# Optimizing Antiretroviral Therapy in the Setting of Viral Suppression

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Key Considerations and Recommendations		
•	Advances in antiretroviral (ARV) treatment and a better understanding of HIV drug resistance have made it possible to consider switching a person with HIV from an effective ARV regimen to an alternative ARV regimen in some situations.	
•	The fundamental principle of ARV regimen optimization is to maintain viral suppression without jeopardizing future treatment options.	
•	Adverse events, drug–drug or drug–food interactions, pill burden, pregnancy, cost, or the desire to simplify a regimen may prompt regimen optimization.	
•	It is critical to review a patient's full ARV history, including virologic responses, past ARV-associated toxicities and intolerances, and cumulative resistance test results before selecting a new ARV regimen (AI).	
•	People with HIV who have no history of drug-resistance mutations or virologic failure can likely switch to any regimen that has been shown to be highly effective in ARV-naive patients (AI).	
•	For regimen optimization in the setting of existing nucleoside reverse transcriptase inhibitor (NRTI) resistance, two NRTIs—tenofovir alafenamide or tenofovir disoproxil fumarate plus emtricitabine (FTC) or lamivudine (3TC)—should be included in the regimen with a fully active, high resistance barrier drug, such as dolutegravir, boosted-darunavir <b>(BIII)</b> , or bictegravir <b>(CIII)</b> .	
•	A long-acting ARV regimen of injectable cabotegravir (CAB) and rilpivirine (RPV) given every 1 or <mark>2 months</mark> is an optimization option for patients who are engaged with their health care, virologically suppressed on oral therapy for 3 to 6 months, and who agree to make the frequent clinic visits needed to receive the injectable drugs <b>(AI)</b> .	
•	Pregnant persons who present to care on long-acting CAB and RPV should be switched to a <i>Preferred</i> or an Alternative three-drug ARV regimen recommended for use in pregnancy per the <u>Perinatal Guidelines</u> (AIII).	
•	Monotherapy with either a boosted protease inhibitor or an integrase strand transfer inhibitor has been associated with unacceptable rates of virologic failure and the development of resistance; therefore, monotherapy as a switch strategy is not recommended (AI).	
•	When switching an ARV regimen in a person with hepatitis B virus (HBV)/HIV coinfection, ARV drugs that are active against HBV should be continued <b>(AII)</b> or specific anti-HBV drugs should be initiated. Using 3TC or FTC as the only drug in a regimen with HBV activity is not recommended <b>(AII)</b> , because HBV resistance to these drugs can emerge. Discontinuation of HBV drugs may lead to reactivation of HBV, which may result in serious hepatocellular damage.	
•	Consultation with an HIV specialist is recommended when planning a regimen switch for a patient with a history of resistance to one or more drug classes (AIII).	
•	Close monitoring to assess tolerability, viral suppression, adherence, and safety is recommended during the first 3 months after a regimen switch (AIII).	
Rating of Recommendations: A = Strong; B = Moderate; C = Weak		
<b>Rating of Evidence:</b> I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion		

With currently available antiretroviral therapy (ART), most people with HIV can achieve and maintain HIV viral suppression. Furthermore, advances in antiretroviral (ARV) treatment and a better understanding of drug resistance have made it possible to consider switching a person with HIV from one effective regimen to another in some situations. When considering optimization—a switch in therapy to improve some aspect of therapy—clinicians must keep several key principles in mind to maintain viral suppression while addressing the concerns with the current regimen.

# Reasons to Consider Regimen Optimization in the Setting of Viral Suppression

- To simplify a regimen by reducing pill burden and/or dosing frequency
- To enhance tolerability and/or decrease short- or long-term toxicity (see <u>Adverse Effects of</u> <u>Antiretroviral Agents</u> and <u>Table 21</u> for a more in-depth discussion of possible toxicities)
- To prevent or mitigate drug-drug interactions (see <u>Drug-Drug Interactions</u>)
- To eliminate food or fluid requirements
- To switch to a long-acting injectable regimen to relieve pill fatigue or to decrease potential stigma or disclosure concerns associated with taking daily oral medications
- To allow optimal use of ART during pregnancy or when pregnancy is desired or may occur (see <u>Perinatal Guidelines</u>)
- To reduce costs (see <u>Cost Considerations and Antiretroviral Therapy</u>)

# General Principles of Regimen Optimization

#### **Maintain Viral Suppression**

The fundamental principle of ARV regimen optimization is to maintain viral suppression without jeopardizing future treatment options. If a regimen switch results in virologic failure with the emergence of new resistance mutations, the patient may require more complex and/or less tolerated regimens.

