not be delayed for resistance testing results in either acute or chronic HIV infection for resistance testing results if the individual is willing and able to begin treatment immediately. Once results are reported, the regimen can be modified if warranted (see the **BC-CfE Therapeutic Guidelines: Management of Acute HIV Infections**).

2.   HIV-1 RNA Viral Load

Plasma HIV-1 RNA viral load should be assessed before starting ART (or when ART is changed for any reason) and monitored frequently thereafter: every 4 to 6 weeks until HIV-1 RNA viral load is suppressed (i.e. below 40 copies/mL), every 3 months until HIV-1 RNA viral load is suppressed for at least 2 years, and then every 6 months (B-III). This statement is in line with recommendations of the International ARV Society [13].

In the HIV Out Patient Study (HOPS), which included patients who had maintained viral load <50 copies/mL for at least 2 years between 1999 and 2013, there was no statistically significant difference in frequency of virologic failure among patients undergoing frequent (≥3 tests/year) versus less frequent viral load testing (two tests/year) [14]. In patients on a stable, suppressive ART regimen, HIV-1 RNA viral load should be repeated every 3 months

or as clinically indicated to confirm continuous viral suppression. Clinicians may extend the interval to 6 months for patients who maintain medication adherence, whose viral load has been suppressed for more than 2 years, and whose clinical and immunologic status is stable [15]. If monitoring intervals extend and the patient's adherence decreases, therapy may fail and allow drug resistance to emerge [16].

3. CD4 cell count

The CD4 cell count is the most important laboratory indicator of immune function in patients with HIV. It is used to predict HIV disease progression and patient survival [17,18] and to determine whether prophylaxis for opportunistic infections (OIs) should be initiated (see the **BC-CfE Primary Care Guidelines for the Management of HIV/AIDS in British Columbia**) [19].

In patients who initiate or change ART, **CD4 cell count should be performed in tandem with HIV-1 RNA viral load test every 3 months until HIV-1 RNA virus is suppressed for 2 years (B-III)**. CD4 cell counts are highly variable. The absolute CD4 cell count is a calculated value based on the total white blood cell (WBC) count and the percentages of total and CD4 T-lymphocytes. This absolute number may fluctuate in individuals or may be influenced by factors that affect the total WBC count and lymphocyte percentages, such as the use of bone marrow-suppressive medications or the presence of acute infections. Splenectomy or co-infection with human T-lymphotropic virus type I (HTLV-1) may cause misleadingly elevated CD4 cell counts [20-22]. Alpha-interferon may reduce the absolute CD4 cell count without changing the CD4 percentage [23]. In all these settings, CD4 percentage remains stable and may be a more appropriate parameter to assess a patient's immune function.

Patients who are diagnosed late in their disease progression (CD4 cell count reaching below 100 cells/μL) and those who are over 50 years of age may demonstrate a blunted increase in their CD4 cell counts upon ART initiation, despite viral suppression [24-26].

Once viral suppression occurs and is sustained, CD4 cell counts usually increase. In a cohort study of 423 individuals who initiated highly active ART (HAART) before 1998 and who achieved viral load <1000 copies/mL by 48 weeks, a 4-year analysis showed significant increases in their CD4 cell counts (p=0.05) with continued viral suppression, regardless of pre-ART CD4 cell counts [27]. **We recommend reducing the frequency of CD4 cell count monitoring to every 6 months, if the patient maintains consistent medication adherence and viral suppression and their CD4 cell count is over 300 cells/μL for at least 2 years (A-III).** In patients with sustained viral suppression, frequent CD4 cell count testing is unnecessary because the results rarely lead to a change in clinical management [28].

In patients with CD4 cell count >500 cells/μL and consistently suppressed HIV-1 RNA viral load while on ART for at least 2 years, CD4 cell count should be performed on an annual basis (B-II). Several large cohort studies (USA, South Africa, Uganda) have shown that HIV-positive individuals with ongoing viral suppression maintained CD4 cell counts ≥200 cells/μL beyond 2 years of starting ART or changing ARV regimen [14].

CD4 cell counts should be monitored more frequently when there are changes in a patient's clinical status that may decrease CD4 cell count and thus prompt prophylaxis for opportunistic infections. Examples of such changes include the appearance of new HIV-related symptoms or initiation of treatment known to reduce CD4 cell count (e.g. interferon, chronic corticosteroids, or anti-neoplastic agents) [14]. In patients who fail to maintain viral suppression while on ART, CD4 cell count monitoring should be performed every 3 to 6 months. Recommendations for monitoring frequency differ for pregnant individuals due to physiologic changes associated

with pregnancy. Please refer to guidelines for the care of HIV positive pregnant individuals (see [British Columbia guidelines for the care of HIV positive pregnant women and interventions to reduce perinatal transmission]).

In patients who remain untreated for whatever reason, CD4 cell counts should be monitored every 3 to 6 months to assess the urgency of ART initiation and the need for prophylaxis for opportunistic infections.

4. Testing for HLA-B*5701

Abacavir can cause hypersensitivity reaction (HSR). This multi-organ clinical syndrome was typically seen within the first 6 weeks of abacavir treatment in 5% to 8% of patients participating in clinical trials [29,30]. In general, abacavir HSR promptly reverses once the drug is discontinued. Abacavir HSR is associated with the presence of a specific human leukocyte antigen, HLA-B*5701. **A one-time HLA-B*5701 testing is strongly recommended before initiating ART or prescribing abacavir (A-I).** This test only needs to be done once in the lifetime of a patient. HLA-B*5701-positive patients should not be prescribed abacavir and the positive status should be recorded as an abacavir allergy in the patient's medical record. In a double-blind, prospective, randomized study that involved 1956 HIV-infected individuals who had not previously received abacavir, there was a 5.6% prevalence of HLA-B*5701. Screening eliminated immunologically confirmed HSR (0% in the prospective-screening group vs. 2.7% in the control group, p<0.001), with a negative predictive value of 100% and a positive predictive value of 47.9% [29].

5. Testing for CCR5 tropism

CCR5 co-receptor antagonists (maraviroc) prevent HIV's entry into target cells by binding to the HIV co-receptor CCR5. **CCR5 tropism testing is strongly recommended each time maraviroc is considered as part of ART (A-I)**, or if virologic failure occurs while the patient is receiving a CCR5 antagonist [31-33]. CCR5 tropism testing should be performed on the most recent plasma sample with a HIV-1 RNA viral load >500 copies/mL. If a CCR5 co-receptor antagonist is being considered in a patient with a HIV-1 RNA viral load lower than 500 copies/mL (e.g. in cases of regimen simplification or a toxicity-related switch), a proviral DNA tropism assay can be used [34-36]. If other co-receptor tropism (CXCR4-utlizing or dual/mixed-tropic viruses) are detected, then the CCR5 co-receptor antagonist should not be used. A cross-sectional study (of the AIDS Clinical Trial Group) found that, among ARV-experienced patients in whom a CCR5 inhibitor was used, 50% had virus that used the CCR5 co-receptor and 46% had dual-tropic or mixed HIV-1 population that used CCR5 and CXCR4 co-receptors [37].

6. Other assessments

We recommend age- and risk-appropriate screening for sexually transmitted infections (STIs) at various anatomical sites, anal or cervical dysplasia, tuberculosis, hepatitis A, B and C, medication toxicity, and general health (A-III).

Co-infection screening recommendations include hepatitis A, B, and C, tuberculosis, and sexually transmitted infections. Hepatitis B and hepatitis C virus infections should be monitored periodically after ART initiation (see [Table 6]), as treatment of these co-infections may affect the choice of ART. Sexually transmitted infections are more common in some individuals with HIV and appropriate screening is recommended (see the [BC-CfE Primary Care Guidelines for the management of HIV/AIDS in British Columbia]). Specific recommendations for cervical cancer screening of immunocompromised individuals in Canada have been published [38].

The baseline assessment should include an evaluation of the patient's readiness for ART initiation, history of substance use disorder, mental health-related conditions, co-morbidities, economic and social factors (e.g. unstable housing), and other factors that are known to affect adherence to ART. The baseline evaluation should also include a discussion of risk reduction and disclosure to sexual and/or needle-sharing partners, especially with untreated patients who are still at high risk of HIV transmission.

g. Monitoring During ART

1. Detectable HIV-1 RNA Viral Levels

Optimal viral suppression is defined as a HIV-1 RNA viral load persistently below the level of detection (<40 copies/mL). However, isolated viral blips (defined as HIV-1 RNA viral loads transiently detectable at low levels [<400 copies/mL]) are not uncommon in successfully treated patients and are not predictive of virologic failure [39].

Virologic failure is defined as HIV-1 RNA level above 200 copies/mL on at least two consecutive measurements. **In patients who have achieved viral suppression on ART and whose HIV-1 RNA viral load subsequently becomes detectable (>200 copies/mL), we recommend a repeat viral load measurement within 4 weeks and a reassessment of the patient's medication adherence and tolerability (A-III).**

Once virologic failure is confirmed, a HIV genotype drug resistance test should be performed while the patient is taking the failing regimen [12]. **HIV genotype assay is recommended when HIV-1 RNA viral load exceeds 250 copies/mL in patients already receiving ART (A-III).** For virologic failure of INSTI-containing ART or for those patients with previous history of INSTI exposure, INSTI resistance testing is recommended [40,41]. Since 2015 in British Columbia, for patients with a prior history of INTSI exposure, genotyping HIV resistance testing includes testing for INSTI resistance. If a new ART regimen is started, HIV-1 RNA level should be checked 4 to 6 weeks after initiation, following the same schedule as for monitoring initial ART.

Expert advice should be sought for the management of patients with persistently detectable HIV-1 RNA levels [42].

2. Therapeutic Drug Monitoring

Therapeutic drug monitoring (TDM) of ART medications is not generally recommended, but it may be useful in some settings, such as patients with kidney or liver impairment, to minimize overexposure and adverse effects, manage potential drug-drug interactions, or to evaluate virologic failure in the absence of resistance [43]. TDM may also prove valuable in the management of HIV in children and pregnant individuals [44,45]. The BC-CfE Laboratory performs TDM testing under "research protocol" and as such it requires special approval and written consent from the individual. In these situations, expert advice should be sought to determine if TDM is appropriate. Untimed drug levels (UDL) can be requested to be performed by the BC-CfE Laboratory to confirm adequate drug exposure in individuals for whom adherence or poor drug absorption is a consideration. In these situations, expert advice should be sought to determine if TDM or UDL is appropriate.

Requisition forms to request HIV genotype drug resistance testing, CCR5 tropism test, HLA-B* 5701, and Therapeutic Drug Monitoring are available on the **BC-CfE website**.

TABLE 6: **Laboratory Testing Schedule for Monitoring Patients with HIV Before and After Initiation of Antiretroviral Therapy**

LABORATORY TEST	FREQUENCY OF TESTING						
	ENTRY INTO CARE	ART INITIATION OR MODIFICATION	4-6 WEEKS POST ART INITIATION OR CHANGE	EVERY 3 MONTHS	EVERY 6 MONTHS	EVERY 12 MONTHS	TREATMENT FAILURE
CD4 cell count	√	√	√	For the first 2 years of ART, or if viremia develops while patient is on ART	After 2 years on ART with consistently suppressed HIV-1 RNA viral load and CD4 cell count between 300 and 500 cells/µL	After 2 years of CD4 cell count >500 cells/µL and with consistently suppressed HIV-1 RNA viral load while on ART	√
HIV-1 RNA viral load	√	√	Repeat every 4 to 6 weeks until HIV-1 RNA viral load <40 copies/mL	During first 2 years of ART with HIV-1 RNA viral load suppression	Once HIV-1 RNA viral load is suppressed for >2 years		√
Genotypic Resistance test[a]	√	√[b]					√
HLA-B*5701	√	If considering abacavir and test was not already done at baseline					

[a] Baseline resistance test should be requested in the very first HIV-1 RNA viral load after diagnosis and should include test for standard HIV protease and reverse transcriptase resistance. A resistance test should be repeated before starting ART if it was delayed from the time of diagnosis and again when there is confirmed treatment failure with HIV-1 RNA >250 copies/mL. In British Columbia, resistance tests can be requested in archived plasma samples from HIV-1 RNA viral load testing if sufficient volume is still available.

[b] Recommended for all samples with HIV-1 RNA viral load >250 copies/mL when receiving therapy. Testing for INSTI resistance is recommended for patients with prior INSTI exposure.

LABORATORY TEST	FREQUENCY OF TESTING						
	ENTRY INTO CARE	ART INITIATION OR MODIFICATION	4-6 WEEKS POST ART INITIATION OR CHANGE	EVERY 3 MONTHS	EVERY 6 MONTHS	EVERY 12 MONTHS	TREATMENT FAILURE
Tropism Test		If considering a CCR5 antagonist. Request RNA plasma test when plasma viral load is >500 copies/ml, and proviral DNA test when plasma viral load <500 copies/mL					If considering a CCR5 antagonist or for failure of CCR5 antagonist-based regimen
HBV Serology (HBsAg, HBsAb, HBc Ab total)[c]	√	May repeat if patient is nonimmune and does not have chronic HBV infection				May repeat if patient is nonimmune and does not have chronic HBV infection	
HCV Ab and RNA if indicated[d]	√				Repeat HCV screening for at-risk patients		
Renal Monitoring[e]	√	√	√	√	In tandem with HIV-1 RNA viral load when done every 6 months		

[c] If patient has an HBV infection (as determined by a positive HBsAg), TDF or TAF plus either FTC or 3TC should be used as part of the ARV regimen to treat both HBV and HIV infections. If HBsAg, HBsAb, and HBcAb are negative, hepatitis B vaccine series should be administered. Refer to *BC-CfE Primary Care Guidelines for the Management of HIV/AIDS in British Columbia* and *BC-CfE Therapeutic Guidelines for Opportunistic Infections* for more detailed recommendations. Most patients with isolated HBcAb have resolved HBV infection with loss of HBsAb. Consider performing an HBV viral load for confirmation. If the HBV viral load is positive, the patient may be acutely infected (and will usually display other signs of acute hepatitis) or chronically infected. If negative, the patient should be vaccinated.

[d] HCV antibody may not be adequate for screening in the setting of recent HCV infection (acquisition within past 6 months) or advanced immune deficiency (CD4 cell count <100 cells/μL). HCV RNA screening is indicated in persons who have been successfully treated for HCV or who spontaneously cleared prior infection. HCV antibody-negative patients with elevated ALT may need HCV RNA testing.

[e] Renal monitoring includes creatinine and creatinine-based eGFR. Serum phosphorus should be monitored in patients with chronic kidney disease and those who are on TAF- or TDF-containing regimens. More frequent monitoring may be indicated for patients with evidence of kidney disease (e.g. proteinuria, decreased eGFR) or increased risk of renal deficiency (e.g. patients with diabetes, hypertension).

