



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

# 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)

Reviewed and endorsed by:

Dr. Julio Montaner, OC, OBC, MD, FRCPC, FCCP  
Director and Physician in Chief of the BC-CfE; Director of the  
John Ruedy Clinic (JRC)

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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](#)<sup>a</sup>.

## 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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<sup>a</sup> Linked address: <https://bccfe.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	<i>Atazanavir</i> + ritonavir + <i>abacavir/lamivudine</i> <sup>a,b</sup>	3	Y	+++
PI	<i>Atazanavir</i> + ritonavir + <i>emtricitabine/tenofovir DF</i>	3	Y	+++
PI	<i>Darunavir</i> + ritonavir + <i>abacavir/lamivudine</i> <sup>a,b</sup>	3	Y	+++
PI	<i>Darunavir</i> + ritonavir + <i>emtricitabine/tenofovir DF</i>	3	Y	+++
NNRTI	<i>Efavirenz/emtricitabine/tenofovir DF</i>	1	N	+++
InSTI	Dolutegravir/lamivudine <sup>c,d</sup>	1	N	++
InSTI	Dolutegravir + <i>abacavir/lamivudine</i> <sup>a</sup>	2	N	++
InSTI	Dolutegravir + <i>emtricitabine/tenofovir DF</i>	2	N	++
InSTI	Bictegravir/emtricitabine/tenofovir alafenamide	1	N	+

Drugs in **bold italics** are generic products

<sup>a</sup>abacavir use contraindicated if HLA-B\*57:01 allele positive

<sup>b</sup>regimen acceptable if baseline HIV plasma viral load <100,000 copies/mL

<sup>c</sup>acceptable as initial regimen if baseline pVL <500,000 c/mL, CD4 count >200 cells/mm<sup>3</sup>, no resistance to dolutegravir or lamivudine, not pregnant, *and* absence of hepatitis B (HBV) chronic infection

<sup>d</sup>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 <https://bccfe.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](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.



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**THERAPEUTIC GUIDELINES FOR  
ANTIRETROVIRAL TREATMENT OF  
ADULT HIV INFECTION  
SCIENTIFIC REVIEW AND  
RECOMMENDATIONS**

**INITIAL RELEASE: DECEMBER 2019**

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

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## SECTION 2: SCIENTIFIC REVIEW AND RECOMMENDATIONS FOR THE THERAPEUTIC GUIDELINES

### TREATMENT GUIDELINES SCIENTIFIC REVIEW WORKING GROUP:

**Rolando Barrios, MD, MCFP, FRCPC (Chair)**

Senior Medical Director & Director of Epidemiology & Population Health and Drug Treatment Program, BC Centre for Excellence in HIV/AIDS; Clinical Assistant Professor, School of Population and Public Health, University of British Columbia; Associate Member, Division of AIDS, Department of Medicine, University of British Columbia

**Silvia Guillemi, MD, MCFP**

Clinical Professor, Department of Family Practice, Faculty of Medicine, University of British Columbia; Director of Clinical Education, BC Centre for Excellence in HIV/AIDS.

**Marianne Harris, MD, CCFP**

Clinical Assistant Professor, Department of Family Practice, Faculty of Medicine, University of British Columbia; AIDS Research Program, St. Paul's Hospital.

**David Moore, MD**

Family Physician in the John Ruedy Clinic; Clinical Assistant Professor, Department of Family Practice, Faculty of Medicine, University of British Columbia; Research Scientist with the BC Centre for Excellence in HIV/AIDS.

**Junine Toy, PharmD**

Senior Manager, Drug Treatment Program, BC Centre for Excellence in HIV/AIDS; Clinical Instructor, Faculty of Pharmaceutical Sciences, University of British Columbia; Clinical Pharmacy Specialist, St. Paul's Hospital.

### EXPERT AD HOC CONSULTANTS:

**Chanson Brumme, PhD**

Assistant Director - Research Laboratories, BC Centre for Excellence in HIV/AIDS, St. Paul's Hospital.

**Zabrina Brumme, PhD**

Laboratory Director, BC Centre for Excellence in HIV/AIDS; Professor, Faculty of Health Sciences, Simon Fraser University; Scholar, Michael Smith Foundation for Health Research

**Peter Phillips, MD, FRCPC**

Clinical Professor, Division of Infectious Diseases, University of British Columbia; Department Head, Division of Infectious Diseases; St. Paul's Hospital & University of British Columbia.

**Mark Hull, MHSc, FRCPC**

Research Scientist with the BC Centre for Excellence in HIV/AIDS, and Associate Professor with the University of British Columbia's Faculty of Medicine Division of Infectious Diseases.

**Neora Pick, MD, FRCPC**

Medical Director, Oak Tree Clinic, B.C. Women and Children's Hospital; Associate Professor, Division of Infectious Diseases; Department of Medicine, University of British Columbia & Oak Tree Clinic.