#### **Careful Review of Antiretroviral Treatment and Drug Resistance History Before Optimization**

The review of a patient's full ARV history, including virologic responses, cumulative resistance test results, and past ARV-associated intolerances, toxicities, and adverse reactions, is critical before any treatment switch (AI).

If a patient with pre-ART wild-type HIV achieves and maintains viral suppression after ART initiation, one can safely assume that no new drug-resistance mutations emerged while the patient was on the suppressive regimen. In patients with a history of virologic failure or pre-treatment drug resistance, a review of cumulative resistance test results and clinical and virologic response to prior regimens is essential when designing a new regimen. Cumulative resistance test results refer to all previous and currently available results from standard genotype, proviral DNA genotype (if available), phenotype, and tropism assays that can be used to guide the selection of a new regimen. Once selected, a drug-resistance mutation—even when it is not detected in the patient's most recent drug-resistance test—can be archived in the HIV reservoir and reemerge under the appropriate selective drug pressure. Resistance often can be inferred from a patient's ARV history. For patients with documented failure on a regimen that includes drugs with relatively low barriers to resistance—such as a non-nucleoside reverse transcriptase inhibitor (NNRTI), elvitegravir (EVG), raltegravir (RAL), lamivudine (3TC), or emtricitabine (FTC)—a clinician should assume that there is resistance to these drugs, so-called inferred resistance. When uncertain about prior resistance, it is generally not

advisable to switch from a suppressive ARV regimen, unless the new regimen is likely to be at least as active against potential resistant virus as the current suppressive regimen. This principle is particularly applicable when switching ARV-experienced individuals from a regimen with a relatively high barrier to resistance—such as those that include pharmacologically-boosted protease inhibitors (PIs), dolutegravir (DTG), or bictegravir (BIC)—to one with a lower barrier to resistance.<sup>1</sup> The Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel) recommends that clinicians consult an HIV specialist when contemplating optimization for a patient with a history of resistance to one or more drug classes (**AIII**).

If optimization is considered in patients with suppressed viral loads who do not have prior drug resistance data, proviral DNA genotypic resistance testing can be considered. For patients who have no prior virologic failures and who are on their first or second regimen, or for those who have genotypic test results from prior virologic failures, the use of the proviral DNA genotypic test is unlikely to provide valuable information. In individuals with a history of multiple prior failures or multiple prior ARV regimens, the use of proviral DNA genotypic testing may be useful. However, whenever proviral DNA genotypic testing is used, the results must be interpreted with caution because these assays may not detect all of a patient's drug-resistance mutations, especially those that were selected by a previous ARV regimen.<sup>2</sup> In addition, these assays may identify mutations that appear inconsistent with a patient's response to treatment, making the clinical relevance of the assay results questionable. Overall, the clinical utility of these assays remains an area of active investigation (see <u>Drug-Resistance Testing</u>).

#### Optimization in a Person with Active Hepatitis B Virus Coinfection

When switching an ARV regimen in a patient with active hepatitis B virus (HBV)/HIV coinfection (HBsAg positive), tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF) should be continued as part of the new regimen, unless another first-line HBV antiviral (e.g., entecavir) is initiated. Refer to the <u>Hepatitis B Virus/HIV Coinfection</u> section for specific recommendations. Both TDF and TAF are active against HBV and can be used as HBV monotherapy.<sup>3</sup> Discontinuation of HBV antivirals may lead to reactivation of HBV, which can result in serious hepatocellular damage. In people with HBV/HIV coinfection, using 3TC or FTC as the only drug in a regimen with HBV activity **is not recommended (AII)**, because HBV resistance to these drugs is likely to emerge. In patients with no documented history of or with no immunity to HBV infection, repeat HBV serology and re-vaccination should be completed if needed before optimization with a regimen that is not active against HBV.

#### **Assessment for Potential Drug Interactions**

Before switching a regimen, it is important to review each ARV drug in the new regimen and concomitant medications to assess whether any potential drug–drug interaction exists. For example, oral rilpivirine (RPV) and atazanavir interact with acid-lowering agents, and many ARV drugs may interact with rifamycin antibiotics (see <u>Drug–Drug Interactions</u>). In addition to new drug interactions, the discontinuation of some ARV drugs also may necessitate adjusting the dosage of concomitant medications. For example, discontinuation of pharmacokinetic (PK) boosters (ritonavir or cobicistat) may reduce the concentrations of some concomitant medications. Concomitant medications, which may have been previously managed with dose adjustments, will need to be reevaluated in the context of the new ARV regimen.