LABORATORY TEST	FREQUENCY OF TESTING						
	ENTRY INTO CARE	ART INITIATION OR MODIFICATION	4-6 WEEKS POST ART INITIATION OR CHANGE	EVERY 3 MONTHS	EVERY 6 MONTHS	EVERY 12 MONTHS	TREATMENT FAILURE
AST, ALT, total bilirubin	√	√	√	√	In tandem with HIV-1 RNA viral load when done every 6 months		
CBC and differential	√	√	√	√	In tandem with HIV-1 RNA viral load when done every 6 months		
Fasting lipid profile[f]	√	√			If abnormal at last measurement	If normal at last measurement	
Fasting Glucose (FG) and Hemoglobin A1C (HgbA1C)	√	√			If abnormal at last measurement	If normal at last measurement	
Urinalysis[g] and UACR or UPCR[h]	√	√			In tandem with HIV-1 RNA viral load when done every 6 months		
Pregnancy test in individuals of child-bearing potential		√					

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[f] Consult the Canadian Cardiovascular Society's Guidelines for **recommendations in managing dyslipidemia.**

[g] Urine glucose and protein should be assessed before initiating TAF- or TDF-containing regimens and monitored during treatment with these regimens.

[h] UACR: Urine albumin to creatinine ratio, UPCR: Urine protein to creatinine ratio.

TABLE 7: **Recommendations on the Indications and Frequency of Viral Load and CD4 Cell Count Monitoring**

CLINICAL SCENARIO	VIRAL LOAD MONITORING	CD4 CELL COUNT MONITORING
Before initiating ART	At entry into care If ART initiation is deferred, repeat before initiating ART In patients not initiating ART, repeat testing is optional	At entry into care If ART is deferred, every 3 to 6 months
After initiating ART	Preferably within 2 to 4 weeks (and no later than 8 weeks) after initiation of ART Thereafter, every 4 to 6 weeks until viral load is suppressed	In tandem with HIV-1 RNA viral load
After modifying ART because of drug toxicities or for regimen simplification in a patient with viral suppression	4 to 6 weeks after modification of ART to confirm effectiveness of new regimen	Monitor according to prior CD4 cell count and duration on ART
After modifying ART because of virologic failure	Preferably within 2 to 4 weeks (and no later than 8 weeks) after modification Thereafter, every 4 to 6 weeks until viral load is suppressed. If viral suppression is not possible, repeat viral load every 3 months or more frequently if indicated	Every 3 to 6 months
During the first 2 years of ART	Every 3 to 4 months	Every 3 to 4 months
After 2 years of ART (HIV-1 RNA VL consistently suppressed, CD4 cell count consistently between 300 and 500 cells/μL)	Can extend to every 6 months for patients with consistent viral suppression for ≥2 years	Every 6 months
After 2 years of ART (VL consistently suppressed, CD4 cell count consistently >500 cells/μL)	Can extend to every 6 months for patients with consistent viral suppression for ≥2 years	Every 12 months
While on ART with detectable viremia (VL repeatedly >200 copies/mL)	Every 3 months or more frequently if clinically indicated	Every 3 to 6 months
Change in clinical status (e.g. new HIV clinical symptom or initiation of interferon, chronic systemic corticosteroids, or antineoplastic therapy)	Every 3 months	Perform CD4 cell count and repeat every 3 months

VL, viral load

C. REFERENCES

1. Spicer CM, Ford MA, editors. Monitoring HIV care in the United States: indicators and data systems. National Academies Press; 2012 Aug 13.

2. Locutura J, Blanco JR, Riera M, Suárez-Lozano I, Saura RM, Vallejo P. GESIDA quality care indicators for the care of persons infected by HIV/AIDS. Enfermedades infecciosas y microbiologia clinica. 2010 Nov; 28:6-88.

3. Wandeler G, Keiser O, Hirschel B, Günthard HF, Bernasconi E, Battegay M, Clerc O, Vernazza PL, Furrer H, Swiss HIV Cohort Study. A comparison of initial antiretroviral therapy in the Swiss HIV Cohort Study and the recommendations of the International AIDS Society-USA. PLoS One. 2011 Dec 20; 6(12): e27903.

4. Sangsari S, Milloy MJ, Ibrahim A, Kerr T, Zhang R, Montaner J, Wood E. Physician experience and rates of plasma HIV-1 RNA suppression among illicit drug users: an observational study. BMC infectious diseases. 2012 Dec; 12(1):22.

5. Little SJ, Holte S, Routy JP, Daar ES, Markowitz M, Collier AC, Koup RA, Mellors JW, Connick E, Conway B, Kilby M. Antiretroviral-drug resistance among patients recently infected with HIV. New England Journal of Medicine. 2002 Aug 8; 347(6):385-94.

6. G. Rocheleau 1, 2, C.J. Brumme 2, J. Shoveller 2, 3, V.D. Lima 2, 3, P.R. Harrigan. Longitudinal trends of HIV drug resistance in a large Canadian cohort, 1996-2016 Clinical Microbiology and Infection. 2018 Feb; 24(2):185-191.

7. Borroto-Esoda K, Waters JM, Bae AS, Harris JL, Hinkle JE, Quinn JB, Rousseau FS. Baseline genotype as a predictor of virological failure to emtricitabine or stavudine in combination with didanosine and efavirenz. AIDS research and human retroviruses. 2007 Aug 1; 23(8):988-95.

8. Kuritzkes DR, Lalama CM, Ribaudo HJ, Marcial M, Meyer III WA, Shikuma C, Johnson VA, Fiscus SA, D'Aquila RT, Schackman BR, Acosta EP. Preexisting resistance to non-nucleoside reverse-transcriptase inhibitors predicts virologic failure of an efavirenz-based regimen in treatment-naive HIV-1–infected subjects. The Journal of infectious diseases. 2008 Mar 15; 197(6):867-70.

9. Koullias Y, Sax PE, Fields NF, Walensky RP, Hyle EP. Should We Be Testing for Baseline Integrase Resistance in Patients Newly Diagnosed With Human Immunodeficiency Virus? Clinical Infectious Diseases. 2017 Jun 9; 65(8):1274-81.

10. Kamelian K, Lepik K, Chau W, et al. Prevalence of Human Immunodeficiency Virus-1 Integrase Strand Transfer Inhibitor Resistance in British Columbia, Canada Between 2009 and 2016: A Longitudinal Analysis. Open Forum Infectious Diseases, 2019; 1:8.

11. CASCADE Virology Collaboration. The impact of transmitted drug resistance on the natural history of HIV infection and response to first-line therapy. Aids. 2006 Jan 2;20(1):21-8.

12. Sax PE, Islam R, Walensky RP, Losina E, Weinstein MC, Goldie SJ, Sadownik SN, Freedberg KA. Should resistance testing be performed for treatment-naive HIV-infected patients? A cost-effectiveness analysis. Clinical infectious diseases. 2005 Nov 1; 41(9):1316-23.

13. Saag M, Benson C, Gandhi, Hoy J, Landovitz R, Mugavero M, Sax P, Smith D, Thompson M, Buchbinder S, del Rio C, Eron J, G Ftkenheuer, Günthard H, Molina, JM, Jacobse D, Volberding P, Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2018 recommendations of the International Antiviral Society–USA panel. JAMA. 2018; 320(4):379-396.

14. Young B, Hart B, Buchacz K, Scott M, Palella F, and Brooks J, for the HIV Outpatient Study (HOPS). HIV Viral Load Monitoring Frequency and Risk of Treatment Failure among Immunologically Stable HIV-Infected Patients Prescribed Combination Antiretroviral Therapy. Journal of the International Association of Providers of AIDS Care 2015, Vol. 14(6) 536–543

15. Ford N, Meintjes G, Pozniak A, Bygrave H, Hill A, Peter T, Davies MA, Grinsztejn B, Calmy A, Kumarasamy N, Phanuphak P. The future role of CD4 cell count for monitoring antiretroviral therapy. The Lancet Infectious Diseases. 2015 Feb 1; 15(2):241-7.

16. Scherrer AU, Yang WL, Kouyos RD, Böni J, Yerly S, Klimkait T, Aubert V, Cavassini M, Battegay M, Hauser C, Calmy A. Successful prevention of transmission of integrase resistance in the Swiss HIV Cohort Study. The Journal of infectious diseases. 2016 Apr 29; 214(3):399-402.

17. Mellors JW, Munoz A, Giorgi JV, Margolick JB, Tassoni CJ, Gupta P, Kingsley LA, Todd JA, Saah AJ, Detels R, Phair JP. Plasma viral load and CD4+ lymphocytes as prognostic markers of HIV-1 infection. Annals of internal medicine. 1997 Jun 15; 126(12):946-54.

18. Egger M, May M, Chêne G, Phillips AN, Ledergerber B, Dabis F, Costagliola D, Monforte AD, De Wolf F, Reiss P, Lundgren JD. Prognosis of HIV-1-infected patients starting highly active antiretroviral therapy: a collaborative analysis of prospective studies. The Lancet. 2002 Jul 13; 360(9327):119-29.

19. Benson CA, Brooks JT, Holmes KK, Kaplan JE, Masur H, Pau A. Guidelines for prevention and treatment opportunistic infections in HIV-infected adults and adolescents; recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association/Infectious Diseases Society of America.

20. Moore RD, Keruly JC. CD4+ cell count 6 years after commencement of highly active antiretroviral therapy in persons with sustained virologic suppression. Clinical infectious diseases. 2007 Feb 1; 44(3):441-6.

21. Zurlo JJ, Wood L, Gaglione MM, Polis MA. Effect of splenectomy on T lymphocyte subsets in patients infected with the human immunodeficiency virus. *Clin Infect Dis.* Apr 1995; 20(4):768-771.

22. Bernard NF, Chernoff DN, Tsoukas CM. Effect of splenectomy on T-cell subsets and plasma HIV viral titers in HIV-infected patients. *J Hum Virol.* Jul-Aug 1998; 1(5):338-345.

23. Casseb J, Posada-Vergara MP, Montanheiro P, et al. T CD4+ cells count among patients co-infected with human immunodeficiency virus type 1 (HIV-1) and human T-cell leukemia virus type 1 (HTLV-1): high prevalence of tropical spastic paraparesis/HTLV-1-associated myelopathy (TSP/HAM). *Rev Inst Med Trop Sao Paulo.* Jul-Aug 2007; 49(4):231-233.

24. Berglund O, Engman K, Ehrnst A, et al. Combined treatment of symptomatic human immunodeficiency virus type 1 infection with native interferon-alpha and zidovudine. *J Infect Dis.* Apr 1991; 163(4):710-715.

25. Palella Jr FJ, Armon C, Chmiel JS, Brooks JT, Hart R, Lichtenstein K, Novak RM, Yangco B, Wood K, Durham M, Buchacz K. CD4 cell count at initiation of ART, long-term likelihood of achieving CD4> 750 cells/µL and mortality risk. Journal of Antimicrobial Chemotherapy. 2016 Jun 20; 71(9):2654-62.

26. Althoff KN, Justice AC, Gange SJ, Deeks SG, Saag MS, Silverberg MJ, Gill MJ, Lau B, Napravnik S, Tedaldi E, Klein MB. Virologic and immunologic response to HAART, by age and regimen class. AIDS (London, England). 2010 Oct 23; 24(16):2469.

27. Hunt PW, Deeks SG, Rodriguez B, Valdez H, Shade SB, Abrams DI, Kitahata MM, Krone M, Neilands TB, Brand RJ, Lederman MM. Continued CD4 cell count increases in HIV-infected adults experiencing 4 years of viral suppression on antiretroviral therapy. Aids. 2003 Sep 5; 17(13):1907-15.

28. Wong NS, Chan KCW, Cheung EKH, Wong KH, Lee SS. Immune recovery of middle-aged HIV patients following antiretroviral therapy: An observational cohort study. *Medicine (Baltimore).* 2017; 96(28):e7493.

29. Hetherington S, McGuirk S, Powell G, et al. Hypersensitivity reactions during therapy with the nucleoside reverse transcriptase inhibitor abacavir. Clinical Therapeutics. 2001; 23(10):1603-1614.

30. Mallal S, Phillips E, Carosi G, et al. HLA-B*5701 screening for hypersensitivity to abacavir. New England Journal of Medicine. 2008;358(6):568-579.

31. Fatkenheuer G, Pozniak AL, Johnson MA, et al. Efficacy of short-term monotherapy with maraviroc, a new CCR5 antagonist, in patients infected with HIV-1. Nature Medicine. 2005;11(11):1170-1172.

32. Zhu T, Mo H, Wang N, et al. Genotypic and phenotypic characterization of HIV-1 patients with primary infection. Science. 1993;261(5125):1179-1181.

33. Brumme ZL, Goodrich J, Mayer HB, et al. Molecular and clinical epidemiology of CXCR4-using HIV-1 in a large population of antiretroviral-naive individuals. Journal of Infectious Diseases. 2005;192(3):466-474.

34. Vitiello P, Brudney D, MacCartney M, et al. Responses to switching to maraviroc-based antiretroviral therapy in treated patients with suppressed plasma HIV-1-RNA load. Intervirology. 2012;55(2):172-178.

35. Bonjoch A, Pou C, Perez-Alvarez N, et al. Switching the third drug of antiretroviral therapy to maraviroc in aviraemic subjects: a pilot, prospective, randomized clinical trial. Journal of Antimicrobial Chemotherapy. 2013;68(6):1382-1387.

36. Pett SL, Amin J, Horban A, et al. Maraviroc, as a switch option, in HIV-1-infected individuals with stable, well controlled HIV replication and R5-tropic virus on their first nucleoside/nucleotide reverse transcriptase inhibitor plus ritonavir-boosted protease inhibitor regimen: Week 48 results of the randomized, multicenter MARCH Study. Clinical Infectious Diseases. 2016;63(1):122-132.

37. Havlir DV, Bassett R, Levitan D, et al. Prevalence and predictive value of intermittent viremia with combination hiv therapy. *JAMA*. Jul 11 2001;286(2):171-179. Available at **https://www.ncbi.nlm.nih.gov/pubmed/11448280**

38. McClymont E, Lee M, Elwood C, et al. Cervical Cancer Screening in Immunocompromised Women. J Obstet Gynaecol Can. 2019 Aug;41(8):1177-1180.

39. Wilkin TJ, Su Z, Kuritzkes DR, et al. HIV type 1 chemokine co-receptor use among antiretroviral-experienced patients screened for a clinical trial of a CCR5 inhibitor: AIDS Clinical Trial Group A5211. *Clin Infect Dis*. 2007;44(4):591-595.