**Viviane Dias Lima, MSc, PhD**

Career Investigator, Michael Smith Foundation for Health Research; New Investigator, Canadian Institutes of

---

Health Research; Associate Professor, Division of Infectious Diseases, Faculty of Medicine, University of British Columbia; Research Scientist, Senior Statistician, BC Centre for Excellence in HIV/AIDS.

---

## SUPPORTED BY:

Aditi Bhardwaj

Helen Kang, PhD (Consulting Medical Writer)

Angie Semple

Joanna Ferguson

## CONFLICT OF INTEREST DISCLOSURES:

Zabrina Brumme disclosed that she previously had shares in a pharmaceutical company, which she has sold and of which she no longer has possession.

Viviane Dias Lima has received grants and salary awards from Canadian Institutes of Health Research (CIHR) and Michael Smith Foundation for Health Research (MSFHR), which were paid to the BC-CfE.

Silvia Guillemi reported participating on advisory board meetings and receiving honoraria from Gilead Sciences and ViiV Healthcare.

Marianne Harris has received honoraria, paid to the BC-CfE, for speaking engagements and participation on advisory boards, from Gilead Sciences, Merck Canada Inc. and ViiV Healthcare.

Mark Hull has received honoraria for advisory boards and speakers; bureaux paid to the BC-CfE from Gilead Sciences, Merck Canada Inc., and ViiV Healthcare.

David Moore has received grants and research support from the Canadian Institutes of Health Research (CIHR), Michael Smith Foundation for Health Research (MSFHR), Canadian Foundation for AIDS Research, and US National Institutes of Health. He has received in-kind support from Biolytical Laboratories for the Momentum Study.

Peter Phillips has received honoraria or participated in advisory boards for the following companies: Astellas Canada, Pfizer Inc., Merck and Sunovion Pharmaceuticals.

Neora Pick reported participating in advisory boards for ViiV Healthcare, Gilead Sciences and Merck.

No other authors reported disclosures.



## 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](#)<sup>a</sup>

### 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 I—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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<sup>a</sup>Text for link: <https://bccfe.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
<b>A</b>	Recommendation based on consistent and good quality patient-oriented evidence.
<b>B</b>	Recommendation based on inconsistent or limited quality patient-oriented evidence.
<b>C</b>	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
<b>I: Good quality, patient-oriented evidence</b>	<ul style="list-style-type: none"> <li>→ Validated clinical decision rule</li> <li>→ Systematic Review (SR)/meta-analysis of high quality studies</li> <li>→ High quality diagnostic cohort study</li> </ul>	<ul style="list-style-type: none"> <li>→ SR/meta-analysis of randomized controlled trials (RCTs) with consistent findings</li> <li>→ High quality RCT</li> <li>→ All or none study</li> </ul>	<ul style="list-style-type: none"> <li>→ SR/meta-analysis of good quality cohort studies</li> <li>→ Prospective cohort study with good follow-up</li> </ul>
<b>II: Limited quality patient-oriented evidence</b>	<ul style="list-style-type: none"> <li>→ Unvalidated clinical decision rule</li> <li>→ SR/meta-analysis of lower quality studies or studies with inconsistent findings</li> <li>→ Lower quality diagnostic cohort study or diagnostic case-control study</li> </ul>	<ul style="list-style-type: none"> <li>→ SR/meta-analysis of lower quality clinical trials or of studies with inconsistent findings.</li> <li>→ Lower quality clinical trial</li> <li>→ Cohort study</li> <li>→ Case-control study</li> </ul>	<ul style="list-style-type: none"> <li>→ SR/meta-analysis of lower quality cohort studies or with inconsistent results</li> <li>→ Retrospective cohort study or prospective cohort study with poor follow-up</li> <li>→ Case-control study</li> <li>→ Case series</li> </ul>
<b>III: Other evidence</b>	<ul style="list-style-type: none"> <li>→ 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.</li> </ul>		

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.





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## 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/ $\mu\text{L}$  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  $>350/\mu\text{L}$ ) 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/ $\mu\text{L}$ ) (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/ $\mu$ L and 550 cells/ $\mu$ L 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/ $\mu$ L (median CD4 cell count nadir 465 cells/ $\mu$ L) received ART either immediately or when indicated according to WHO guidelines at the time (i.e. when CD4 cell count <200 cells/ $\mu$ L from 2008-2009, CD4 cell count <350 cells/ $\mu$ L from 2010-2012, and CD4 cell count <500 cells/ $\mu$ L 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/ $\mu$ L.
3. More recently, the large, international INSIGHT START trial demonstrated the benefit of initiating ART immediately in patients with CD4 cell count >500 cells/ $\mu$ L as compared to deferring ART initiation until the CD4 cell count had declined to 350 cells/ $\mu$ L [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/ $\mu$ L, 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/ $\mu$ L 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/ $\text{mm}^3$  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 ( $\geq 4$  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/ $\mu\text{L}$ , 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/ $\mu\text{L}$  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].