## Assessment for Pregnancy or Pregnancy Potential

People of childbearing potential should have a pregnancy test before switching ART. If a person with HIV is found to be pregnant or desires pregnancy, clinicians should refer to the <u>Perinatal Guidelines</u> for recommendations on the safety and efficacy of ARV use at the time of conception or during pregnancy. Recent controversies, based on observational data, about the use of integrase strand transfer inhibitors (INSTIs) pre-conception or during pregnancy are discussed further in the <u>Perinatal Guidelines</u>. All pregnancies that occur while an individual is receiving ART should be reported to the <u>Antiretroviral Pregnancy Registry</u>.

## **Monitoring After Switching Antiretroviral Therapy**

After a treatment switch, patients should be evaluated closely for 3 months (e.g., a clinic visit or telephone call 1 to 2 weeks after the change and a viral load test to check for rebound viremia 4 to 8 weeks after the switch) (**AIII**). The purpose of this close monitoring is to assess medication tolerance and to conduct targeted laboratory testing if the patient has preexisting laboratory abnormalities or if there are potential concerns with the new regimen. For example, if lipid abnormality is a reason for the ARV change or is a concern with the new regimen, fasting cholesterol subsets and triglycerides should be assessed within 3 months after the change in therapy. In the absence of any new complaints, laboratory abnormalities, or evidence of viral rebound at this 3-month visit, clinical and laboratory monitoring of the patient may resume on a regularly scheduled basis (see Laboratory Testing for Initial Assessment and Monitoring).

# Specific Regimen Optimization Considerations

As with ART-naive patients, the use of a two- or three-drug combination regimen (as discussed below) is generally recommended when switching patients with suppressed viral loads (AI). Patients who have no history of resistance mutations or virologic failure can likely switch to any regimen that has been shown to be highly effective in ART-naive patients (AI). Patients with prior drug resistance can be switched to a new regimen based on their ARV history and cumulative resistance testing results. Monotherapy with either a boosted PI or an INSTI has been explored in several trials or cohort studies. Monotherapy has been associated with a higher rate of virologic failure than combination regimens and has been associated with the development of resistance, especially INSTI monotherapy; therefore, monotherapy as an optimization strategy is *not recommended* (AI).

# Optimization Strategies with Good Supporting Evidence for People Without Known Drug Resistance

Many clinical trials have enrolled participants with stable, suppressed viral loads without known underlying drug resistance and switched them to another regimen. Most of these studies demonstrated maintenance of viral suppression; some of these studies are referenced below. However, some regimen switches have had limited success in clinical trials but have informed optimization strategies. The SWITCHMRK 1 and 2 studies illustrated the importance of considering the possibility of underlying drug resistance before switching therapy in those with virologic suppression.<sup>1</sup> This is particularly important when the new regimen may not include three fully active agents and when the new regimen may have a lower overall barrier to resistance. In the two SWITCHMRK studies, those with viral suppression on two nucleoside reverse transcriptase inhibitors (NRTIs) plus lopinavir/ritonavir (LPV/r) were switched to two NRTIs plus RAL. The studies showed that individuals with a history of previous virologic failure had an increased risk of

virologic failure when switching to the RAL-based regimen. A possible explanation for this finding is that when only one of the accompanying NRTIs is fully active, viral suppression can be maintained by drugs with relatively high barriers to resistance, such as boosted PIs, DTG, and BIC, but not by those with lower barriers to resistance, such as EVG, RAL, and NNRTIs. The strategies listed below support these observations and principles of optimizing therapy.

# Three-Drug Regimens

## Within-Class Switches

Within-class switches may be prompted by adverse events or the availability of ARVs in the same class that offer a better safety profile, reduced dosing frequency, higher barrier to resistance, or lower pill burden or do not require PK boosting. Within-class switches usually maintain viral suppression, provided there is no drug resistance to the new ARV. Examples of within-class switch strategies that have been studied in individuals without underlying drug resistance include the following:

- From TDF<sup>4,5</sup> or abacavir (ABC)<sup>6</sup> to TAF
- From RAL to DTG
- From DTG,<sup>7-9</sup> elvitegravir/cobicistat (EVG/c),<sup>10</sup> or RAL to BIC
- From efavirenz to RPV<sup>5,11</sup> or doravirine (DOR)<sup>12</sup>

## **Between-Class Switches**

Between-class switches generally maintain viral suppression, provided there is no resistance to the other components of the regimen. In general, such switches should be avoided if any doubt exists about the activity of the other agents in the regimen. As noted earlier, prior resistance test results will be very informative in guiding this switch. The following are between-class switches that have been studied:

- Replacing a boosted PI with an INSTI (e.g., DTG,<sup>13</sup> BIC<sup>14</sup> or EVG<sup>15,16</sup>)
- Replacing a boosted PI with RPV<sup>17</sup> or DOR<sup>12</sup>
- Replacing an NNRTI with an INSTI<sup>18,19</sup>

# Two-Drug Regimens

Growing evidence indicates that some two-drug regimens are effective in maintaining virologic control in patients who initiated therapy and achieved sustained virologic suppression for at least 3 to 6 months with three-drug regimens, provided their HIV is susceptible to both ARV drugs in the new regimen. However, because none of the two-drug regimens discussed below meet the standard of care for HBV treatment, these regimens are not recommended for individuals with HBV coinfection, unless the patient is also on a specific anti-HBV active regimen (e.g., entecavir) (AIII). Also see the section above on HBV considerations during optimization. The following are examples of successful strategies for switching from three- to two-drug regimens in people with suppressed HIV.