40. Doyle T, Dunn DT, Ceccherini-Silberstein F, De Mendoza C, Garcia F, Smit E, Fearnhill E, Marcelin AG, Martinez-Picado J, Kaiser R, Geretti AM. Integrase inhibitor (INI) genotypic resistance in treatment-naive and raltegravir-experienced patients infected with diverse HIV-1 clades. Journal of Antimicrobial Chemotherapy. 2015 Aug 26; 70(11):3080-6.

41. Hurt CB, Sebastian J, Hicks CB, Eron JJ. Resistance to HIV integrase strand transfer inhibitors among clinical specimens in the United States, 2009–2012. Clinical infectious diseases. 2013 Oct 21;58(3):423-31.Wong NS, Chan KCW, Cheung EKH, Wong KH, Lee SS. Immune recovery of middle-aged HIV patients following antiretroviral therapy: An observational cohort study. *Medicine (Baltimore)*. 2017; 96(28):e7493.

42. Günthard HF, Calvez V, Paredes R, Pillay D, Shafer RW, Wensing AM, Jacobsen DM, Richman DD. Human Immunodeficiency Virus Drug Resistance: 2018 Recommendations of the International Antiviral Society–USA Panel. Clinical Infectious Diseases. 2018 Jul 20.

43. Schoenenberger JA, Aragones AM, Cano SM, Puig T, Castello A, Gomez-Arbones X, Porcel JM. The advantages of therapeutic drug monitoring in patients receiving antiretroviral treatment and experiencing medication-related problems. Therapeutic drug monitoring. 2013 Feb 1; 35(1):71-7.

44. Colbers A, Greupink R, Burger D. Pharmacological considerations on the use of antiretrovirals in pregnancy. Current opinion in infectious diseases. 2013 Dec 1; 26(6):575-88.

45. Rakhmanina N, Phelps BR. Pharmacotherapy of pediatric HIV infection. Pediatric Clinics. 2012 Oct 1; 59(5):1093-115.

IV CHANGING THE ARV REGIMEN

A. RECOMMENDATIONS

i.   In the setting of viral suppression:

1.   Treatment switches in patients with sustained viral suppression should address medication-related adverse events, improve safety or tolerability of ART, or simplify a regimen (B-III).

2.   Before considering a new ARV treatment, we strongly recommend reviewing the patient's full ART history, including virologic responses, past ARV-associated toxicities, potential drug-drug interactions, and cumulative resistance test results (if available) (A-I).

3.   When considering switching ARVs within-class and between-class, we strongly recommend ensuring that there is no viral resistance to the ARV agents in the new regimen (A-I).

4.   Clinicians should consult with an HIV specialist when planning a regimen change for a patient with a history of resistance to one or more drug classes (B-III).

5.   Patients receiving tenofovir disoproxil fumarate (TDF), who are at high risk for renal and bone toxicity and who cannot be switched to abacavir (ABC), should be switched to tenofovir alafenamide (TAF) (B-I). When using with boosters (i.e. ritonavir or cobicistat), TAF dosing should be adjusted to 10 mg (vs. 25 mg with un-boosted regimen).

6.   In non-pregnant patients with no prior virologic failure, no documented HIV-1 RNA resistance, no HBV coinfection, and viral suppression for at least 6 months, clinicians may consider switching from a three-drug regimen to one of the following recommended two-drug regimens: dolutegravir-lamivudine (A-I) or dolutegravir-rilpivirine (A-I). Alternatively, for patients with viral suppression for at least 12 months, a switch to a boosted PI/lamivudine may be considered (A-II).

7.   In patients with HBV co-infection, we recommend a regimen that contains two active drugs for treatment of HBV; this includes TAF or TDF with lamivudine or emtricitabine in addition to a third active anti-HIV drug (A-II).

8.   We do not recommend monotherapy (A-II).

9.   We recommend performing a pregnancy test in patients of childbearing potential prior to switching ART and ascertaining the patient's pregnancy desires and contraception plans(A-III).

ii. Antiretroviral switches in the setting of virologic failure[a]

1.   In patients who demonstrate virologic failure and HIV-1 RNA >250 copies/mL, we strongly recommend performing HIV-1 RNA genotypic resistance testing while the patient is taking the failing ARV regimen (A-I) or within 4 weeks of treatment discontinuation if ART was stopped to guide future treatment selection (A-II).

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[a] Virologic failure is defined as HIV-1 RNA level above 200 copies/mL on at least 2 consecutive measurements.

2. As part of evaluating virologic failure, we recommend assessing adherence and medication tolerability, drug-drug and drug-food interactions, ART history, and prior and current HIV genotypic resistance test results (A-III).

3. We strongly recommend a new regimen of at least two, and preferably three, fully active drugs, based on HIV-1 RNA genotypic resistance testing results (both past and present), treatment history, tolerability, adherence issues, and drug-drug and drug-food interactions (A-I) (see Table 10). In general, adding a single ARV agent to a virologically failing regimen is not recommended (A-1), as this change may not be sufficient to prevent the development of resistance to all drugs in the regimen.

4. Clinicians should seek expert advice for the management of multi-drug resistance; for multi-class resistance, the next regimen should be constructed using drugs from new classes if available (B-III).

5. Coadministration of Biktarvy® with darunavir/cobicistat, darunavir/ritonavir, doravirine, or rilpivirine is off-label. However, it may be considered an option in selected patients who require treatment with a multi-class antiretroviral regimen, and for whom more well-established regimens are not appropriate.

B. DISCUSSION OF EVIDENCE

i. Viral Suppression

Switching from older ARV regimens is not always necessary, but it should be considered when there is evidence of, or potential for, chronic toxicity. **Treatment switches in patients with sustained viral suppression should address medication-related adverse events, improve safety or tolerability of ART, or simplify a regimen (B-III)**. These reasons include:

- Decreasing short- or long-term toxicity (see **Chapter V: Adverse Drug Reactions**)
- Preventing or mitigating drug-drug interactions
- Eliminating food requirements
- Reducing pill burden and/or dosing frequency
- Allowing for optimal use of ART during pregnancy or in cases where pregnancy may occur
- Mitigating the effect of ARVs in some co-morbidities

A three-drug combination regimen is generally recommended when switching patients with suppressed viral loads to a new regimen. Patients with no resistance mutations can switch to any regimen that has been shown to be highly effective in ART-naive patients.

Before considering a new ARV treatment, we strongly recommend reviewing the patient's full ART history, including virologic responses, past ARV-associated toxicities, potential drug-drug interactions, and cumulative resistance test results (if available) (A-I).[b]

a. Assessment of HIV-1 RNA resistance

Previous and current genotypic resistance test results need to be reviewed before switching to a new regimen.

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[b] Adapted from the recommendations by the Panel on ARV Guidelines for Adults and Adolescents [1].

When considering switching ARVs within-class and between-class, we strongly recommend ensuring that there is no viral resistance to the ARV agents in the new regimen (A-I) (see Chapter III: Assessment and Monitoring for more about genotypic resistance testing).

When resistance data is not available, resistance may be inferred from a patient's treatment history [2]. For example, in patients with documented virologic failure on a regimen that contains elvitegravir, raltegravir, or a non-nucleoside reverse transcriptase inhibitor (NNRTI), resistance to these drugs should be assumed since generally they have a lower barrier to resistance than other ARV drugs. If there is uncertainty about prior resistance, it is generally not advisable to switch a successfully suppressive ARV regimen unless the new regimen is likely to be at least as active against potential resistant virus as the suppressive regimen. This is particularly important when switching ARV-experienced individuals from a regimen with a high barrier to resistance to one with a lower barrier to resistance [3]. Due to complexities of prescribing in the context of resistance mutation, **clinicians should consult with an HIV specialist when planning a regimen change for a patient with a history of resistance to one or more drug classes (B-III).**

3. Assessment of potential drug-drug interactions

Before changing a regimen, it is important to review the ARV drugs in the new regimen and concomitant medications to assess whether there are any potential drug-drug interactions. In addition to new drug interactions, the discontinuation of some ARV drugs may also necessitate adjusting the dosage of concomitant medications. Concomitant medications which may have previously been managed with dose adjustments will need to be re-evaluated in the context of the new ART regimen (refer to **HIV drug interactions guidelines**).

4. Switching from TDF

Patients receiving tenofovir disoproxil fumarate (TDF), who are at high risk for renal and bone toxicity and who cannot be switched to abacavir (ABC), should be switched to tenofovir alafenamide (TAF) (B-I). Post and colleagues randomized 663 patients to either switch to emtricitabine/TAF or continue on a regimen of emtricitabine/TDF; at 48 weeks the authors found the emtricitabine/TAF arm to be superior in renal function and bone mineral density (p<0.05), with minimal difference between patients receiving boosted vs. unboosted third agent [4].

In patients without a history of treatment failure, existing data support switching from regimens containing TDF to single-tablet regimens (STR), including switches to:

- bictegravir/emtricitabine/TAF [5]
- dolutegravir/abacavir/lamivudine [6,7]
- elvitegravir/cobicistat/emtricitabine/TAF [8]
- rilpivirine/emtricitabine/TAF [9]
- darunavir/cobicistat/emtricitabine/TAF [10]

A randomized controlled trial compared 290 patients on bictegravir/emtricitabine/TAF single-tablet regimen with 281 patients on boosted protease inhibitor (PI) regimens (atazanavir or darunavir/abacavir/lamivudine) and found the single-tablet regimen to be non-inferior to the boosted PI regimens with HIV-1 RNA levels <50 copies/mL maintained by 92.1% of study patients (compared to 88.9% in the boosted PI study arm) at week-48

[11]. Similarly, Sax and colleagues randomized 65 patients to switch to bictegravir/emtricitabine/TAF and 33 patients to remain on a regimen of dolutegravir/emtricitabine/TAF and found over 90% viral suppression level (i.e. HIV-1 RNA levels <50 copies/mL) in both groups at week 72 [12].

When using with boosting agents (i.e. ritonavir or cobicistat), TAF dosing should be adjusted to 10 mg (vs. 25 mg with un-boosted regimen), as drugs that strongly affect P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) activity may lead to changes in TAF absorption [4].

5. Two active drugs

Switching to regimens containing two ARV drugs can be considered, particularly to reduce NRTI-related bone, kidney, and cardiovascular complications.

In non-pregnant patients with no prior virologic failure, no documented HIV-1 RNA resistance, no HBV coinfection, and viral suppression for at least 6 months, clinicians may consider switching from a three-drug regimen to one of the following recommended two-drug regimens: dolutegravir-lamivudine (A-I) or dolutegravir-rilpivirine (A-I). Alternatively, in patients with viral suppression for at least 12 months, a switch to a boosted PI/lamivudine may be considered (A-II).

Data from a large randomized controlled trial showed that switching to dolutegravir (DTG) plus lamivudine(3TC) was non-inferior to continuing on the current three-drug regimen, with 93% of participants in both arms maintaining HIV RNA 50 copies/mL [13]. A retrospective observational study in addition to two smaller studies have also showed that virologically-suppressed individuals switching from a standard three-drug ART regimen to DTG plus 3TC remained virologically suppressed [14, 15, 16]. Of note, in all these studies individuals infected with Hepatitis B (HBV) were excluded. Furthermore, in most of these studies the participants were males (>80%), had high CD4 cell counts, were virologically suppressed for over 6 months at the time of the switch, and had no previously documented genotypic resistance to DTG or 3TC.

Two randomized controlled trials found that among patients who were virologically suppressed (no viral load >50 copies/ml in the past 6 months) and had no previous drug resistance switching to dolutegravir (DTG)-rilpivirine (RPV) maintained viral suppression in >95% of participants at 48 weeks [17]. DTG-RPV should not be given to patients who are pregnant, have chronic HBV infection, have evidence of resistance to either DTG or RPV, or are taking any medication that may have a significant drug-drug interaction that might reduce the concentration of either drug (e.g. proton pump inhibitors).

There is evidence that a boosted protease inhibitor (PI) (lopinavir, atazanavir, or darunavir) with 3TC was non-inferior to three drug regimens in maintaining virologic suppression [18,21] in patients who initiated triple-drug therapy and achieved sustained viral suppression for ≥ 12 months, and without evidence of or risk for resistance to either the boosted PI or 3TC. However, this strategy should be avoided in patients who are pregnant or co-infected with HBV.

6. Patients co-infected with HBV

In patients with HBV co-infection, we recommend a regimen that contains two active drugs for treatment of HBV; this includes TAF or TDF with lamivudine or emtricitabine in addition to a third active anti-HIV

drug (A-II). When switching an ARV regimen in a patient with HBV/HIV co-infection, TDF or TAF should be continued as part of the new regimen, unless these drugs are contraindicated [22]. An open-label non-comparative switch cohort study examining the efficacy and safety of emtricitabine/cobicistat/emtricitabine/TAF in HIV-HBV co-infected adults found that 91.7% of the 72 participants achieved or maintained viral suppression at 48 weeks (HIV-1 RNA <50 copies/mL; HBV DNA <29 IU/mL), with improved renal function and reduced bone turnover [23].

Since both TDF and TAF are active against HBV, discontinuing these drugs may lead to reactivation of HBV. Using lamivudine or emtricitabine as the only active drug for HBV co-infection is not recommended, as HBV resistance to these drugs can emerge rapidly. If TDF or TAF cannot be used as part of the ARV regimen, consult with an HBV specialist for alternative treatments.

7. Patients with previous treatment failures

Fewer options exist for regimen simplification in virologically suppressed individuals in whom several previous regimens have failed over time. Elvitegravir/cobicistat/emtricitabine/TDF or TAF combined with darunavir taken once daily effectively maintained virologic suppression in patients with two-class drug resistance (up to three thymidine analogue-associated mutations but no multi-nucleoside reverse transcriptase inhibitor [NRTI], integrase strand transfer inhibitor [INSTI], or darunavir mutations) while taking multi-drug regimens [24,25]. Consultation with an HIV specialist is recommended in these cases.

8. Monotherapy

Monotherapy with either a boosted PI or an INSTI has been explored in several randomized trials:

- DOMONO trial: In this open-label, phase 2, randomised non-inferiority trial, 104 patients were randomized to either switch to a dolutegravir monotherapy immediately or after 24 weeks of continued combination ART (all patients had HIV-1 RNA <50 copies/mL for at least 6 months, had CD4 cell count nadirs of 200 cells/μL or higher, HIV-1 RNA zeniths of 100,000 copies/mL or less, and no history of virologic failure). Eight (8%) of the 95 patients who remained on dolutegravir monotherapy had virologic failure. In three (38%) of these eight patients, mutations associated with resistance were detected in the integrase gene [26].