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## 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/mm<sup>3</sup>.
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 of 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
<b>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 <a href="#">Table 3</a>) (A-II).</b>	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].
<b>If genotypic resistance test results are not available, a robust regimen able to overcome common resistance mutations is suggested (C-III).</b>	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
<p><b>Where possible, clinicians should prescribe an ARV regimen with a high barrier to resistance and without the need of a boosting agent (B-III).</b></p>	<p>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.</p>



**TABLE 3: Factors to Consider when Selecting an ARV Regimen**

FACTOR	CHARACTERISTICS	
Regimen	<ul style="list-style-type: none"> <li>Regimen efficacy</li> <li>Genetic barrier to resistance</li> <li>Tolerability and short-term adverse events</li> <li>Potential for drug-drug interactions</li> </ul>	<ul style="list-style-type: none"> <li>Toxicity and long-term safety</li> <li>Pill burden and dosing frequency</li> <li>Food requirements</li> </ul>
Virus	<ul style="list-style-type: none"> <li>Resistance test results</li> </ul>	
Individual	<ul style="list-style-type: none"> <li>HIV infection               <ul style="list-style-type: none"> <li>→ Baseline CD4 cell count and HIV viral load</li> </ul> </li> <li>HLA-B*5701 test result</li> <li>Co-existing conditions               <ul style="list-style-type: none"> <li>→ Bone disease (osteoporosis)</li> <li>→ Cardiovascular disease</li> <li>→ Chronic kidney disease</li> <li>→ Hepatitis B co-infection</li> <li>→ Hepatitis C co-infection</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>→ Liver disease with severe hepatic impairment</li> <li>→ Opportunistic infections and cancers<sup>b</sup></li> <li>→ Pregnancy/child-bearing potential<sup>c</sup></li> <li>→ Psychiatric illness, depression</li> <li>→ Substance use disorder</li> <li>Concomitant medications</li> <li>Psychosocial factors               <ul style="list-style-type: none"> <li>→ Food security</li> <li>→ Potential barriers to adherence</li> </ul> </li> </ul>

**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.

<sup>b</sup> Selection of an ARV regimen in the presence of an opportunistic infection should be done with the expert guidance of an Infectious Disease specialist.

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

\*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  $\geq 100,000$  copies/mL, emtricitabine/tenofovir DF showed significantly greater virologic efficacy (14% virologic

<sup>d</sup> See [Chapter III: Assessment and Monitoring](#) for more about the HLA-B\*5701 test.

<sup>e</sup> Kivexa® Product Monograph. ViiV Healthcare, Laval, Quebec. 2018 December 20.

<sup>f</sup> Truvada® Product Monograph. Gilead Sciences, Inc. Mississauga, Ontario. 2018 July 5.

<sup>g</sup> 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.]

<sup>h</sup> 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.<sup>1</sup>

## 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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<sup>1</sup> 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
<b>INTEGRASE STRAND TRANSFER INHIBITORS (INSTIs)</b>			
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
<b>PROTEASE INHIBITORS (PIs)</b>			
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)
<b>NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTIs)</b>			
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



\*available as generic formulation

### 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 bicitegravir, showed “a clear hierarchy within the INSTI class, with dolutegravir being the most efficacious, followed by raltegravir, and then elvitegravir” [39].

#### 1. Bicitegravir

Bicitegravir 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 bicitegravir appears to be generally similar to that of dolutegravir. The bicitegravir/FTC/TAF fixed-dose combination was approved by Health Canada in July 2018.

#### b. Dolutegravir

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. Elvitegravir

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 raltegravir, 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<sup>TM</sup> 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 darunavir and atazanavir 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  $\geq$ Grade III hyperbilirubinemia (total bilirubin  $\geq 2.5$ x 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. Efavirenz

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  $\leq 100,000$  copies/mL [68,69]. Furthermore, since rates of virologic failure were higher in clinical trials among participants with baseline CD4 cell counts  $< 200$  cells/mm<sup>3</sup> [61,63], rilpivirine-based regimens are recommended only for ARV-naïve patients with baseline CD4 cell counts  $> 200$  cells/mm<sup>3</sup>. 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/mm<sup>3</sup>.**
- **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<sup>3</sup> 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.



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## 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/ $\mu$ L for at least 2 years (A-III). In patients with CD4 cell count  $>500$  cells/ $\mu$ L 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 ( $\geq 3$  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/ $\mu$ L) 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/ $\mu$ L 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/ $\mu$ L 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  $\geq 200$  cells/ $\mu$ L 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-utilizing 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 <sup>a</sup>	√	√ <sup>b</sup>					√
HLA-B*5701	√	If considering abacavir and test was not already done at baseline					

<sup>a</sup> 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.