## **Dolutegravir plus Rilpivirine**

Two Phase 3 trials, SWORD-1 and SWORD-2, demonstrated noninferior efficacy of DTG with RPV compared to continuing a first or second ARV regimen in individuals with suppressed HIV-RNA and without prior virologic failure, active Hepatitis B (unless the patient is also on a specific HBV active regimen), resistance to DTG or RPV, or significant drug interactions (**AI**).

## Dolutegravir plus Lamivudine or Emtricitabine

A switch from a stable three-drug ARV regimen to DTG plus 3TC or FTC as a maintenance strategy in patients with ongoing virologic suppression and no history of prior virologic failure or resistance to these agents was noninferior to continuing a three-drug therapy in a large randomized clinical trial (TANGO),<sup>20</sup> in smaller clinical trials,<sup>21-23</sup> and in observational studies<sup>24-26</sup> (**AI**). Individuals with active Hepatitis B infection need to be on a specific HBV active regimen, because 3TC or FTC monotherapy is not considered standard of care for HBV therapy.<sup>3</sup>

## **Boosted Protease Inhibitor plus Lamivudine**

A boosted PI plus 3TC is a reasonable two-drug optimization option in individuals without resistance who are suppressed on a current regimen and who do not have active HBV infection. Pill burden and potential drug interactions are limitations compared to the above two-drug regimens. Several boosted PI plus 3TC regimens have been shown to be effective in clinical trials, including darunavir/ritonavir (DRV/r) (**BI**)<sup>27</sup> or darunavir/cobicistat (DRV/c) (**BIII**), atazanavir/ritonavir (ATV/r) (**CI**),<sup>28,29</sup> and LPV/r (**CI**).<sup>30</sup>

## **Boosted Darunavir plus Dolutegravir**

An open-label, Phase 3b, noninferiority clinical trial evaluated continuation of DRV/r plus two NRTIs versus a switch to DRV/r plus DTG; the switched regimen was noninferior.<sup>31</sup> Because of the small sample size of this study, the regimen of DRV/r plus DTG is recommended only in the absence of other alternative options, but can be considered in particular for individuals with resistance and/or intolerance to 3TC (or FTC), ABC, and TDF (or TAF) (**CI**). Similar results were observed in two small observational studies.<sup>32,33</sup> This regimen is not suitable for individuals with active HBV infection, unless the patient is also on a specific HBV active regimen (e.g., entecavir).

# Long-Acting Antiretroviral Therapy

Parenteral ARV medications with innate or enhanced long half-lives (by extended-release formulation) have been evaluated for use with less than daily dosing. Here, "long-acting" is defined as any medication that is dosed once weekly or less frequently. In 2018, in the United States, the first long-acting ARV medication—ibalizumab, an anti-CD4 monoclonal antibody, given intravenously every 2 weeks—was approved for use in combination with optimized background therapy in heavily treatment-experienced patients (see <u>Virologic Failure</u>). In January 2021, long-acting injectable formulations of the INSTI cabotegravir (CAB) and the NNRTI RPV were approved by the U.S. Food and Drug Administration (FDA). Multiple other long-acting ARV medications and/or drug delivery systems are being studied.<sup>34</sup>

Long-acting ARV medications provide the convenience of reduced dosing frequency and may improve quality of life for individuals with pill fatigue or concerns about disclosure of HIV status or stigma associated with daily oral medication. To date, ARV-experienced populations enrolled in completed clinical trials were selected based on their history of good adherence to their prescribed oral ART and were engaged in care as documented by a sustained undetectable viral load for at least **3** to 6 months at baseline. Thus, these therapies are recommended for similar populations that are consistently engaged in care. Concern exists that individuals who are less adherent to their medical care may miss doses or discontinue therapy, which can lead to an increased risk of virologic failure with resistance development. The long PK tail of long-acting ARVs can lead to prolonged periods of low drug levels or to differential exposure to just one drug in a regimen. The Panel awaits data from ongoing clinical trials in patients with suboptimal adherence and poor viremic control to assess the safety and efficacy of long-acting regimens in these patients.<sup>35</sup>