- MODat trial: This prospective, multi-centre, open-label, non-inferiority, randomized trial compared efficacy of atazanavir/ritonavir monotherapy versus atazanavir/ritonavir triple therapy. At 96 weeks, 64% in the atazanavir/ritonavir monotherapy arm had two consecutive HIV-1 RNA >50 copies/mL and 63% in the triple-therapy arm (difference 1.3%, 95% CI, −17.5 to 20.1). In the monotherapy arm, treatment failure was more frequent in patients co-infected with hepatitis C virus [64% vs. 28% (difference 35.4%, 95% CI, 3.7 to 67.2)] [27].

- PROTEA trial: In this randomized controlled trial, patients fully suppressed on first-line ARV (viral load <50 HIV-1 RNA copies/mL) were switched to darunavir/ritonavir 800 mg/100 mg once daily, either as monotherapy or with two NRTIs. There were 10.1% fewer patients who achieved HIV-1 RNA <50 copies/mL in the monotherapy arm (95% CI, 19.5% to 0.7%) [28].

In a case review, two patients (Montreal and Barcelona) developed viral failure (HIV-1 RNA <1000 copies/mL) within 2 weeks of switching to dolutegravir monotherapy; genetic analysis in one of the patients

showed the development of cross-resistance to all integrase inhibitors [29]. Due to its association with a high rate of virologic failure and development of resistance, **we do not recommend monotherapy (A-II).**

9.   Patients of childbearing potential

We recommend performing a pregnancy test in patients of childbearing potential prior to switching ART(A-III). If a person with HIV is found to be pregnant, this individual should be referred to a specialty clinic (Women and Family HIV Centre [Oak Tree Clinic] at the BC Women's Hospital and Health Centre) for recommendations on the safety and efficacy of ARV use in pregnancy.

TABLE 8: **Strategies for Regimen Switches in Virologically Suppressed Patients (expert advice is recommended)**

WITHIN-CLASS SWITCHES

FROM	TO	REFERENCE
TDF	Abacavir or TAF	30,31
Abacavir	TAF	32
Dolutegravir, Elvitegravir/cobicistat, or Raltegravir	Bictegravir	33
Raltegravir twice daily	Raltegravir HD or Elvitegravir/cobicistat or Dolutegravir	34
Efavirenz	Rilpivirine	35,36
Darunavir/ritonavir	Darunavir/cobicistat	37
Atazanavir/ritonavir	Unboosted atazanavir[c]	38-40

BETWEEN-CLASS SWITCHES

FROM	TO	REFERENCE
Ritonavir-boosted PI	INSTI	41-44
Ritonavir-boosted PI	Rilpivirine	45
NNRTI	INSTI	46-47

SWITCHING TO TWO DRUG REGIMEN

FROM	TO	REFERENCE
Current antiretroviral regimen[d]	Dolutegravir/lamivudine	13-16
Current antiretroviral regimen[d]	Dolutegravir/rilpivirine	17,48
Atazanavir/ritonavir plus 2 NRTIs	Atazanavir/ritonavir plus lamivudine	18-19,49
Darunavir/ritonavir plus 2 NRTIs	Darunavir/ritonavir plus lamivudine	20
Lopinavir/ritonavir plus 2 NRTIs	Lopinavir/ritonavir plus lamivudine	50

INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor

10. Monitoring after switching ART

After changing ARV therapy, patients should be evaluated closely. Clinic visit should be scheduled, along with HIV-1 RNA viral load test, for 4 to 6 weeks after the switch to assess medication tolerance and response. Targeted laboratory testing should be repeated if the patient has pre-existing laboratory abnormalities or if there are potential concerns with the new regimen. In the absence of any new complaints, laboratory abnormalities, or evidence of viral rebound at 3 months, clinical and laboratory monitoring of the patient may resume on a regularly scheduled basis. (See **Chapter III: Assessment and Monitoring**).

ii.   Virologic failure

The goal of ART is to suppress HIV-1 RNA replication to undetectable levels where drug-resistance mutations

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[c] When used with abacavir/lamivudine backbone.

[d] Included patients receiving the following combinations: 2 NRTIs + 1 INSTI, 2NRTIs + 1 NNRTI, or 2 NRTIs + 1 PI.

will not emerge [51]. With currently recommended ART regimens, virologic failure is increasingly uncommon.

Virologic blips, defined as an isolated detectable HIV-1 RNA level (<1000 copies/mL) [52] that is followed by a return to virologic suppression, are not usually associated with subsequent virologic failure [53]. In contrast, there is controversy regarding the clinical implications of persistently low HIV-1 RNA levels that are between the lower limit of detection (40 copies/mL) and 200 copies/mL in patients on ART [54-56]. Recent retrospective studies support the concept that virologic rebound is more likely to occur in patients with viral loads >200 copies/mL than in those with low-level viremia between 50 and 199 copies/mL [57, 58]. Persistent HIV-1 RNA levels ≥200 copies/mL are often associated with evidence of viral evolution and accumulation of drug-resistance mutations [59]. This association is particularly common when HIV-1 RNA levels are >500 copies/mL [60]. Therefore, persistent plasma HIV-1 RNA levels ≥200 copies/mL should be assessed and managed as a virologic failure.

Virologic failure may be associated with various issues related to the individual patient, the HIV virus, and the ARV regimen (see **Table 9** below). Once virologic failure is suspected or confirmed, a thorough assessment is indicated to determine whether one or more of the factors below could have been the cause(s) of virologic failure. It is important to distinguish among the causes of virologic failure, as the approaches to subsequent therapy may differ.

TABLE 9:   Factors Associated with Virologic Failure

FACTOR	CHARACTERISTICS
Individual	Adherence challenges
	→Co-morbidities (e.g. active substance use disorder, mental health disorders, neurocognitive impairment)
	→Unstable housing and other psychosocial factors
	→Poor ARV tolerability or adverse events
	→High pill burden and/or dosing frequency
	Challenges in engagement or access to care
	Interruption of or intermittent access to ART
HIV	Presence of transmitted or acquired drug-resistant virus
	Prior treatment failure
	Inactivity of the CCR5 antagonist class of ARVs due to the presence or selection of HIV variants that use the CXCR4 co-receptor
	Presence of HIV-2 RNA infection/co-infection[e]
	Higher pre-treatment HIV-1 RNA level (some regimens may be less effective at higher levels)
ARV regimen	Suboptimal pharmacokinetics (e.g. variable absorption, metabolism, or possible penetration into reservoirs)
	Suboptimal virologic potency
	Low genetic barrier to resistance
	Reduced efficacy due to prior exposure to suboptimal regimens (e.g. monotherapy, dual NRTI therapy, or the sequential introduction of drugs)
	Food requirements
	Adverse drug-drug interactions with concomitant medications or supplements

[e] HIV-2 RNA infection is endemic in West Africa. Although HIV-2 RNA has had limited spread outside this area, it should be considered when treating persons of West African origin or in those who had high risk contact with persons of West African origin. HIV-2 RNA is intrinsically resistant to NNRTIs and to enfuvirtide; thus, these drugs should not be included in an ARV regimen for a patient with HIV-2 RNA infection [1].

1. HIV-1 RNA genotypic resistance

In British Columbia, HIV-1 RNA genotypic resistance testing should be requested when viral loads exceed 250 copies/mL while on ARV. **In patients who demonstrate virologic failure, we strongly recommend performing HIV-1 RNA genotypic resistance testing while the patient is taking the failing ARV regimen (A-I) or within 4 weeks of treatment discontinuation if ART was stopped, to guide future treatment selection (A-II).** Even if more than 4 weeks have elapsed since ARVs were discontinued, HIV-1 RNA genotypic resistance testing can still provide useful information to guide therapy. Clinicians should note that the lack of evidence of resistance in this setting does not exclude the possibility that resistance mutations may be present.

Since drug resistance is cumulative, **we recommend assessing adherence and medication tolerability, drug-drug and drug-food interactions, ART history, and prior and current HIV genotypic resistance test results (A-III).** Upon request, the BC-CfE Laboratory may be able to re-evaluate past viral load assays obtained at baseline or during a period of prior virologic failure and provides a virtual phenotype report with the resistance profile from archived specimens. This re-evaluation of past viral load assays is restricted to samples collected in British Columbia; the BC-CfE Laboratory cannot link to prior resistance results for patients who transfer their care to the Drug Treatment Program in British Columbia from another province.

Standard HIV-1 RNA genotype resistance assays assess resistance to NRTIs, NNRTIs, and PIs, whereas INSTI-resistance testing needs to be specifically requested on the BC-CfE virology requisition form. For virologic failure of INSTI-containing ART or for patients with previous history of INSTI exposure, INSTI drug resistance genotype testing is recommended. Since 2015, for patients with a prior history of INSTI exposure genotyping HIV resistance, testing includes the INSTI resistance test. Additional drug-resistance tests are also available upon request for patients who experience failure on a fusion inhibitor, as well as viral tropism tests for patients who experience virologic failure on a CCR5 co-receptor antagonist.

2. Choosing a new ARV regimen

We strongly recommend a new regimen of at least two, and preferably three, fully active drugs, based on HIV-1 RNA genotypic resistance testing results (both past and present), treatment history, tolerability, adherence issues, and drug-drug and drug-food interactions (A-I) (see **Table 10**). Numerous clinical trials assessing efficacy and safety of ARVs have shown favorable effects of multi-drug combinations [61-68].

- For failure of an initial <u>NNRTI-based regimen</u>, dolutegravir plus NRTIs has been shown to be superior to lopinavir plus NRTIs when the next regimen included at least one active NRTI. (DAWNING trial: Adults experiencing virologic failure [HIV-1 RNA ≥400 copies/mL] were randomized to 52 weeks of dolutegravir or lopinavir-ritonavir plus dual NRTI background. At 24 weeks, 78% of dolutegravir arm achieved HIV-1 RNA <50 copies/mL versus 69% of lopinavir-ritonavir arm [adjusted difference 9.6%, 95% CI, 2.7% to 16.4%, p=0.006 for superiority] [69].)

- For failure of initial <u>PI-based or INSTI-based regimen</u> (without resistance), boosted PI- or dolutegravir-based therapy with one or two fully active NRTIs should be an effective alternative.

- For failure of initial raltegravir- or elvitegravir-based regimens with the presence of INSTI mutations, dolutegravir (50 mg twice daily) with an active backbone regimen may be effective, but clinical data is lacking [70].

- For treatment failure with more complex history, therapy with at least two fully active drugs from different ARV classes, perhaps including maraviroc in the setting of CCR5-tropic virus, is recommended [70].

In general, adding a single ARV agent to a virologically failing regimen is not recommended (A-I), as this change may not be sufficient to prevent the development of resistance to all drugs in the regimen.

TABLE 10:   Switching ART in the Setting of a Failing Regimen

TYPE OF FAILING REGIMEN	RESISTANCE CONSIDERATIONS	NEW REGIMEN OPTIONS[f] (IN ORDER OF PREFERENCE)
NNRTI plus two NRTIs	Most likely resistant to NNRTI +/- lamivudine/emtricitabine (3TC/FTC) (i.e. NNRTI mutations +/- M184V/I)[g] Additional NRTI mutations may also be present	→Boosted PI plus two NRTIs (at least one active); or →Dolutegravir plus two NRTIs (at least one active); or →Boosted PI plus INSTI
Boosted PI plus two NRTIs	Most likely no resistance, or resistance only to 3TC/FTC (i.e. M184V/I, without resistance to other NRTIs)	→Continue the same regimen; or →Another boosted PI plus two NRTIs (at least one active); or →INSTI plus two NRTIs (at least one active; if only one of the NRTIs is fully active, or if adherence is a concern, dolutegravir[f] is preferred over the other INSTIs); or →Another boosted PI plus INSTI
INSTI plus two NRTIs (no INSTI resistance)	Can have 3TC/FTC resistance, i.e. only M184V/I, usually without resistance to other NRTIs	→Boosted PI plus two NRTIs (at least one active); or →Dolutegravir[f] plus two NRTIs (at least one active); or →Boosted PI plus INSTI

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[f] There are insufficient data to provide a recommendation for the continuation of 3TC/FTC in the presence of M184V/I. When switching an ARV regimen in a patient with HIV/HBV co-infection, ARV drugs that are active against HBV should be continued as part of the new regimen. Discontinuation of these drugs may lead to the reactivation of HBV, which may result in serious hepatocellular damage.

[g] If other NRTI resistance mutations are present, use resistance test results to guide NRTI usage in the new regimen. Abacavir susceptibility could be compromise when the 184V mutation is present.

TYPE OF FAILING REGIMEN	RESISTANCE CONSIDERATIONS	NEW REGIMEN OPTIONS[f] (IN ORDER OF PREFERENCE)
INSTI plus two NRTIs	Resistance to first-line bictegravir or dolutegravir is rare Elvitegravir or raltegravir +/- 3TC/FTC resistance Resistance to first-line bictegravir or dolutegravir is rare	→ Boosted PIs plus two NRTIs (at least one active); or → Bictegravir has not been studied in this setting and cannot be recommended → Dolutegravir[f,h] twice daily (if patient is sensitive to dolutegravir) plus a boosted PI → Bictegravir has not been studied in this setting and cannot be recommended

NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; INSTI, integrase strand transfer inhibitor

The management of HIV in treatment-experienced patients with virologic failure often requires expert advice to construct virologically suppressive regimens.

Coadministration of Biktarvy® with darunavir/cobicistat, darunavir/ritonavir, doravirine, or rilpivirine is off-label, but may be considered an option in selected patients who require treatment with a multi-class antiretroviral regimen, and for whom more well-established regimens are not appropriate. Close monitoring of viral load, renal function, and potentially bone health is advised due to limited clinical data supporting the safety or efficacy of these regimens.

Coadministration of Biktarvy® with atazanavir (with or without ritonavir), etravirine, efavirenz, or nevirapine is not recommended due to clinically significant drug interactions which could affect the safety or efficacy of the regimen (71).

Use of currently available ARVs has resulted in a dramatic decline in the number of patients who have few treatment options because of multi-class drug resistance [72,73]. Despite this progress, there remain patients who have experienced toxicities and/or developed resistance to all or most currently available drugs. If maximal virologic suppression cannot be achieved, the goals of ART will be to preserve immunologic function, prevent clinical progression, and minimize the development of further resistance that may compromise future regimens [73,74]. **Clinicians should seek expert advice for the management of multi-drug resistance; for multi-class resistance, the next regimen should be constructed using drugs from new classes if available (B-III).**

[h] Response to dolutegravir depends on the type and number of INSTI mutations.

C. REFERENCES

1.   Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV. Department of Health and Human Services. Available at http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. 25-10 2018, H-22.