<sup>b</sup> 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) <sup>c</sup>	√	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 <sup>d</sup>	√				Repeat HCV screening for at-risk patients		
Renal Monitoring <sup>e</sup>	√	√	√	√	In tandem with HIV-1 RNA viral load when done every 6 months		

<sup>c</sup> 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.

<sup>d</sup> 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.

<sup>e</sup> 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 <sup>f</sup>	√	√			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 <sup>g</sup> and UACR or UPCR <sup>h</sup>	√	√			In tandem with HIV-1 RNA viral load when done every 6 months		
Pregnancy test in individuals of child-bearing potential		√					

<sup>f</sup> Consult the Canadian Cardiovascular Society's Guidelines for [recommendations in managing dyslipidemia](#).

<sup>g</sup> Urine glucose and protein should be assessed before initiating TAF- or TDF-containing regimens and monitored during treatment with these regimens.

<sup>h</sup> 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/ $\mu$ L)	Can extend to every 6 months for patients with consistent viral suppression for $\geq 2$ years	Every 6 months
After 2 years of ART (VL consistently suppressed, CD4 cell count consistently $>500$ cells/ $\mu$ L)	Can extend to every 6 months for patients with consistent viral suppression for $\geq 2$ 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



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## 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<sup>a</sup>

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).

<sup>a</sup> 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-naïve 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).<sup>b</sup>**

#### 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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<sup>b</sup> 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 bicitegravir/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  $\geq 12$  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/ $\mu$ L 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 <sup>c</sup>	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 <sup>d</sup>	Dolutegravir/lamivudine	13-16
Current antiretroviral regimen <sup>d</sup>	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

<sup>c</sup> When used with abacavir/lamivudine backbone.

<sup>d</sup> 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  $\geq$ 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  $\geq$ 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	<ul style="list-style-type: none"> <li>Adherence challenges               <ul style="list-style-type: none"> <li>→Co-morbidities (e.g. active substance use disorder, mental health disorders, neurocognitive impairment)</li> <li>→Unstable housing and other psychosocial factors</li> <li>→Poor ARV tolerability or adverse events</li> <li>→High pill burden and/or dosing frequency</li> </ul> </li> <li>Challenges in engagement or access to care</li> <li>Interruption of or intermittent access to ART</li> </ul>
HIV	<ul style="list-style-type: none"> <li>Presence of transmitted or acquired drug-resistant virus</li> <li>Prior treatment failure</li> <li>Inactivity of the CCR5 antagonist class of ARVs due to the presence or selection of HIV variants that use the CXCR4 co-receptor</li> <li>Presence of HIV-2 RNA infection/co-infection<sup>e</sup></li> <li>Higher pre-treatment HIV-1 RNA level (some regimens may be less effective at higher levels)</li> </ul>
ARV regimen	<ul style="list-style-type: none"> <li>Suboptimal pharmacokinetics (e.g. variable absorption, metabolism, or possible penetration into reservoirs)</li> <li>Suboptimal virologic potency</li> <li>Low genetic barrier to resistance</li> <li>Reduced efficacy due to prior exposure to suboptimal regimens (e.g. monotherapy, dual NRTI therapy, or the sequential introduction of drugs)</li> <li>Food requirements</li> <li>Adverse drug-drug interactions with concomitant medications or supplements</li> </ul>

<sup>e</sup> 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 **NNRTI-based regimen**, 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  $\geq$ 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 **PI-based or INSTI-based regimen** (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 <sup>f</sup> (IN ORDER OF PREFERENCE)
NNRTI plus two NRTIs	Most likely resistant to NNRTI +/- lamivudine/emtricitabine (3TC/FTC) (i.e. NNRTI mutations +/- M184V/I) <sup>g</sup> 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 <sup>f</sup> 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 <sup>f</sup> plus two NRTIs (at least one active); or → Boosted PI plus INSTI

<sup>f</sup> 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.

<sup>g</sup> If other NRTI resistance mutations are present, use resistance test results to guide NRTI usage in the new regimen. Abacavir susceptibility could be compromised when the 184V mutation is present.



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

<sup>h</sup> Response to dolutegravir depends on the type and number of INSTI mutations.



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## V ADVERSE DRUG REACTIONS

### A. RECOMMENDATIONS

#### i. Sensitivity Reaction

1. We strongly recommend against 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 against 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 against 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 bicitgravir (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/ $\mu$ L and in ARV-naive men with pre-NVP CD4 cell counts >400 cells/ $\mu$ L (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.<sup>h</sup> Approximate ADR frequencies<sup>i</sup> 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](#)

<sup>h</sup> 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.