#### Cabotegravir plus Rilpivirine

Long-acting injectable CAB plus RPV is indicated in individuals with sustained (e.g., 3 to 6 months) virologic suppression (HIV-1 RNA <50 copies/mL) on a stable ARV regimen, with no history of treatment failure, and with no known or suspected resistance to either CAB or RPV.<sup>36</sup> CAB is an INSTI and a structural analogue of DTG. RPV is an NNRTI first approved in an oral tablet formulation in 2011. A tablet formulation of CAB, available through the manufacturer but not in community pharmacies, was concurrently approved by the FDA to be used with RPV tablets as a 4-week oral lead-in therapy (dosing below, oral lead-in is not required) before initiation of the long-acting regimen and as oral bridging in the event of planned missed injections. This long-acting injectable combination can be given as once monthly or as an every 2-month therapy. Clinical trial data supporting these regimens are discussed below.

#### Clinical Trial Data

Two Phase 3 clinical trials (ATLAS and FLAIR), which enrolled almost 1,200 participants with HIV-1, evaluated once-monthly intramuscular (IM) injections of CAB combined with RPV.<sup>37,38</sup> Participants could not have prior resistance to INSTIs or NNRTIs (except the K103N mutation), previous virologic failure (ATLAS trial), or HBV infection that was active or occult. In ATLAS, participants were virally suppressed for at least 6 months on standard oral ART prior to randomization. In FLAIR, ARV-naive participants who achieved HIV viral suppression by 16 to 20 weeks on oral DTG/ABC/3TC were then randomized to long-acting injectable CAB and RPV once monthly versus continued oral therapy. Both studies used a 1-month oral lead-in of once-daily CAB 30 mg with RPV 25 mg taken with food. On the day of the last oral doses, injectable CAB 600 mg (3 mL) with injectable RPV 900 mg (3 mL) were administered via separate ventrogluteal IM injections. After the loading dose, separate ventrogluteal IM injections of CAB 400 mg (2 mL) with RPV 600 mg (2 mL) were administered monthly.

In the intention to treat exposed population, HIV RNA >50 copies/mL at Week 48 occurred in 11 participants (1.9%) in the IM long-acting arm and 10 participants (1.7%) in the oral therapy arm (combining data from both studies).<sup>39</sup> This demonstrated noninferiority of long-acting injectable CAB and RPV compared with continuing the oral three-drug standard of care. Virologic failure was rare; however, when it occurred, resistance to INSTIs, NNRTIs, or both was common. Week 96 results confirmed noninferiority of every 4-week long-acting injectable CAB and RPV compared with oral regimens.<sup>40</sup>

ATLAS-2M was an open-label, Phase 3b, noninferiority study of long-acting injectable CAB plus RPV administered IM every 8 weeks (CAB 600 mg plus RPV 900 mg) (n = 522) versus every 4 weeks (CAB 400 mg plus RPV 600 mg) (n = 523) to treatment-experienced adults with HIV-1. Thirty-seven percent of patients were rolled over from the ATLAS trial.<sup>41</sup> Other enrollees had undetectable HIV viral load for at least 6 months on a stable, oral ARV regimen. Every 8-week dosing in individuals naive to long-acting therapy consisted of a month-long oral lead-in (same as in the ATLAS and FLAIR trials above), followed by injections beginning on the last day of oral therapy, repeated 4 weeks later, then given every 8 weeks. All doses were CAB 600 mg (3 mL) plus RPV 900 mg (3 mL) administered IM in separate ventrogluteal sites. At 48 weeks, long-acting CAB plus RPV administered every 8 weeks was noninferior to the every 4-week dosing (HIV RNA ≥50 copies/mL; 2% vs. 1%).<sup>40</sup> These results were confirmed at 96 weeks. Safety was similar between the long-acting CAB plus RPV 8-week versus 4-week administration groups.<sup>42</sup> Resistance analyses are discussed below. The results of this study led to the approval of every 2-month IM dosing for long-acting injectable CAB 600 mg (3 mL) plus RPV 900 mg (3 mL) by the FDA in January 2022.