2.   Günthard H, Calvez, V, Paredes R, et al. Human Immunodeciency Virus Drug Resistance: 2018 Recommendations of the International Antiviral Society–USA Panel. CID Jan 2018; 2019:68.

3.   Eron JJ, Young B, Cooper DA, et al. Switch to a raltegravir-based regimen versus continuation of a lopinavir-ritonavir-based regimen in stable HIV-infected patients with suppressed viraemia (SWITCHMRK 1 and 2): two multicentre, double-blind, randomised controlled trials. Lancet. 2010; 375(9712):396-407.

4.   Post FA, Yazdanpanah Y, Schembri G, et al. Efficacy and safety of emtricitabine/tenofovir alafenamide (FTC/TAF) vs. emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) as a backbone for treatment of HIV-1 infection in virologically suppressed adults: subgroup analysis by third agent of a randomized, double-blind, active-controlled phase 3 trial. HIV Clin Trials. 2017; 18(3):135-140.

5.   Gallant J, Lazzarin A, Mills A, et al. Bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir, abacavir, and lamivudine for initial treatment of HIV-1 infection (GS-US-380-1489): a double-blind, multicentre, phase 3, randomised controlled non-inferiority trial. Lancet. 2017; 390 (10107):2063-2072.

6.   Trottier B, Lake JE, Logue K, et al. Dolutegravir/abacavir/lamivudine versus current ART in virally suppressed patients (STRIIVING): a 48-week, randomized, non-inferiority, open-label, phase IIIb study. Antivir Ther. 2017; 22(4):295-305.

7.   Negredo E, Estrada V, Domingo P, et al. Switching from a ritonavir-boosted PI to dolutegravir as an alternative strategy in virologically suppressed HIV-infected individuals. J Antimicrob Chemother. 2017; 72(3):844-849.

8.   Mills A, Arribas J, Andrade-Villanueva J et al Switching from tenofovir disoproxil fumarate to tenofovir alafenamide in antiretroviral regimens for virologically suppressed adults with HIV-1 infection: a randomised, active-controlled, multicentre, open-label, phase 3, non-inferiority study Lancet Infect Dis 2016; 16: 43-52.

9.   Orkin C, DeJesus E, Ra mgopal M, et al. Switching from tenofovir disoproxil fumarate to tenofovir alafenamide coformulated with rilpivirine and emtricitabine in virally suppressed adults with HIV-1 infection: a randomised, double-blind, multicentre, phase 3b, non-inferiority study. Lancet HIV. 2017; 4(5):e195-e204.

10. Orkin C, Molina JM, Negredo E, et al; EMERALD Study Group. Efficacy and safety of switching from boosted protease inhibitors plus emtricitabine and tenofovir disoproxil fumarate regimens to single-tablet darunavir, cobicistat, emtricitabine, and tenofovir alafenamide at 48 weeks in adults with virologically suppressed HIV-1 (EMERALD): a phase 3, randomised, non-inferiority trial. Lancet HIV. 2018; 5(1):e23-e34.

11. Daar E, DeJesus E, Ruane P et al. Phase 3 Randomized, Controlled Trial of Switching to Fixed-dose Bictegravir/Emtricitabine/Tenofovir Alafenamide (B/F/TAF) from Boosted Protease Inhibitor-based Regimens in Virologically Suppressed Adults: Week 48 Results Open Forum Infectious Diseases, Volume 4, Issue suppl_1, 1 October 2017, Pages S735.

12. Sax P, Dejesus E, Crofoot G, et al. A Randomized Trial of Bictegravir or Dolutegravir with Emtricitabine and Tenofovir Alafenamide (F/TAF) Followed by Open Label Switch to Bictegravir/F/TAF Fixed Dose Combination. Open Forum Infect Dis. 2017 Fall; 4(Suppl 1): S426–S427.

13. van Wyk J, Ajana F, Bisshop F, De Wit S, Osiyemi O, Portilla Sogorb J, Routy JP, Wyen C, Ait-Khaled M, Nascimento M, Pappa K, Wang R, Wright J, Tenorio A, Wynne B, Aboud M, Gartland M, Smith K. Efficacy and Safety of Switching to Dolutegravir/Lamivudine Fixed-Dose 2-Drug Regimen vs Continuing a Tenofovir Alafenamide–Based 3- or 4-Drug Regimen for Maintenance of Virologic Suppression in Adults Living With Human Immunodeficiency Virus Type 1: Phase 3, Randomized, Noninferiority TANGO Study. Clinical Infectious Diseases, ciz1243,

14. Baldin G, Ciccullo A, Rusconi S, Capetti A, Sterrantino G, Colafigli M, d'Ettore G, Giacometti A, Cossu MV, Borghetti A, Gennari W, Mussini C, Borghi V, DiGiambenedetoo S. Long-term data on the efficacy and tolerability of lamivudine plus dolutegravir as a switch strategy in a multi-centre cohort of HIV-1-infected, virologically suppressed patients. International Journal of Antimicrobial Agents, 54, (2019):728-734

15. Joly V, Burdet C, Landman R, et al. Dolutegravir and lamivudine maintenance therapy in HIV-1 virologically suppressed patients: results of the ANRS 167 trial (LAMIDOL). J Antimicrob Chemother. 2019;74(3):739-745.

16. Taiwo BO, Marconi VC, Berzins B, et al. Dolutegravir plus lamivudine maintains human immunodeficiency virus-1 suppression through week 48 in a pilot randomized trial. Clin Infect Dis. 2018; 66(11):1794-1797.

17. Libre J, Hung C-C, Brinson C, et al. Efficacy, safety and tolerability of dolutegravir-rilpivirine for the maintenance of virological suppression in adults with HIV-1: phase 3, randomized, non-inferiority Sword-1 and Sword 2 studies. The Lancet. 2018; 391, (10123), 839-849.

18. Di Giambenedetto S, Fabbiani M, Quiros Roldan E, et al; Atlas-M Study Group. Treatment simplification to atazanavir/ritonavir +lamivudine versus maintenance of atazanavir/ritonavir + two NRTIs in virologically suppressed HIV-1-infected patients: 48 week results from a randomized trial (ATLAS-M). J Antimicrob Chemother. 2017; 72(4):1163-1171.

19. Perez-Molina JA, Rubio R, Rivero A, et al; GeSIDA 7011 Study Group. Simplification to dual therapy (atazanavir/ritonavir+lamivudine) versus standard triple therapy [atazanavir/ritonavir+two nucleos(t)ides] in virologically stable patients on antiretroviral therapy: 96 week results from an open-label, non-inferiority, randomized clinical trial (SALT study). J Antimicrob Chemother. 2017; 72(1):246-253.

20. Pulido F, Ribera E, Lagarde M, et al; DUAL-GESIDA-8014-RIS-EST45 Study Group. Dual therapy with darunavir and ritonavir plus lamivudine vs triple therapy with darunavir and ritonavir plus tenofovir disoproxil fumarate and emtricitabine or abacavir and lamivudine for maintenance of human immunodeficiency virus type 1 viral suppression: randomized, open-label, noninferiority DUAL-GESIDA 8014-RIS-EST45 trial. Clin Infect Dis. 2017; 65(12):2112-2118.

21. Corado KC, Caplan M, Daar ES. Two-drug regimens for treatment of naïve HIV-1 infection and as maintenance therapy. Drug Design, Development and Therapy 2018; 12:3731-3740.

22. Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology. 2018; 67(4):1560-1599.

23. Gallant J, Brunetta J, Crofoot G et al. Brief Report: Efficacy and Safety of Switching to a Single-Tablet Regimen of Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide in HIV-1/Hepatitis B-Co-infected Adults. J Acquir Immune Defic Syndr. 2016 Nov 1; 73(3): 294–298.

24. Harris M, Ganase B, Watson B, Harrigan PR, Montaner JSG, Hull M. HIV treatment simplification to elvitegravir/cobicistat/emtricitabine/tenofovir disproxil fumarate (E/C/F/TDF) plus darunavir: a pharmacokinetic study. AIDS Research and Therapy 2017, 14:59. DOI: 10.1186/s12981-017-0185-4.

25. Huhn GD, Tebas P, Gallant J, et al. A randomized, open-label trial to evaluate switching toelvitegravir/cobicistat/emtricitabine/tenofovir alafenamide plus darunavir in treatment-experienced HIV-1-infected adults. J Acquir Immune Defic Syndr. 2017; 74(2):193-200.

26. Wijting I, Rokx C, Boucher C, et al. Dolutegravir as maintenance monotherapy for HIV (DOMONO): a phase 2, randomised non-inferiority trial. Lancet HIV. 2017; 4(12):e547-e554.

27. Galli L, Spagnuolo V, Bigoloni A, et al; MODAt Study Group. Atazanavir/ritonavir monotherapy: 96 week efficacy, safety and bone mineral density from the MODAt randomized trial. J Antimicrob Chemother. 2016;71(6):1637-1642.

28. Girard PM, Antinori A, Arribas JR, et al. Week 96 efficacy and safety of darunavir/ritonavir monotherapy vs. darunavir/ritonavir with two nucleoside reverse transcriptase inhibitors in the PROTEA trial. HIV Med. 2017; 18(1):5-12.

29. Brenner BG, Thomas R, Blanco JL, et al. Development of a G118R mutation in HIV-1 integrase following a switch to dolutegravir monotherapy leading to cross-resistance to integrase inhibitors. J Antimicrob Chemother. 2016; 71(7):1948-1953.

30. Gallant JE, Daar ES, Raffi F, et al. Efficacy and safety of tenofovir alafenamide versus tenofovir disoproxil fumarate given as fixed-dose combinations containing emtricitabine as backbones for treatment of HIV-1 infection in virologically suppressed adults: a randomised, double-blind, active-controlled phase 3 trial. The Lancet HIV. 2016; 3(4): e 158-e165.

31. Wohl DA, Bhatti L, Small CB, et al. The ASSURE Study: HIV-1 suppression is maintained with bone and renal biomarker improvement 48 weeks after ritonavir discontinuation and randomized switch to abacavir/lamivudine + atazanavir. HIV Med 2016; 17:106-117.

32. Winston A, Post FA, DeJesus E, et al. Tenofovir alafenamide plus emtricitabine versus abacavir plus lamivudine for treatment of virologically suppressed HIV-1-infected adults: a randomised, double-blind, active-controlled, non-inferiority phase 3 trial. Lancet HIV. 2018; 5(4):e162-e171.

33. Molina JM, Ward D, Brar I, et al. Switching to fixed-dose bictegravir, emtricitabine, and tenofovir alafenamide from dolutegravir plus abacavir and lamivudine in virologically suppressed adults with HIV-1: 48 week results of a randomised, double-blind, multicentre, active-controlled, phase 3, non-inferiority trial. Lancet HIV. 2018; 5(7):e357-e365.

34. Mills A, Crofoot G, Ortiz R, et al. Switching from twice-daily raltegravir plus tenofovir disoproxil fumarate/emtricitabine to once-daily elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate in virologically suppressed, HIV-1-infected subjects: 48 weeks data. HIV Clin Trials.2014; 15(2):51-56.

35. Hagins D, Orkin C, Daar ES, et al. Switching to coformulated rilpivirine (RPV), emtricitabine (FTC) and tenofovir alafenamide from either RPV, FTC and tenofovir disoproxil fumarate (TDF) or efavirenz, FTC and TDF: 96-week results from two randomized clinical trials. HIV Med. 2018; 19;724-733.

36. Mills AM, Cohen C, Dejesus E, et al. Efficacy and safety 48 weeks after switching from efavirenz to rilpivirine using emtricitabine/tenofovir disoproxil fumarate-based single-tablet regimens. HIV Clin Trials. 2013; 14(5):216-223.

37. de la Fuente S, Díaz A, Vicente N, Ángel-Moreno A (2018) Switching Darunavir/Ritonavir to Darunavir/ Cobicistat in Clinical practice - Experience with 150 patients through 48 weeks. J Aids Hiv Infec 4(1): 101.

38. Squires KE, Young B, DeJesus E, et al. ARIES 144 week results: durable virologic suppression in HIV-infected patients simplified to unboosted atazanavir/abacavir/lamivudine. HIV Clin Trials. 2012; 13(5):233-244.

39. Ghosn J, Carosi G, Moreno S, et al. Unboosted atazanavir-based therapy maintains control of HIV type-1 replication as effectively as a ritonavir-boosted regimen. Antivir Ther. 2010; 15(7):993-1002.

40. Wohl DA, Bhatti L, Small CB, et al. The ASSURE study: HIV-1 suppression is maintained with bone and renal biomarker improvement 48 weeks after ritonavir discontinuation and randomized switch to abacavir/lamivudine + atazanavir. HIV Med. 2016; 17(2):106-117.

41. Gatell JM, Assoumou L, Moyle G, et al. Switching from a ritonavir-boosted protease inhibitor to a dolutegravir-based regimen for maintenance of HIV viral suppression in patients with high cardiovascular risk. AIDS. 2017; 31(18):2503-2514.

42. Daar ES, DeJesus E, Ruane P, et al. Efficacy and safety of switching to fixed-dose bictegravir, emtricitabine, and tenofovir alafenamide from boosted protease inhibitor-based regimens in virologically suppressed adults with HIV-1: 48 week results of a randomised, open-label, multicentre, phase 3, non-inferiority trial. Lancet HIV. 2018; 5(7):e347-e356.

43. Arribas JR, DeJesus E, van Lunzen J, et al. Simplification to single-tablet regimen of elvitegravir, cobicistat, emtricitabine, tenofovir DF from multi-tablet ritonavir-boosted protease inhibitor plus coformulated emtricitabine and tenofovir DF regimens: week 96 results of STRATEGY-PI. HIV Clin Trials. 2017; 18(3):118-125.

44. Hodder S, Squires K, Kityo C, et al. Brief report: efficacy and safety of switching to coformulated elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide (E/C/F/TAF) in virologically suppressed women. J Acquir Immune Defic Syndr. 2018; 78(2):209-213.

45. Palella FJ Jr, Fisher M, Tebas P, et al. Simplification to rilpivirine/emtricitabine/tenofovir disoproxil fumarate from ritonavir-boosted protease inhibitor antiretroviral therapy in a randomized trial of HIV-1 RNA-suppressed participants. AIDS. 2014; 28(3):335-344.

46. Pozniak A, Markowitz M, Mills A, et al. Switching to coformulated elvitegravir, cobicistat, emtricitabine, and tenofovir versus continuation of non-nucleoside reverse transcriptase inhibitor with emtricitabine and tenofovir in virologically suppressed adults with HIV (STRATEGY-NNRTI): 48 week results of a randomised, open-label, phase 3b non-inferiority trial. Lancet Infect Dis. 2014; 14(7):590-599.