<sup>i</sup> 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)	<ul style="list-style-type: none"> <li>→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).</li> <li>→Recent use of abacavir may be associated with increased risk of myocardial infarction (MI) [2,3], but this association remains controversial [4].</li> </ul>	<p>We strongly recommend <u>against</u> 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).</p>
Emtricitabine (FTC)	<ul style="list-style-type: none"> <li>→Usually safe and well-tolerated</li> <li>→Skin rash [5] (17-30%)</li> <li>→Nausea (13-18%), diarrhea [6] (9-23%)</li> <li>→Headache (6-22%)</li> <li>→Hyperpigmentation/skin discolouration (2-4%)</li> <li>→Severe acute exacerbation of hepatitis may occur in hepatitis B virus (HBV) co-infected patients who discontinue FTC.</li> </ul>	
Lamivudine (3TC)	<ul style="list-style-type: none"> <li>→Usually safe and well-tolerated</li> <li>→Severe acute exacerbation of hepatitis may occur in HBV co-infected patients who discontinue 3TC.</li> </ul>	
Tenofovir alafenamide (TAF)	<ul style="list-style-type: none"> <li>→Diarrhea (5%), nausea (6%), headache (12%)</li> <li>→Dyslipidemia: ↑ LDL cholesterol (Grade 3-4: 6%)</li> <li>→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])</li> <li>→Decreased bone mineral density (5%-11% incidence after 1 to 2 years of use, then stable).</li> <li>→Bone fractures (&lt;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]</li> <li>→Severe acute exacerbation of hepatitis may occur in HBV co-infected patients who discontinue TAF.</li> </ul>	<p>We recommend <u>against</u> the use of TAF in individuals with eGFR &lt;30 mL/min, due to lack of information on safety and dosage adjustment (A-II).</p>



NRTI	ADVERSE DRUG REACTIONS	RECOMMENDATIONS
<p>Tenofovir disoproxil fumarate (TDF)</p>	<ul style="list-style-type: none"> <li>→Asthenia (6-11%), headache (5-14%), diarrhea (9-16%), nausea (8-20%), vomiting (2-13%), flatulence (3-4%)</li> <li>→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]</li> <li>→Acute renal insufficiency, proximal renal tubulopathy (Fanconi syndrome) (&lt;1%): increased risk with concomitant nephrotoxic medications [9-13] (e.g. NSAIDS, especially oral diclofenac [14]) and/or cobicistat or ritonavir [7]</li> <li>→Decreased bone mineral density (28% incidence after 1 to 2 years of use, then stable)</li> <li>→Increased risk of osteoporotic fractures (&lt;1% per year) [7,15,16]</li> <li>→Osteomalacia (&lt;1%)</li> <li>→Severe acute exacerbation of hepatitis may occur in HBV-co-infected patients who discontinue TDF</li> </ul>	<p>We strongly recommend <u>against</u> prescribing tenofovir DF for individuals with established CKD (eGFR &lt;60 mL/min) or at high risk of CKD (A-I).</p> <p>We strongly recommend <u>against</u> prescribing tenofovir DF for individuals with established osteoporosis or at high risk for osteoporosis (e.g. post-menopausal individuals) (A-I).</p>
<p>Zidovudine (AZT, ZDV)</p>	<ul style="list-style-type: none"> <li>→Headache (63%)</li> <li>→Malaise (53%), asthenia (9%), fatigue (≥5%)</li> <li>→Nausea and vomiting (17%)</li> <li>→Lipoatrophy (10-20% with long-term use)</li> <li>→Insomnia (5%)</li> <li>→Myopathy and myositis (5%)</li> <li>→Bone marrow suppression: macrocytic anemia, neutropenia</li> <li>→Rash, nail pigmentation</li> <li>→Lactic acidosis/severe hepatomegaly with hepatic steatosis (rare [&lt;1%] but potentially life-threatening), increased risk in obese individuals and women</li> </ul>	<p>We recommend <u>against</u> the use of zidovudine for ART when other options are available (A-II).</p>

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

INSTI	ADVERSE DRUG REACTIONS	RECOMMENDATIONS
All (class effect)	<p>Generally safe and well-tolerated, especially unboosted INSTIs</p> <ul style="list-style-type: none"> <li>→Insomnia, sleep disturbances, abnormal dreams: More frequent with DTG (<math>\leq 7\%</math>) than with RAL or EVG/c (2-4%) [17-19]. Frequency with BIC similar to DTG [20].</li> <li>→Headache (<math>\leq 2-7\%</math>)</li> <li>→Possible increases in body weight, especially among older patients (<math>\geq 60</math> years), black races, and women [21,22]</li> </ul>	
Bictegravir (BIC)	<ul style="list-style-type: none"> <li>→Nausea (3-5%), diarrhea (3-6%)</li> <li>→Rash (<math>&lt; 2\%</math>)</li> <li>→Increased serum creatinine (inhibits creatinine secretion without reducing renal glomerular function)<sup>a</sup></li> </ul>	<p>We recommend <u>against</u> the use of BIC in a person who is pregnant due to insufficient safety data (A-III).</p>
Dolutegravir (DTG)	<ul style="list-style-type: none"> <li>→Hyperglycemia (<math>\leq 14\%</math>)</li> <li>→Hepatotoxicity: increased ALT (<math>\leq 18\%</math>), increased AST (<math>\leq 8\%</math>), hyperbilirubinemia (<math>\leq 3\%</math>), hepatitis (<math>&lt; 2\%</math>)</li> <li>→CPK elevation (1-7%), myalgia (<math>&lt; 1\%</math>), myositis (<math>&lt; 2\%</math>), rhabdomyolysis (rare)</li> <li>→Depression (<math>\leq 1\%</math>) and suicidal ideation (<math>&lt; 2\%</math>) (usually in patients with pre-existing psychiatric conditions)</li> <li>→Hypersensitivity reactions (<math>\leq 1\%</math>), including rash, constitutional symptoms, and organ dysfunction (including liver injury)</li> <li>→Increased serum creatinine (inhibits creatinine secretion without reducing renal glomerular function)<sup>b</sup></li> </ul>	<p>If DTG is dosed once daily, we suggest it be taken in the morning to reduce insomnia and sleep disturbances (C-III).</p> <p>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).</p> <p style="text-align: right;"><i>Continued next page</i></p> <p>Decreases in eGFR <math>&gt; 25\%</math> 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</p>