#### Adverse Events When Using Long-Acting Cabotegravir and Rilpivirine

Adverse events were more common in individuals receiving IM long-acting CAB and RPV in both the ATLAS and FLAIR trials compared to those continuing oral therapy. Injection site reactions (ISRs) were the most common adverse events and occurred in more than 80% of participants, at least once. ISRs were less common over time, occurring in about 10% to 30% of participants at each monthly IM injection timepoint after the first year. ISRs were generally mild to moderate, with 99% being Grade 1 or 2 and the median duration of symptoms being 3 days. Four percent of patients experienced at least one Grade 3 ISR; 1% discontinued long-acting injectable treatment because of an ISR. Hypersensitivity reactions, post-injection reactions, hepatotoxicity, and depressive disorders also have been reported.<sup>40,43</sup>

#### Panel's Recommendation

Data from the ATLAS, FLAIR, and ATLAS-2M trials support that separate monthly or every 2month ventrogluteal IM injections of CAB and RPV can be used to replace an existing oral ARV regimen in people with HIV with sustained viral suppression for 3 to 6 months (optimal duration is not defined) (**AI**). Criteria for use should include individuals who have good adherence and engagement in care, with no baseline resistance to either medication, no prior virologic failures; who do not have active or occult HBV infection (unless the patient also is receiving an HBV active regimen [e.g., entecavir]); who are not pregnant or planning on becoming pregnant; and who are not receiving medications with significant drug interactions with oral (during lead-in or bridging therapy) or injectable CAB or RPV. Oral lead-in therapy with CAB and RPV is optional and can be done based on provider–patient discussion. In the FLAIR Extension study, after 100 weeks in the oral standard of care ART arm, 232 participants switched to long-acting CAB with RPV with or without an oral lead-in per patient preference.<sup>43</sup> After 24 weeks, there were no differences in adverse events, tolerability, efficacy, or PKs between the direct-to-inject and oral lead-in extension arms.

## Practical Considerations When Using Long-Acting Injectable Cabotegravir and Rilpivirine

Practical considerations regarding the feasibility of monthly or every 2-month IM administration of CAB and RPV deserve attention. Because the currently approved formulations are recommended to be administered only by a health care provider, the potential exists for strain on clinical systems, pharmacies, and patients. A 23-gauge, 1<sup>1</sup>/<sub>2</sub>-inch IM needle is recommended for the injection and is provided in the product packaging. However, longer, 2-inch needles should be used in patients with body mass index >30 kg/m<sup>2</sup>. Ventrogluteal IM injections should be given on opposite sides when

possible, or at least 2 cm apart if given on the same side. Individuals with buttock implants or fillers may not be appropriate candidates because of concerns regarding drug absorption. Care should be taken to administer only into gluteal muscle, preferably ventrogluteal. Several drugs, particularly those interacting with cytochrome P450 3A or uridine diphosphate glucuronosyltransferase 1A1, are contraindicated with CAB and RPV (oral and/or IM) due to significant drug interactions, including certain anticonvulsants and rifamycins. For other specific storage, preparation, and administration details, please review the Drug-Drug Interaction Tables 24b and 24d.

#### Management of Missed Doses of Long-Acting Injectable Cabotegravir and Rilpivirine

Long-acting CAB and RPV have extended half-lives (6 to 12 weeks for CAB and 13 to 28 weeks for RPV), and detectable concentrations may be present for  $\geq$ 12 months after the last dose.<sup>36</sup> Individuals who miss doses or discontinue therapy without starting an oral regimen are at increased risk of virologic failure with development of drug resistance. Population PK modeling of delayed injections in the bimonthly dosing suggests that delays of over 1 week will lead to significantly reduced drug exposure. Patients should be fully informed of this risk. The prescribing information for IM CAB and RPV should be consulted for guidance on managing missed doses. Recommendations differ based on the dosing being utilized (monthly vs. every 2 months), as well as the timing of the missed doses. Oral-bridging therapy should be made available for planned missed doses. Unplanned missed doses (beyond the 7-day window) should prompt reevaluation of whether the person remains an appropriate candidate for injectable therapy. When stopping therapy, transition to a suppressive oral regimen should occur within 4 weeks of the last IM doses on monthly dosing and 8 weeks of the last IM doses for every 2-month dosing.

#### HIV Viral Load and Drug-Resistance Testing Monitoring

HIV viral load monitoring should be performed 4 to 8 weeks after a switch to long-acting CAB and RPV. HIV viral load also should be checked in patients with unplanned missed visits and delayed dosing of long-acting CAB and RPV. When viremia develops during long-acting therapy, resistance testing, including integrase resistance testing, should be performed. Follow-up dosing in patients with missed IM doses should not be delayed while waiting for viral load and resistance test results. In a pooled analysis from the FLAIR, ATLAS, and ATLAS-2M trials, confirmed virologic failure was more common in the setting of baseline, proviral, RPV resistance-associated mutations; HIV-1 subtype A6/A1 (rare in the United States); higher baseline body mass index; and lower Week-8 trough RPV concentration.<sup>44</sup>

In ATLAS-2M, in the every 8-week arm, of 11 participants with confirmed virologic failure at 152 weeks, six had baseline proviral DNA-resistance mutations to NNRTIs and one to INSTIs. The study suggested that baseline, proviral, RPV resistance-associated mutations had a greater impact on virologic failure and resistance in the every 8-week arm compared with the every 4-week arm. At virologic failure, 9 of 11 participants in the every 8-week arm had NNRTI resistance, and 7 of these 9 participants also had INSTI resistance. Two participants in the every 4-week arm had virologic failure, neither had baseline proviral DNA resistance; although both had dual-class resistance to NNRTIs and INSTIs at virologic failure.<sup>45</sup> In patients who develop resistance to CAB or RPV or both drugs, the regimen should be changed based on resistance test results (see <u>Virologic Failure</u>). Consultation with an expert in HIV drug resistance should be considered.