47. Arribas JR, Pialoux G, Gathe J, et al. Simplification to coformulated elvitegravir, cobicistat, emtricitabine, and tenofovir versus continuation of ritonavir-boosted protease inhibitor with emtricitabine and tenofovir in adults with virologically suppressed HIV (STRATEGY-PI): 48 week results of a randomised, open-label, phase 3b, non-inferiority trial. Lancet Infect Dis: 2014; 14 (7):581-589.

48. Wandeler G, Buzzi M, Anderegg N, et al. Virologic failure and HIV drug resistance on simplified, dolutegravir-based maintenance therapy: Systematic review and meta-analysis. F1000Research 2019; 7:1359.

49. Fabbiani M, Gagliardini R, Ciccarelli N, et al. Atazanavir/ritonavir with lamivudine as maintenance therapy in virologically suppressed HIV-infected patients: 96 week outcomes of a randomized trial. J Antimicrob Chemother. 2018; 13 (7):1955-1964.

50. Arribas JR, Girard PM, Landman R, et al. Dual treatment with lopinavir-ritonavir plus lamivudine versus triple treatment with lopinavir-ritonavir plus lamivudine or emtricitabine and a second nucleos(t)ide reverse transcriptase inhibitor for maintenance of HIV-1 viral suppression (OLE): a randomised, open-label, non-inferiority trial. Lancet Infect Dis. 2015; 15(7):785-792.

51. Kieffer TL, Finucane MM, Nettles RE, et al. Genotypic analysis of HIV-1 drug resistance at the limit of detection:virus production without evolution in treated adults with undetectable HIV loads. J Infect Dis 2004; 189(8):1452-1465.

52. Farmer A, Wang X, Ganesan A, Deiss R, Agan B, O'Bryan T, Akers K and Okulicz J. Factors associated with HIV viral load "blips" and the relationship between self-reported adherence and efavirenz blood levels on blip occurrence: a case-control study. AIDS Research and Therapy. 2016; 13:16.

53. Nettles RE, Kieffer TL, Kwon P, et al. Intermittent HIV-1 viremia (blips) and drug resistance in patients receiving HAART. JAMA. 2005; 293(7):817-829.

54. Lima V, Harrigan R, Montaner JS. Increased reporting of detectable plasma HIV-1 RNA levels at the critical threshold of 50 copies per milliliter with the Taqman assay in comparison to the Amplicor assay. J Acquir Immune Defic Syndr. 2009; 51(1):3-6.

55. Gatanaga H, Tsukada K, Honda H, et al. Detection of HIV type 1 load by the Roche Cobas TaqMan assay in patients with viral loads previously undetectable by the Roche Cobas Amplicor Monitor. Clin Infect Dis. 2009; 48(2):260-262.

56. Willig JH, Nevin CR, Raper JL, et al. Cost ramifications of increased reporting of detectable plasma HIV-1 RNA levels by the Roche COBAS AmpliPrep/COBAS TaqMan HIV-1 version 1.0 viral load test. J Acquir Immune Defic Syndr 2010; 54(4):442-444.

57. Antiretroviral Therapy Cohort Collaboration. Impact of low-level viremia on clinical and virological outcomes in treated HIV-1-infected patients. AIDS. 2015; 29(3):373-383.

58. Boillat-Blanco N, Darling KE, Schoni-Affolter F, et al. Virological outcome and management of persistent low-level viraemia in HIV-1-infected patients: 11 years of the Swiss HIV Cohort Study. Antivir Ther. 2014; 165-175.

59. Aleman S, Soderbarg K, Visco-Comandini U, Sitbon G, Sonnerborg A. Drug resistance at low viraemia in HIV-1-infected patients with antiretroviral combination therapy. AIDS. 2002; 16(7):1039-1044.

60. Karlsson AC, Younger SR, Martin JN, et al. Immunologic and virologic evolution during periods of intermittent and persistent low-level viremia. AIDS. 2004.

61. Eron JJ, Cooper DA, Steigbigel RT, et al. Efficacy and safety of raltegravir for treatment of HIV for 5 years in the BENCHMRK studies: final results of two randomised, placebo-controlled trials. Lancet Infect Dis. 2013; 13(7):587-596.

62. Cooper DA, Steigbigel RT, Gatell JM, et al. Subgroup and resistance analyses of raltegravir for resistant HIV-1 infection. N Engl J Med. 2008; 359(4):355-365.

63. Lalezari JP, Henry K, O'Hearn M, et al. Enfuvirtide, an HIV-1 fusion inhibitor, for drug-resistant HIV infection in North and South America. N Engl J Med. 2003; 348(22):2175-2185.

64. Reynes J, Arasteh K, Clotet B, et al. TORO: ninety-six-week virologic and immunologic response and safety evaluation of enfuvirtide with an optimized background of antiretrovirals. AIDS Patient Care STDS. 2007; 21(8):533-543.

65. Clotet B, Bellos N, Molina JM, et al. Efficacy and safety of darunavir-ritonavir at week 48 in treatment-experienced patients with HIV-1 infection in POWER 1 and 2: a pooled subgroup analysis of data from two randomised trials. Lancet. 2007; 369(9568):1169-1178.

66. Steigbigel RT, Cooper DA, Kumar PN, et al. Raltegravir with optimized background therapy for resistant HIV-1 infection. N Engl J Med. 2008; 359(4):339-354.

67. Katlama C, Haubrich R, Lalezari J, et al. Efficacy and safety of etravirine in treatment-experienced, HIV-1 patients: pooled 48 week analysis of two randomized, controlled trials. AIDS. 2009; 23(17):2289-2300.

68. Gulick RM, Lalezari J, Goodrich J, et al. Maraviroc for previously treated patients with R5 HIV-1 infection. N Engl J Med. 2008; 359(14):1429-1441.

69. Aboud M, Kaplan R, Lombaard J, et al. Superior efficacy of dolutegravir (DTG) plus 2 nucleoside reverse transcriptase inhibitors (NRTIs) compared with lopinavir/ritonavir (LPV/RTV) plus 2 NRTIs in second-line treatment: 48 week data from the DAWNING study. Presented at: 22nd International AIDS Conference; July 23-27, 2018; Amsterdam, the Netherlands.

70. Saag M, Benson C, Gandhi R et al. Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults 2018 Recommendations of the International Antiviral Society–USA Panel. JAMA. 2018; 320(4):379-396.

71. Harris M, Akagi L. Bictegravir 50mg/emtricitabine 200mg/tenofovir alafenamide 25mg (Biktarvy®) with other antiretrovirals. Available from: http://www.cfenet.ubc.ca/sites/default/files/uploads/guidelines-updates/bictegravir-50mg_emtricitabine-200mg_tenofovir-alafenamide-25mg-biktarvy-with-other-antiretrovirals_0.pdf. 24-02-2020.

72. De Luca A, Dunn D, Zazzi M, et al. Declining prevalence of HIV-1 drug resistance in antiretroviral treatment-exposed individuals in Western Europe. J Infect Dis. 2013; 207(8):1216-1220.

73. Paquet AC, Solberg OD, Napolitano LA, et al. A decade of HIV-1 drug resistance in the United States: trends and characteristics in a large protease/reverse transcriptase and co-receptor tropism database from 2003 to 2012. Antivir Ther. 2014; 19(4):435-441.

74. Ledergerber B, Lundgren JD, Walker AS, et al. Predictors of trend in CD4 cell count-positive T-cell count and mortality among HIV-1-infected individuals with virological failure to all three antiretroviral-drug classes. Lancet. 2004; 364(9428):51-62.

V ADVERSE DRUG REACTIONS

A. RECOMMENDATIONS

i. Sensitivity Reaction

1. We strongly recommend <u>against</u> prescribing abacavir (ABC) to patients who test positive for HLA-B*5701, for whom no test result is available, or who have a history of abacavir hypersensitivity reaction (HSR) (A-I).

2. Darunavir (DRV) and tipranavir/ritonavir (TPV/r) should be used with caution and appropriate monitoring in patients with a history of sulfonamide allergy (B-II).

3. We strongly recommend discontinuing darunavir, fosamprenavir/ritonavir (FPV/r), and tipranavir/ritonavir (TPV/r) in the presence of rash which is severe, persistent, extensive, or accompanied by systemic symptoms (A-I).

ii. Co-morbid Cardiovascular Disease

1. Abacavir should be used with caution in persons with high risk of cardiovascular disease (B-II).

2. Atazanavir (ATV), atazanavir/ritonavir (ATV/r), lopinavir/ritonavir (LPV/r), and saquinavir/ritonavir (SQV/r) should be used with caution in patients who have underlying cardiac conduction defects or who are on concomitant medications that prolong the PR interval (B-II). In such patients, an ECG should be obtained before prescribing these four ARVs, and they should be monitored periodically at intervals determined by the degree of risk (B-II). LPV/r and SQV/r should not be used in patients with hypokalemia, congenital long QT syndrome, or pre-LPV/r or pre-SQV/r QT interval >450 msec (B-II).

3. Efavirenz (EFV) and rilpivirine (RPV) should be used with caution in patients who have underlying cardiac conduction defects or who are on concomitant medications that can cause QT prolongation (B-II). In such patients, an ECG should be obtained before prescribing EFV or RPV, and they should be monitored periodically at intervals determined by the degree of risk. EFV and RPV should not be used in patients with pre-EFV or pre-RPV QT interval >450 msec (B-II).

iii. Co-morbid Renal Condition

1. We recommend <u>against</u> the use of tenofovir alafenamide (TAF) in individuals with eGFR <30 mL/min, due to lack of information on safety and dosage adjustment (A-II).

2. We strongly recommend <u>against</u> prescribing tenofovir DF for individuals with established CKD (eGFR <60 mL/min) or at high risk of CKD (A-I).

3. We recommend that atazanavir (ATV) be discontinued if a diagnosis of kidney stones is confirmed (A-II).

4. We strongly recommend that eGFR be measured prior to starting darunavir/cobicistat (DRV/c) or rilpivirine (RPV), and that eGFR, urinalysis, and urine albumin to creatinine ratio (UACR) or urine protein to creatinine ratio (UPCR) be monitored regularly thereafter (A-II). Clinicians are recommended to further investigate decreases in eGFR >25% of the baseline level, that start later or continue to progress after the first 2 to 8 weeks of therapy, or that are accompanied by signs of renal tubular dysfunction (e.g. proteinuria) to rule out true renal function impairment (A-II).

iv.   Co-morbid Hepatic Condition

1. In patients with hepatic insufficiency (Child Pugh class B or C), we recommend against the use of tipranavir/ritonavir (TPV/r) (A-I) or efavirenz (EFV) (A-II).

2. We strongly recommend against using nevirapine (NVP) in patients with moderate to severe hepatic impairment (Child-Pugh class B or C) (A-I).

v.   Neurocognitive Effects

1. If dolutegravir (DTG) is dosed once daily, we suggest it be taken in the morning to reduce insomnia and sleep disturbances (C-III).

2. We suggest efavirenz (EFV) be taken on an empty stomach, preferably at bedtime, to reduce side effects (C-III).

vi.   Pregnancy

1. We recommend against the use of bictegravir (BIC) in a person who is pregnant due to insufficient safety data (A-III).

2. We recommend against the use of doravirine (DOR) in a person who is pregnant due to insufficient safety data (A-III). We do not suggest using efavirenz (EFV) in a person of child-bearing potential, particularly during the first trimester of pregnancy (C-III).

3. We recommend against the use of cobicistat-containing regimens in pregnancy.(C-III).

vii.   Other

1. We recommend against the use of lopinavir/ritonavir (LPV/r), nelfinavir (NFV), saquinavir/ritonavir (SQV/r), tipranavir/ritonavir (TPV/r), or zidovudine (ZDV) for ART when other options are available. (A-II)

2. We strongly recommend against prescribing tenofovir DF for individuals with established osteoporosis or at high risk for osteoporosis (e.g. post-menopausal individuals) (A-I).

3. We strongly recommend against using nevirapine (NVP) in ARV-naive women with pre-NVP CD4 cell counts >250 cells/µL and in ARV-naive men with pre-NVP CD4 cell counts >400 cells/µL (A-I) and new starts in pregnancy regardless of CD4 cell counts.

4. DISCUSSION OF EVIDENCE

As with any other medications, all antiretroviral (ARV) agents can be associated with adverse drug reactions (ADRs). Newer ARV agents currently in use are considerably safer and more tolerable than older agents, and treatment-limiting toxicities are now uncommon. However, ADRs may still have an important impact on tolerability and adherence, and ultimately affect ARV regimen efficacy. Also, ARV therapy is now started earlier in the course of the disease and, in the absence of a cure, is a lifelong proposition; therefore, the long-term effects of ARV exposure are important considerations when choosing an ARV regimen. As the HIV population becomes older, health care providers need to be aware of the overlap between long-term ADRs and the effects of aging (e.g. on glucose and lipid metabolism, cardiovascular disease, renal function, and bone density).

Potential ADRs should be considered when selecting an ARV regimen, taking into account patient factors such as:

- Previous history of ADRs to ARVs and other medications
- Presence of, or risk factors for, co-morbid medical or psychiatric conditions
- Concomitant medications with overlapping toxicities or drug-drug interactions that can affect ADR risk
- Genetic predisposition, e.g. presence of the HLA-B*5701 allele predicts hypersensitivity reaction to abacavir[1]; history of sulfonamide allergy may predict cross-sensitivity to darunavir, fosamprenavir, and tipranavir.

B. Adverse Drug Reaction Tables

ADRs which are common and/or serious are shown in the following tables by ARV drug class and individual agent. The tables have been adapted from the Panel on Antiretroviral Guidelines for Adults and Adolescents.[h] Approximate ADR frequencies[i] are listed for each agent when given in combination with other ARV agents.

Click on the drug class below to link to the adverse reactions and recommendations pertaining to the agents in that class.

TABLE 11: Adverse Drug Reactions of Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs)

TABLE 12: Adverse Drug Reactions of Integrase Strand Transfer Inhibitors (INSTIs)

TABLE 13: Adverse Drug Reactions of Protease Inhibitors (PIs)

TABLE 14: Adverse Drug Reactions of Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

TABLE 15: Adverse Drug Reactions of Entry Inhibitors

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[h] Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV. Department of Health and Human Services. Available at **http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf**. Accessed March 25, 2019. Table 15 and Appendix B, Tables 1 to 6.

[i] Source (except where otherwise cited): Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Hudson (OH). Available at: **http://online.lexi.com**. Accessed April 5-17, 2019.