<sup>a</sup> 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].

<sup>b</sup> 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
Elvitegravir/ cobicistat (EVG/c)	<ul style="list-style-type: none"> <li>→Nausea (4-16%), diarrhea (12%)</li> <li>→Dyslipidemia: ↑ LDL cholesterol (Grade 3-4: 11%)</li> <li>→Fatigue (4-5%), malaise (4-5%)</li> <li>→Rash (4%)</li> <li>→Depression and suicidal ideation (&lt;1%; usually in patients with pre-existing psychiatric conditions)</li> <li>→Increased serum creatinine (inhibits creatinine secretion without reducing renal glomerular function)<sup>b</sup></li> </ul>	<p>impairment (A-II).</p> <p>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 &gt;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).</p> <p>We recommend <u>against</u> the use of cobicistat in pregnancy.</p>
Raltegravir (RAL)	<ul style="list-style-type: none"> <li>→Nausea (≤3%), diarrhea (2%)</li> <li>→CPK elevation (1-4%), muscle weakness (&lt;2%), myopathy, myositis, rhabdomyolysis (&lt;1%)</li> <li>→Depression and suicidal ideation (rare [&lt;2%]; usually in patients with pre-existing psychiatric conditions)</li> <li>→Rash, including Stevens-Johnson syndrome, HSR, and toxic epidermal necrolysis (&lt;1%)</li> <li>→Lipohypertrophy (increased trunk fat; causal relationship not established)</li> </ul>	

<sup>d</sup> 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)	<ul style="list-style-type: none"> <li>→GI intolerance (diarrhea, nausea, vomiting): LPV/r (<math>\leq 28\%</math>), NFV (<math>\leq 20\%</math>), TPV/r (<math>\leq 15\%</math>), DRV/c (<math>\leq 14\%</math>), DRV/r (<math>\leq 14\%</math>), ATV/r (<math>\leq 14\%</math>), FPV/r (<math>\leq 13\%</math>), SQV/r (<math>\leq 11\%</math>)</li> <li>→↑ LDL cholesterol and triglycerides (especially ritonavir- or cobicistat-boosted PIs): TPV/r (22-61%) &gt; other PIs (1-14%)</li> <li>→Hyperglycemia (2-11%)</li> <li>→Serum transaminase elevations: TPV/r 26-32% &gt; other PIs (1-9%)</li> <li>→Hepatotoxicity, drug-induced clinical hepatitis and hepatic decompensation: most frequent with TPV/r; rare with other PIs (&lt;1%)</li> <li>→Lipohypertrophy (increased trunk fat): causal relationship not established</li> <li>→Possible increase in the frequency of bleeding episodes (spontaneous bleeding, hematuria) in patients with hemophilia</li> </ul>	
Atazanavir (ATV), atazanavir/ritonavir (ATV/r)	<ul style="list-style-type: none"> <li>→Indirect hyperbilirubinemia (Grade 3-4: 35-49%), jaundice (5-9%), scleral icterus.</li> <li>→Crystalluria; nephrolithiasis (7.3-23.7 per 1000 person-years) [25,26]; high rate of recurrent stones (33%) if ATV is continued [27].</li> <li>→PR interval prolongation; first degree symptomatic AV block (6%); second degree AV block (&lt;1%).</li> <li>→Skin rash (3-21%)</li> <li>→Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis (&lt;1%)</li> <li>→Cholelithiasis (&gt;1 year of exposure) (&lt;1%).</li> <li>→Acute and chronic interstitial nephritis (&lt;1%)</li> <li>→Increased risk of chronic kidney disease (20% increased risk per year of exposure) [11].</li> </ul>	<p>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).</p>