#### Pregnancy Considerations

Oral CAB and the long-acting injectable regimen of CAB and RPV have been classified as **not recommended** for use in pregnancy, because insufficient data exist for people who are trying to conceive or who become pregnant while on this regimen. Management of patients who become pregnant while on therapy will need close oversight. Because data about the use of CAB and RPV during pregnancy are extremely limited, the Panel recommends that pregnant individuals who present to care on this regimen should be switched to a *Preferred* or *Alternative* three-drug ARV regimen recommended for use in pregnancy per the <u>Perinatal Guidelines</u> (**AIII**). In clinical trials to date, most participants who became pregnant were switched from IM CAB and RPV to an alternative ARV regimen for the remainder of their pregnancies.<sup>46,47</sup> In 11 live births from individuals with HIV who conceived after receipt of CAB and RPV (1 oral, 10 IM dosing), one congenital anomaly of congenital ptosis in a preterm infant with intrauterine growth restriction occurred.<sup>47</sup> To date, in the small number of individuals who became pregnant during long-acting CAB and RPV dosing, plasma CAB and RPV concentrations have been in the range expected for non-pregnant people. Health care providers are strongly encouraged to register people who become pregnant while receiving IM CAB and RPV with the <u>Antiretroviral Pregnancy Registry</u>.

#### Other Considerations

CAB and RPV do not have HBV activity. Patients with active or occult HBV were excluded from all clinical trials of long-acting CAB and RPV to date. If CAB with RPV is used in patients with active or occult HBV, additional, specific treatment for HBV infection is needed (see <u>Hepatitis B</u> <u>Virus/HIV Coinfection</u>).

Many patients with HIV are on oral therapy for medical, preventive, or mental health comorbidities. Counseling will be needed to emphasize the importance of continued adherence to oral therapies for other indications.

# *Optimization Strategies for People with Viral Suppression and a History of Limited Drug Resistance*

Some existing data demonstrate the safety and efficacy of within-class switches for individuals with underlying drug resistance who are on a stable ARV regimen with suppressed HIV RNA (e.g., for 6 months or longer). However, data are limited regarding between-class switches in this population, and support for such a switch generally depends on findings extrapolated from non-optimization studies, as discussed below.

#### Within-Class Switch from Dolutegravir to Bictegravir (BI)

The GS 4030 study enrolled 565 individuals who were stably suppressed on DTG plus two NRTIs. The participants were randomized to either remain on their current regimen or switch to BIC/FTC/TAF. This is a switch from a high-barrier drug, DTG, to another high-barrier drug, BIC. After 48 weeks, the groups had similar rates of sustained suppression. The rates of viral suppression were similar for those with a documented history of NRTI resistance (approximately 25% of participants) and those without a history of NRTI resistance.<sup>48</sup> Results from this trial lend theoretical support to other optimization strategies that include a switch from one high-barrier drug to another in the setting of a similar NRTI backbone. This study also supports the recommendation that when

using drugs with a high barrier to resistance, only one of the NRTIs needs to be active. This is supported by other lines of evidence, some of which are discussed below.

#### Other Switches to Bictegravir in the Setting of Limited Drug Resistance

The BRAAVE study was an open-label, optimization study for Black people with HIV and viral suppression for  $\geq$ 12 months on a standard regimen of two NRTIs plus a third agent (INSTI, NNRTI, or PI). Individuals were randomized to switch to BIC/FTC/TAF or to remain on current therapy (although individuals on TDF were switched to TAF). Switching to BIC-based therapy was noninferior for maintaining viral suppression compared with continuing current oral therapy. Baseline regimens included 61% INSTI, 31% NNRTI, and 9% PI. Baseline resistance did not affect the outcomes of therapy. In particular, NRTI resistance was present in 14% of participants, and 10% harbored the M184V/I mutation.<sup>49</sup>