TABLE 11: **Adverse Drug Reactions of Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs)**

NRTI	ADVERSE DRUG REACTIONS	RECOMMENDATIONS
Abacavir (ABC)	→Hypersensitivity reaction (HSR) (8-9%). Associated with presence of the HLA-B*5701 allele [1] (~6% prevalence in British Columbia). HSR incidence 1% among HLA-B*5701 negative individuals. HSR symptoms may include fever, rash, malaise, nausea, headache, myalgia, chills, diarrhea, vomiting, abdominal pain, fatigue, arthralgia, or respiratory symptoms (dyspnea, sore throat, cough, or shortness of breath). Onset in first 6 weeks of treatment (median 11 days). →Recent use of abacavir may be associated with increased risk of myocardial infarction (MI) [2,3], but this association remains controversial [4].	We strongly recommend against prescribing abacavir to patients who test positive for HLA-B*5701, for whom no test result is available, or who have a history of abacavir HSR (A-I). Abacavir should be used with caution in persons with a high risk of cardiovascular disease (B-II).
Emtricitabine (FTC)	→Usually safe and well-tolerated →Skin rash [5] (17-30%) →Nausea (13-18%), diarrhea [6] (9-23%) →Headache (6-22%) →Hyperpigmentation/skin discolouration (2-4%) →Severe acute exacerbation of hepatitis may occur in hepatitis B virus (HBV) co-infected patients who discontinue FTC.	
Lamivudine (3TC)	→Usually safe and well-tolerated →Severe acute exacerbation of hepatitis may occur in HBV co-infected patients who discontinue 3TC.	
Tenofovir alafenamide (TAF)	→Diarrhea (5%), nausea (6%), headache (12%) →Dyslipidemia: ↑ LDL cholesterol (Grade 3-4: 6%) →Acute and chronic renal insufficiency and proximal renal tubulopathy (less likely to occur with TAF than with TDF in regimens that also contain cobicistat or ritonavir; incidence similar to TDF in unboosted regimens [7]) →Decreased bone mineral density (5%-11% incidence after 1 to 2 years of use, then stable). →Bone fractures (<1% per year) (less likely to occur with TAF than with TDF in regimens that also contain cobicistat or ritonavir; incidence similar to TDF in unboosted regimens) [7] →Severe acute exacerbation of hepatitis may occur in HBV co-infected patients who discontinue TAF.	We recommend against the use of TAF in individuals with eGFR <30 mL/min, due to lack of information on safety and dosage adjustment (A-II).

NRTI	ADVERSE DRUG REACTIONS	RECOMMENDATIONS
Tenofovir disoproxil fumarate (TDF)	→Asthenia (6-11%), headache (5-14%), diarrhea (9-16%), nausea (8-20%), vomiting (2-13%), flatulence (3-4%) →Chronic kidney disease (CKD), proximal renal tubulopathy (hypophosphatemia, proteinuria, glycosuria) (7-9% during 2 years of use [8]): increased risk with underlying CKD risk factors (e.g. diabetes, hypertension) and/or concomitant nephrotoxic medications [9-13] (e.g. NSAIDS, especially oral diclofenac [14]) and/or cobicistat or ritonavir [7] →Acute renal insufficiency, proximal renal tubulopathy (Fanconi syndrome) (<1%): increased risk with concomitant nephrotoxic medications [9-13] (e.g. NSAIDS, especially oral diclofenac [14]) and/or cobicistat or ritonavir [7] →Decreased bone mineral density (28% incidence after 1 to 2 years of use, then stable) →Increased risk of osteoporotic fractures (<1% per year) [7,15,16] →Osteomalacia (<1%) →Severe acute exacerbation of hepatitis may occur in HBV-co-infected patients who discontinue TDF	We strongly recommend against prescribing tenofovir DF for individuals with established CKD (eGFR <60 mL/min) or at high risk of CKD (A-I). We strongly recommend against prescribing tenofovir DF for individuals with established osteoporosis or at high risk for osteoporosis (e.g. post-menopausal individuals) (A-I).
Zidovudine (AZT, ZDV)	→Headache (63%) →Malaise (53%), asthenia (9%), fatigue (≥5%) →Nausea and vomiting (17%) →Lipoatrophy (10-20% with long-term use) →Insomnia (5%) →Myopathy and myositis (5%) →Bone marrow suppression: macrocytic anemia, neutropenia →Rash, nail pigmentation →Lactic acidosis/severe hepatomegaly with hepatic steatosis (rare [<1%] but potentially life-threatening), increased risk in obese individuals and women	We recommend against the use of zidovudine for ART when other options are available (A-II).

TABLE 12:   Adverse Drug Reactions of Integrase Strand Transfer Inhibitors (INSTIs)

INSTI	ADVERSE DRUG REACTIONS	RECOMMENDATIONS
All (class effect)	Generally safe and well-tolerated, especially unboosted INSTIs →Insomnia, sleep disturbances, abnormal dreams: More frequent with DTG ($\leq$7%) than with RAL or EVG/c (2-4%) [17-19]. Frequency with BIC similar to DTG [20]. →Headache ($\leq$2-7%) →Possible increases in body weight, especially among older patients ($\geq$60 years), black races, and women [21,22]	
Bictegravir (BIC)	→Nausea (3-5%), diarrhea (3-6%) →Rash (<2%) →Increased serum creatinine (inhibits creatinine secretion without reducing renal glomerular function)[a]	We recommend <u>against</u> the use of BIC in a person who is pregnant due to insufficient safety data (**A-III**).
Dolutegravir (DTG)	→Hyperglycemia ($\leq$14%) →Hepatotoxicity: increased ALT ($\leq$18%), increased AST ($\leq$8%), hyperbilirubinemia ($\leq$3%), hepatitis (<2%) →CPK elevation (1-7%), myalgia (<1%), myositis (<2%), rhabdomyolysis (rare) →Depression ($\leq$1%) and suicidal ideation (<2%) (usually in patients with pre-existing psychiatric conditions) →Hypersensitivity reactions ($\leq$1%), including rash, constitutional symptoms, and organ dysfunction (including liver injury) →Increased serum creatinine (inhibits creatinine secretion without reducing renal glomerular function)[b]	If DTG is dosed once daily, we suggest it be taken in the morning to reduce insomnia and sleep disturbances (C-III). We recommend that eGFR be measured prior to starting DTG, and that eGFR, urinalysis, and urine albumin to creatinine ratio (UACR) or urine protein to creatinine ratio (UPCR) be monitored regularly thereafter (A-II). *Continued next page* Decreases in eGFR >25% of the baseline level, that start later or continue to progress after the first 2 to 8 weeks of therapy, or that are accompanied by signs of renal tubular dysfunction (e.g. proteinuria) should be further investigated to rule out true renal function

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[a] ARV regimens including bictegravir may cause an increase in serum creatinine during the first 2 to 8 weeks of therapy, resulting in an apparent reduction of eGFR (usually <25%) from baseline. Decreases in eGFR that are >25% of the baseline level, that start later or continue to progress after the first 2 to 8 weeks of therapy, or that are accompanied by signs of renal tubular dysfunction (e.g. proteinuria), require further investigation to rule out true renal function impairment [23,24].

[b] ARV regimens including dolutegravir may cause an increase in serum creatinine during the first 2 to 8 weeks of therapy, resulting in an apparent reduction of eGFR (usually <25%) from baseline. Decreases in eGFR that are >25% of the baseline level, that start later or continue to progress after the first 2 to 8 weeks of therapy, or that are accompanied by signs of renal tubular dysfunction (e.g. proteinuria) require further investigation to rule out true renal function impairment [23].

INSTI	ADVERSE DRUG REACTIONS	RECOMMENDATIONS
		impairment (A-II).
Elvitegravir/ cobicistat (EVG/c)	→Nausea (4-16%), diarrhea (12%) →Dyslipidemia: ↑ LDL cholesterol (Grade 3-4: 11%) →Fatigue (4-5%), malaise (4-5%) →Rash (4%) →Depression and suicidal ideation (<1%; usually in patients with pre-existing psychiatric conditions) →Increased serum creatinine (inhibits creatinine secretion without reducing renal glomerular function)[b]	We recommend that eGFR be measured prior to starting EVG/c, and that eGFR, urinalysis, and UACR or UPCR be monitored regularly thereafter (A-II). Decreases in eGFR >25% of the baseline level, that start later or continue to progress after the first 2 to 8 weeks of therapy, or that are accompanied by signs of renal tubular dysfunction (e.g. proteinuria) should be further investigated to rule out true renal function impairment (A-II). We recommend against the use of cobicistat in pregnancy.
Raltegravir (RAL)	→Nausea (≤3%), diarrhea (2%) →CPK elevation (1-4%), muscle weakness (<2%), myopathy, myositis, rhabdomyolysis (<1%) →Depression and suicidal ideation (rare [<2%]; usually in patients with pre-existing psychiatric conditions) →Rash, including Stevens-Johnson syndrome, HSR, and toxic epidermal necrolysis (<1%) →Lipohypertrophy (increased trunk fat; causal relationship not established)	

[d] ARV regimens including cobicistat may cause an increase in serum creatinine during the first 2 to 8 weeks of therapy, resulting in an apparent reduction of eGFR (usually <25%) from baseline. Decreases in eGFR that are >25% of the baseline level, that start later or continue to progress after the first 2 to 8 weeks of therapy, or that are accompanied by signs of renal tubular dysfunction (e.g. proteinuria), require further investigation to rule out true renal function impairment [23].

TABLE 13: **Adverse Drug Reactions of Protease Inhibitors (PIs)**

PI	Adverse Drug Reactions	Recommendations
All (class effect)	→GI intolerance (diarrhea, nausea, vomiting): LPV/r (≤28%), NFV (≤20%), TPV/r (≤15%), DRV/c (≤14%), DRV/r (≤14%), ATV/r (≤14%), FPV/r (≤13%), SQV/r (≤11%) →↑ LDL cholesterol and triglycerides (especially ritonavir- or cobicistat-boosted PIs): TPV/r (22-61%) > other PIs (1-14%) →Hyperglycemia (2-11%) →Serum transaminase elevations: TPV/r 26-32% > other PIs (1-9%) →Hepatotoxicity, drug-induced clinical hepatitis and hepatic decompensation: most frequent with TPV/r; rare with other PIs (<1%) →Lipohypertrophy (increased trunk fat): causal relationship not established →Possible increase in the frequency of bleeding episodes (spontaneous bleeding, hematuria) in patients with hemophilia	
Atazanavir (ATV), atazanavir/ ritonavir (ATV/r)	→Indirect hyperbilirubinemia (Grade 3-4: 35-49%), jaundice (5-9%), scleral icterus. →Crystalluria; nephrolithiasis (7.3-23.7 per 1000 person-years) [25,26]; high rate of recurrent stones (33%) if ATV is continued [27]. →PR interval prolongation; first degree symptomatic AV block (6%); second degree AV block (<1%). →Skin rash (3-21%) →Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis (<1%) →Cholelithiasis (>1 year of exposure) (<1%). →Acute and chronic interstitial nephritis (<1%) →Increased risk of chronic kidney disease (20% increased risk per year of exposure) [11].	We recommend that ATV be discontinued if a diagnosis of kidney stones is confirmed (A-II). ATV and ATV/r should be used with caution in patients who have underlying cardiac conduction defects or who are on concomitant medications that prolong the PR interval (B-II). In such patients, ECG should be obtained before prescribing ATV or ATV/r, and they should be monitored periodically at intervals determined by the degree of risk (B-II).

PI	Adverse Drug Reactions	Recommendations
Darunavir/ cobicistat (DRV/c), darunavir/ ritonavir (DRV/r)	→Skin rash (10%): DRV has a sulfonamide moiety. →Headache (3-9%) →Stevens-Johnson syndrome, toxic epidermal necrolysis, acute generalized exanthematous pustulosis, and erythema multiforme (<1%). →Possible modestly increased risk of cardiovascular events (1.59x per 5 years additional use) [27] →Increase in serum creatinine (with cobicistat: inhibits creatinine secretion without reducing renal glomerular function)ᶜ	DRV should be used with caution and appropriate monitoring in patients with a history of sulfonamide allergy (B-II). We strongly recommend discontinuing DRV in the presence of rash which is severe, persistent, extensive, or accompanied by systemic symptoms (A-I). We recommend that eGFR be measured prior to starting DRV/c, and that eGFR, urinalysis, and UACR or UPCR be monitored regularly thereafter (A-II). Clinicians are recommended to further investigate decreases in eGFR >25% of the baseline level, that start later or continue to progress after the first 2 to 8 weeks of therapy, or that are accompanied by signs of renal tubular dysfunction (e.g. proteinuria) to rule out true renal function impairment (A-II). We recommend against the use of cobicistat in pregnancy.
Fosamprenavir/ ritonavir (FPV/r)	→Skin rash (12-19%): FPV has a sulfonamide moiety →Headache (2-4%) →Stevens-Johnson Syndrome/Toxic Epidermal Necrosis (<1%) →Nephrolithiasis (<1%) →Possible increased risk of myocardial infarction [28]	We recommend against the use of FPV/r for ART when other options are available. (A-II) FPV/r should be used with caution and appropriate monitoring in patients with a history of sulfonamide allergy (B-II). We strongly recommend discontinuing FPV/r in the presence of rash which is severe, persistent, extensive, or accompanied by systemic symptoms (A-I).

ᶜ ARV regimens including cobicistat may cause an increase in serum creatinine during the first 2 to 8 weeks of therapy, resulting in an apparent reduction of eGFR (usually <25%) from baseline. Decreases in eGFR that are >25% of the baseline level, that start later or continue to progress after the first 2 to 8 weeks of therapy, or that are accompanied by signs of renal tubular dysfunction (e.g. proteinuria), require further investigation to rule out true renal function impairment [23].

PI	Adverse Drug Reactions	Recommendations
Lopinavir/ ritonavir (LPV/r)	→Fatigue, asthenia (8%) →Skin rash (<5%) →Pancreatitis (<1%) →Insulin resistance/diabetes mellitus (<1%) →PR interval prolongation, second- or third-degree AV block (<1%) →QTc interval prolongation, torsades de pointes (<1%) →Stevens-Johnson Syndrome/Toxic Epidermal Necrosis (<1%) →Possible increased risk of myocardial infarction [2,28] →Possible increased risk of chronic kidney disease (11% increased risk per year of exposure) [11]	We recommend against the use of LPV/r for ART when other options are available. (A-II) LPV/r should be used with caution in patients who have underlying cardiac conduction defects or who are on concomitant medications that can cause PR or QT prolongation[d]. (B-II) In such patients, an ECG should be obtained before prescribing LPV/r, and they should be monitored periodically at intervals determined by the degree of risk. LPV/r should not be used in patients with hypokalemia, congenital long QT syndrome, or pre-LPV/r QT interval >450 msec (B-II).
Nelfinavir (NFV)	→Diarrhea (14-20%)	We recommend against the use of NFV for ART when other options are available (A-II).
Saquinavir/ ritonavir (SQV/r)	→Headache (6%) →PR interval prolongation, second or third degree AV block (<1%) →QT interval prolongation, torsades de pointes (<1%)	We recommend against the use of SQV/r for ART when other options are available. (A-II) SQV/r should be used with caution in patients who have underlying cardiac conduction defects or who are on concomitant medications that can cause PR or QT prolongation[6] (B-II). In such patients, we recommend that an ECG be obtained before prescribing SQV/r, and they should be monitored periodically at intervals determined by the degree of risk. SQV/r should not be used in patients with congenital long QT syndrome or pre-SQV/r QT interval >450 msec (B-II).