PI	Adverse Drug Reactions	Recommendations
<p>Darunavir/cobicistat (DRV/c), darunavir/ritonavir (DRV/r)</p>	<ul style="list-style-type: none"> <li>→Skin rash (10%): DRV has a sulfonamide moiety.</li> <li>→Headache (3-9%)</li> <li>→Stevens-Johnson syndrome, toxic epidermal necrolysis, acute generalized exanthematous pustulosis, and erythema multiforme (&lt;1%).</li> <li>→Possible modestly increased risk of cardiovascular events (1.59x per 5 years additional use) [27]</li> <li>→Increase in serum creatinine (with cobicistat: inhibits creatinine secretion without reducing renal glomerular function)<sup>c</sup></li> </ul>	<p>DRV should be used with caution and appropriate monitoring in patients with a history of sulfonamide allergy (B-II).</p> <p>We strongly recommend discontinuing DRV in the presence of rash which is severe, persistent, extensive, or accompanied by systemic symptoms (A-I).</p> <p>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 &gt;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).</p> <p>We recommend <u>against</u> the use of cobicistat in pregnancy.</p>
<p>Fosamprenavir/ritonavir (FPV/r)</p>	<ul style="list-style-type: none"> <li>→Skin rash (12-19%): FPV has a sulfonamide moiety</li> <li>→Headache (2-4%)</li> <li>→Stevens-Johnson Syndrome/Toxic Epidermal Necrosis (&lt;1%)</li> <li>→Nephrolithiasis (&lt;1%)</li> <li>→Possible increased risk of myocardial infarction [28]</li> </ul>	<p>We recommend <u>against</u> the use of FPV/r for ART when other options are available. (A-II)</p> <p>FPV/r should be used with caution and appropriate monitoring in patients with a history of sulfonamide allergy (B-II).</p> <p>We strongly recommend discontinuing FPV/r in the presence of rash which is severe, persistent, extensive, or accompanied by systemic symptoms (A-I).</p>

<sup>c</sup> 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)	<ul style="list-style-type: none"> <li>→Fatigue, asthenia (8%)</li> <li>→Skin rash (&lt;5%)</li> <li>→Pancreatitis (&lt;1%)</li> <li>→Insulin resistance/diabetes mellitus (&lt;1%)</li> <li>→PR interval prolongation, second- or third-degree AV block (&lt;1%)</li> <li>→QTc interval prolongation, torsades de pointes (&lt;1%)</li> <li>→Stevens-Johnson Syndrome/Toxic Epidermal Necrosis (&lt;1%)</li> <li>→Possible increased risk of myocardial infarction [2,28]</li> <li>→Possible increased risk of chronic kidney disease (11% increased risk per year of exposure) [11]</li> </ul>	<p>We recommend <b>against</b> the use of LPV/r for ART when other options are available. (A-II)</p> <p>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<sup>d</sup>. (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 &gt;450 msec (B-II).</p>
Nelfinavir (NFV)	<ul style="list-style-type: none"> <li>→Diarrhea (14-20%)</li> </ul>	<p>We recommend <b>against</b> the use of NFV for ART when other options are available (A-II).</p>
Saquinavir/ ritonavir (SQV/r)	<ul style="list-style-type: none"> <li>→Headache (6%)</li> <li>→PR interval prolongation, second or third degree AV block (&lt;1%)</li> <li>→QT interval prolongation, torsades de pointes (&lt;1%)</li> </ul>	<p>We recommend <b>against</b> the use of SQV/r for ART when other options are available. (A-II)</p> <p>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<sup>6</sup> (B-II).</p> <p>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 &gt;450 msec (B-II).</p>

<sup>d</sup> Updated list of QT prolonging drugs available at: <https://crediblemeds.org/>



PI	Adverse Drug Reactions	Recommendations
Tipranavir/ ritonavir (TPV/r)	<p>→Skin rash (3-10%): TPV has a sulfonamide moiety</p> <p>→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.</p>	<p>We recommend <u>against</u> the use of TPV/r for ART when other options are available. (A-II)</p> <p>TPV/r should be used with caution and appropriate monitoring in patients with a history of sulfonamide allergy (B-II).</p> <p>We strongly recommend discontinuing TPV/r in the presence of rash which is severe, persistent, extensive, or accompanied by systemic symptoms (A-I).</p> <p>We strongly recommend <u>against</u> the use TPV/r in patients with hepatic insufficiency (Child Pugh class B or C) (A-I).</p>