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[d] Updated list of QT prolonging drugs available at: **https://crediblemeds.org/**

PI	Adverse Drug Reactions	Recommendations
Tipranavir/ ritonavir (TPV/r)	→Skin rash (3-10%): TPV has a sulfonamide moiety →Fatal and nonfatal intracranial hemorrhages (1%). Risks include brain lesion, head trauma, recent neurosurgery, coagulopathy, hypertension, alcohol abuse, and the use of anticoagulant or antiplatelet agents or vitamin E supplements.	We recommend against the use of TPV/r for ART when other options are available. (A-II) TPV/r should be used with caution and appropriate monitoring in patients with a history of sulfonamide allergy (B-II). We strongly recommend discontinuing TPV/r in the presence of rash which is severe, persistent, extensive, or accompanied by systemic symptoms (A-I). We strongly recommend against the use TPV/r in patients with hepatic insufficiency (Child Pugh class B or C) (A-I).

TABLE 14:   Adverse Drug Reactions of Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

NNRTI	ADVERSE DRUG REACTIONS	RECOMMENDATIONS
All (class effect)	→Rash: NVP (16%) > EFV (8-10%) > ETR (2%), RPV [31-34] (1-2%), DOR (1-2%) →Severe rash: Stevens-Johnson syndrome/Toxic Epidermal Necrolysis: NVP (6.5%)>> EFV (<1%) > DOR, ETR, RPV (rare, <1%) [29]	
Doravirine (DOR) [30]	→Nausea (6-7%), diarrhea (4-5%) →Fatigue (6%), headache (6%) →Dizziness (3-5%), abnormal dreams (1-3%)	We recommend against the use of DOR in a person who is pregnant, because of insufficient safety data (A-III).
Efavirenz (EFV) [31]	→Neuropsychiatric symptoms (~50%): Sleep disturbances, somnolence, insomnia, abnormal dreams, dizziness, depression, anxiety, confusion, abnormal thinking, impaired concentration, amnesia, agitation, depersonalization, hallucinations, euphoria →Dyslipidemia: ↑ triglycerides (6-11%), ↑ LDL cholesterol (20-40%), ↑ HDL cholesterol (25-35%) →Suicidality (4%): suicide, suicide attempt or ideation →Increased transaminase levels (2-8%) →QT_c interval prolongation (<1%) →Fulminant hepatitis leading to death or hepatic failure requiring transplantation (<1%) →Lipohypertrophy (trunk fat increase); causal relationship not established. →Teratogenicity: Fetal neural tube defects in primates	We suggest EFV be taken on an empty stomach, preferably at bedtime, to reduce side effects (C-III). We recommend against using EFV in patients with hepatic insufficiency (Child-Pugh class B or C) (A-II). EFV should be used with caution in patients who have underlying cardiac conduction defects or who are on concomitant medications that can cause QT prolongation[e]. (B-II) In such patients, an ECG should be obtained before prescribing EFV, and they should be monitored periodically at intervals determined by the degree of risk. EFV should not be used in patients with pre-EFV QT interval >450 msec (B-II). We do not suggest using EFV in a person of child-bearing potential, particularly during the first trimester of pregnancy (C-III).
Etravirine (ETR) [32]	→HSRs (<2%), characterized by rash, constitutional findings, and sometimes organ dysfunction, including hepatic failure	

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[e] Updated list of QT prolonging drugs available at: **https://crediblemeds.org/**

NNRTI	ADVERSE DRUG REACTIONS	RECOMMENDATIONS
Nevirapine (NVP)	→Severe hepatotoxicity associated with skin rash or hypersensitivity (<1%); symptomatic hepatitis, including fatal hepatic necrosis (<1%): significantly higher frequency in ARV-naive women with pre-NVP CD4 cell counts >250 cells/µL and in ARV-naive men with pre-NVP CD4 cell counts >400 cells/µL.	We strongly recommend against using NVP in patients with moderate to severe hepatic impairment (Child-Pugh class B or C) (A-I). We strongly recommend against using NVP in ARV-naive women with pre-NVP CD4 cell counts >250 cells/µL and in ARV-naive men with pre-NVP CD4 cell counts >400 cells/µL (A-I) and new starts in pregnancy regardless of CD4 cell count [33].
Rilpivirine (RPV)	→Depression (5-9%), headache (3%), insomnia (3%), abnormal dreams (2%), dizziness (1%) →Increased liver transaminases (1-18%) →Hepatitis (<1%) →Suicidality (<1%) →QTc interval prolongation (<1%) →Increase in serum creatinine (inhibits creatinine secretion without reducing renal glomerular function)	RPV should be used with caution in patients who have underlying cardiac conduction defects or who are on concomitant medications that can cause QT prolongation[f] (B-II). In such patients, an ECG should be obtained before prescribing RPV, and they should be monitored periodically at intervals determined by the degree of risk. RPV should not be in patients with pre-RPV QT interval >450 msec (B-II). We recommend that eGFR be measured prior to starting RPV, and that eGFR, urinalysis, and UACR or UPCR be monitored regularly thereafter (A-II). Clinicians are recommended to further investigate decreases in eGFR >25% of the baseline level, that start later or continue to progress after the first 2 to 8 weeks of therapy, or that are accompanied by signs of renal tubular dysfunction (e.g. proteinuria) to rule out true renal dysfunction (A-II).

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[f] Updated list of QT prolonging drugs available at: **https://crediblemeds.org/**

TABLE 15: **Adverse Drug Reactions of Entry Inhibitors**

ENTRY INHIBITOR	ADVERSE DRUG REACTIONS	RECOMMENDATIONS
Fusion inhibitor: Enfuvirtide (T20) [34]	→Local injection site reactions (98%): pain, erythema, induration, nodules and cysts, pruritus, ecchymosis →HSR (<1%): Symptoms may include rash, fever, nausea, vomiting, chills, rigors, hypotension, or elevated serum transaminases. →Increased incidence of bacterial pneumonia	
CCR5 antagonist: Maraviroc (MVC)	→Generally safe and well-tolerated →Upper respiratory tract infections (23-32%) →Cough (14%) →Fever (13%) →Rash (11%) →Abdominal distention or bloating (≤10%) →Dizziness (9%) →Arthropathy (6-7%), myalgia (3%) →Hepatotoxicity, with or without severe rash or HSR (<1%) →Orthostatic hypotension, especially in patients with severe renal insufficiency	

C. REFERENCES

1. Mallal S, Phillips E, Carosi G, et al. HLA-B*5701 Screening for Hypersensitivity to Abacavir. N Engl J Med. 2008; 358(6):568-79.

2. Worm SW, Sabin C, Weber R, et al. Risk of myocardial infarction in patients with HIV infection exposed to specific antiretroviral drugs from the 3 major drug classes: the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study. J Infect Dis. 2010; 201:318-330.

3. Elion RA, Althoff KN, Zhang J, et al. Recent abacavir use increases risk of Type 1 and Type 2 myocardial infarctions among adults with HIV. J Acquir Immune Defic Syndr. 2018; 78(1):62-72

4. Llibre JM, Hill A. Abacavir and cardiovascular disease: A critical look at the data. *Antivir Res*. 2016; 132: 116-21

5. Borrás-Blasco J, Navarro-Ruiz A, Borrás C, Casterá E. Adverse cutaneous reactions associated with the newest antiretroviral drugs in patients with human immunodeficiency virus infection. J Antimicrob Chemoth. 2008; 62: 879–88.

6. Pollock K, Stebbing J, Bower M, Gazzard B, Nelson M. Emtricitabine intolerance in treatment-experienced patients switched from lamivudine: a method of assessing toxicity. Antimicrob Chemoth. 2006; 58(1): 227-8.

7. Hill A, Hughes SL, Gotham D, Pozniak AL. Tenofovir alafenamide versus tenofovir disoproxil fumarate: is there a true difference in efficacy and safety? J Virus Erad. 2018; 4: 72–9.

8. Horberg M, Tang B, Towner W, et al. Impact of tenofovir on renal function in HIV-infected, antiretroviral-naïve patients. J Acquir Immune Defic Syndr. 2010; 53:62-69.

9. Bedimo R, Maalouf NM, Zhang S, Drechsler H, Tebas P. Osteoporotic fracture risk associated with cumulative exposure to tenofovir and other antiretroviral agents. AIDS 2012; 26:825–31.

10. McComsey GA, Tebas P, Shane E, et al. Bone Disease in HIV Infection: A Practical Review and Recommendations for HIV Care Providers. Clin Infect Dis. 2010; 51(8):937-46.

11. Scherzer R, Estrella M, Li Y, et al. Association of tenofovir exposure with kidney disease risk in HIV infection. AIDS 2012; 26: 867-75.

12. Ryom L, Mocroft A, Kirk O, et al. Association Between Antiretroviral Exposure and Renal Impairment Among HIV-Positive Persons With Normal Baseline Renal Function: the D:A:D Study. J Infect Dis. 2013; 207: 1359-69.

13. Mocroft A, Lundgren JD, Ross M, et al. Cumulative and current exposure to potentially nephrotoxic antiretrovirals and development of chronic kidney disease in HIV-positive individuals with a normal baseline estimated glomerular filtration rate: a prospective international cohort study. Lancet HIV 2016;3:e23-32.

14. Morlat P, Vivot A, Vandenhende MA, Dauchy FA, Asselineau J, et al. Role of Traditional Risk Factors and Antiretroviral Drugs in the Incidence of Chronic Kidney Disease, ANRS CO3 Aquitaine Cohort, France, 2004–2012. PLOS ONE 2013; 8(6): e66223.

15. Scherzer R, Gandhi M, Estrella MM, et al. A chronic kidney disease risk score to determine tenofovir safety in a prospective cohort of HIV-positive male veterans. AIDS 2014; 28: 1289-95.

16. Bickel M, Khaykin P, Stephan C, et al. Acute kidney injury caused by tenofovir disoproxil fumarate and diclofenac co-administration. HIV Med. 2103: 14:633-8.

17. Penafiel J, de Lazzari E, Padilla M, et al. Tolerability of integrase inhibitors in a real-life setting. J Antimicrob Chemother. 2017; 72:1752-1759.

18. Lepik K, Yip B, Ulloa AC, et al. Adverse drug reactions to integrase strand transfer inhibitors. AIDS 2018; 32:903-12.

19. Cuzin L, Pugliese P, Katlama C, et al. Integrase strand transfer inhibitors and neuropsychiatric adverse events in a large prospective cohort. J Antimicrob Chemother. 2018; 74:754-760.

20. Sax P, Pozniak A, Montes ML, et al. Coformulated bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir with emtricitabine and tenofovir alafenamide, for initial treatment of HIV-1 infection (GS-US-380-1490): a randomized, double-blind, multicentre, phase 3, non-inferiority trial. Lancet 2017; 390:2073-2082.

21. Hill A, Waters L, Pozniak A. Are new antiretroviral treatments increasing the risks of clinical obesity? J Virus Eradication 2019; 5: e45-e47.

22. Lake JE, Wu K, Erlandson K, et al. Risk factors for excess weight gain following switch to integrase inhibitor-based ART. CROI 2019, Seattle, Washington. March 4-7, 2019. Abstract 669.

23. Maggi P, Montinaro V, Mussini C, et al. Novel antiretroviral drugs and renal function monitoring of HIV patients. AIDS Rev. 2014; 16:144-51.

24. Deeks, E. Bictegravir/emtricitabine/tenofovir alafenamide: A review in HIV-1 infection. Drugs. 2018; 78:1817-1828.

25. Rockwood N, Mandalia S, Bower M, Gazzard B, Nelson M. Ritonavir-boosted atazanavir exposure is associated with an increased rate of renal stones compared with efavirenz, ritonavir-boosted lopinavir and ritonavir-boosted darunavir. AIDS 2011; 25:1671-1673.

26. Hamada Y, Nishijima T, Watanabe K, et al. High incidence of renal stones among HIV-infected patients on ritonavir-boosted atazanavir than in those receiving other protease inhibitor-containing antiretroviral therapy. Clin Infect Dis. 2012; 55: 1262–1269.

27. Ryom L, Lundgren JD, El-Sadr W, et al. Cardiovascular disease and use of contemporary protease inhibitors: the D:A:D international prospective multicohort study. Lancet HIV 2018; 5: PE291-300.

28. Lang S, Mary-Krause M, Cotte L, et al. Impact of individual antiretroviral drugs on the risk of myocardial infarction in Human Immunodeficiency Virus-infected patients. Arch Int Med. 2010; 170:1228-1238.

29. Harris M, Montaner JS. Clinical uses of non-nucleoside reverse transcriptase inhibitors. Rev Med Virol. 2000 Aug; 10(4):217–29.

30. Thompson M, Orkin C, Molina J-M, et al. An integrated safety analysis comparing once-daily doravirine (DOR) to darunavir + ritonavir (DRV +r) and efavirenz (EFV) in HIV-1-infected, antiretroviral therapy (ART)-naïve adults.ID Week, San Francisco, CA. October 3-7, 2018. Poster 543

31. Cohen CJ, Molina JM, Cahn P, et al. Efficacy and safety of rilpivirine (TMC278) versus efavirenz at 48 weeks in treatment-naive HIV-1-infected patients: pooled results from the phase 3 double-blind randomized ECHO and THRIVE Trials. JAIDS 2012; 60:33-42

32. Girard P-M, Campbell TB, Grinsztjen B, et al. Pooled week 96 results of the phase III DUET-1 and DUET-2 trials of etravirine: further analysis of adverse events and laboratory abnormalities of special interest. HIV Med. 2012; 13:427-435.

33. Schalkwyk JE, Alimenti A, Khoo D, et al. Serious toxicity associated with continuous nevirapine-based HAART in pregnancy. BJOG. 2008 Sep; 115(10):1297-302.

34. Trottier B, Walmsley S, Reynes J, et al. Safety of enfuvirtide in combination with an optimized background of antiretrovirals in treatment-experienced HIV-1 infected adults over 48 weeks. J Acquir Immun Defic Syndr. 2005; 40:413-21.