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

NNRTI	ADVERSE DRUG REACTIONS	RECOMMENDATIONS
All (class effect)	<ul style="list-style-type: none"> <li>→Rash: NVP (16%) &gt; EFV (8-10%) &gt; ETR (2%), RPV [31-34] (1-2%), DOR (1-2%)</li> <li>→Severe rash: Stevens-Johnson syndrome/Toxic Epidermal Necrolysis: NVP (6.5%)&gt;&gt; EFV (&lt;1%) &gt; DOR, ETR, RPV (rare, &lt;1%) [29]</li> </ul>	
Doravirine (DOR) [30]	<ul style="list-style-type: none"> <li>→Nausea (6-7%), diarrhea (4-5%)</li> <li>→Fatigue (6%), headache (6%)</li> <li>→Dizziness (3-5%), abnormal dreams (1-3%)</li> </ul>	We recommend <u>against</u> the use of DOR in a person who is pregnant, because of insufficient safety data (A-III).
Efavirenz (EFV) [31]	<ul style="list-style-type: none"> <li>→Neuropsychiatric symptoms (~50%): Sleep disturbances, somnolence, insomnia, abnormal dreams, dizziness, depression, anxiety, confusion, abnormal thinking, impaired concentration, amnesia, agitation, depersonalization, hallucinations, euphoria</li> <li>→Dyslipidemia: ↑ triglycerides (6-11%), ↑ LDL cholesterol (20-40%), ↑ HDL cholesterol (25-35%)</li> <li>→Suicidality (4%): suicide, suicide attempt or ideation</li> <li>→Increased transaminase levels (2-8%)</li> <li>→QT<sub>c</sub> interval prolongation (&lt;1%)</li> <li>→Fulminant hepatitis leading to death or hepatic failure requiring transplantation (&lt;1%)</li> <li>→Lipohypertrophy (trunk fat increase); causal relationship not established.</li> <li>→Teratogenicity: Fetal neural tube defects in primates</li> </ul>	<p>We suggest EFV be taken on an empty stomach, preferably at bedtime, to reduce side effects (C-III).</p> <p>We recommend <u>against</u> using EFV in patients with hepatic insufficiency (Child-Pugh class B or C) (A-II).</p> <p>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<sup>ε</sup>. (B-II)</p> <p>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 &gt;450 msec (B-II).</p> <p>We <u>do not</u> suggest using EFV in a person of child-bearing potential, particularly during the first trimester of pregnancy (C-III).</p>
Etravirine (ETR) [32]	<ul style="list-style-type: none"> <li>→HSRs (&lt;2%), characterized by rash, constitutional findings, and sometimes organ dysfunction, including hepatic failure</li> </ul>	

<sup>ε</sup> Updated list of QT prolonging drugs available at: <https://crediblemeds.org/>

NNRTI	ADVERSE DRUG REACTIONS	RECOMMENDATIONS
Nevirapine (NVP)	<p>→Severe hepatotoxicity associated with skin rash or hypersensitivity (&lt;1%); symptomatic hepatitis, including fatal hepatic necrosis (&lt;1%); significantly higher frequency in ARV-naive women with pre-NVP CD4 cell counts &gt;250 cells/μL and in ARV-naive men with pre-NVP CD4 cell counts &gt;400 cells/μL.</p>	<p>We strongly recommend <b>against</b> using NVP in patients with moderate to severe hepatic impairment (Child-Pugh class B or C) (A-I). We strongly recommend <b>against</b> using NVP in ARV-naive women with pre-NVP CD4 cell counts &gt;250 cells/μL and in ARV-naive men with pre-NVP CD4 cell counts &gt;400 cells/μL (A-I) and new starts in pregnancy regardless of CD4 cell count [33].</p>
Rilpivirine (RPV)	<p>→Depression (5-9%), headache (3%), insomnia (3%), abnormal dreams (2%), dizziness (1%)  →Increased liver transaminases (1-18%)  →Hepatitis (&lt;1%)  →Suicidality (&lt;1%)  →QTc interval prolongation (&lt;1%)  →Increase in serum creatinine (inhibits creatinine secretion without reducing renal glomerular function)</p>	<p>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<sup>f</sup> (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 &gt;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 &gt;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).</p>

<sup>f</sup> 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]	<ul style="list-style-type: none"> <li>→Local injection site reactions (98%): pain, erythema, induration, nodules and cysts, pruritus, ecchymosis</li> <li>→HSR (&lt;1%): Symptoms may include rash, fever, nausea, vomiting, chills, rigors, hypotension, or elevated serum transaminases.</li> <li>→Increased incidence of bacterial pneumonia</li> </ul>	
CCR5 antagonist: Maraviroc (MVC)	<ul style="list-style-type: none"> <li>→Generally safe and well-tolerated</li> <li>→Upper respiratory tract infections (23-32%)</li> <li>→Cough (14%)</li> <li>→Fever (13%)</li> <li>→Rash (11%)</li> <li>→Abdominal distention or bloating (<math>\leq 10\%</math>)</li> <li>→Dizziness (9%)</li> <li>→Arthropathy (6-7%), myalgia (3%)</li> <li>→Hepatotoxicity, with or without severe rash or HSR (&lt;1%)</li> <li>→Orthostatic hypotension, especially in patients with severe renal insufficiency</li> </ul>	



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