#### Data from Non-Optimization Studies Inform Optimization in Clinical Practice

Several studies of ART changes in the setting of first-line NNRTI-based virologic failure support the use of specific treatment combinations for optimization, as well as the fact that drugs with a high barrier to resistance need only one, or possibly no, fully active NRTIs paired with them. In the DAWNING study,<sup>50</sup> in individuals failing first-line NNRTI-based therapy, individuals with one active NRTI in their next regimen had similar virologic responses as those with two active NRTIs. Overall, viral suppression to <50 copies/mL at Week 48 was more common with DTG (84%) than LPV/r (73%). In the NADIA study, 464 participants with virologic failure on initial NNRTI-based therapy (NNRTI plus TDF and either 3TC or FTC) were randomized to either DTG or DRV/r, and within each arm randomized to either TDF/3TC or zidovudine (ZDV)/3TC. At enrollment, resistance to NRTIs was common with 86% of individuals having an M184V mutation and 50% having a K65R mutation. Dual-NRTI resistance was present in 172 (37%) individuals. At 48 weeks, DTG was noninferior to DRV/r with both achieving viral suppression to <400 copies/mL in about 90% of individuals. There were no differences in rates of viral suppression between individuals with resistance to one or both NRTIs in their regimens. At 96 weeks of follow-up, TDF was superior to ZDV, with 92% of those on TDF-based therapy and 85% of those on ZDV-based therapy achieving viral suppression to <400 copies/mL<sup>51</sup>

In both the DAWNING and NADIA trials described above, the presence of baseline NRTI resistance to one or both NRTIs used in the new regimen did not lower rates of viral suppression compared with individuals without NRTI resistance. Although these were studies of ART use in the setting of initial NNRTI-based virologic failure and not optimization in patients with viral suppression, regimens that are effective during viremia should be at least as effective in the setting of viral suppression in individuals with similar ARV resistance patterns (NRTI resistance, but no known or suspected PI or INSTI resistance). These studies support that for optimization in the setting of existing NRTI resistance, two NRTIs (TAF or TDF plus 3TC or FTC) should be included in the regimen with a fully active, high resistance barrier drug, such as DTG (**BIII**), a boosted DRV (**BIII**), or BIC (**CIII**). The use of no fully active NRTIs is not routinely recommended when there are other viable treatment options. However, in some clinical situations—such as when prior resistance testing is not fully available, to avoid major drug-drug interactions, to keep regimens simpler, or for other reasons—a regimen with a fully active, high resistance barrier drug combined with two partially active NRTIs can be considered. Both tenofovir and cytidine analogs may retain partial activity even when resistance is present. Future clinical trials of such regimens are necessary before this practice can be routinely recommended.

# Optimization Strategies for People with Viral Suppression and a History of Complex Underlying Resistance

Before optimization of the ARV regimen of a person with viral suppression who has a history of treatment failure and drug resistance, a careful review of the individual's ARV history and cumulative drug resistance profile should be undertaken. Consultation with a clinician with expertise in HIV drug resistance is recommended (AIII).

#### *Elvitegravir/Cobicistat/Tenofovir Alafenamide/Emtricitabine plus Darunavir*

Switching to the combination of EVG/c/TAF/FTC plus DRV has been shown to be a potential optimization strategy in patients on complicated salvage regimens.<sup>52</sup> A randomized controlled trial enrolled 135 patients with virologic suppression who were receiving DRV-containing ART and had resistance to at least two ARV drug classes, but no INSTI resistance. Participants had up to three thymidine analog resistance mutations and/or the K65R mutation but no history of either the Q151M mutation or T69 insertion. The participants were randomized 2:1 to either switch to a regimen of EVG/c/TAF/FTC plus DRV or remain on their current regimen. At 48 weeks, optimization to EVG/c/TAF/FTC plus DRV was superior to continuation on a current regimen, with 94.4% of participants in the switch arm and 76.1% in the continuation arm maintaining viral suppression. With regimen simplification, the pill burden was reduced from an average of five tablets per day to two tablets per day.<sup>52</sup> EVG/c/TAF/FTC plus DRV would be an appropriate option for individuals who have treatment and drug resistance histories similar to those of participants included in this study **(AI).** 

## **Optimization Strategies Not Recommended**

## **Boosted Protease Inhibitor Monotherapy**

The strategy of switching patients with virologic suppression without PI resistance from one ARV regimen to PI/r monotherapy has been evaluated in several studies. The rationale for this strategy is to avoid NRTI toxicities and to decrease costs while taking advantage of the high barrier to resistance of PIs. PI/r monotherapy maintains virologic suppression in most patients but at lower rates than regimens that include one or two NRTIs.<sup>53-55</sup> Low-level viremia, generally without the emergence of PI resistance, appears to be more common with monotherapy than with regimens that include one or two NRTIs in patients who are experiencing low-level viral rebound has led to re-suppression.<sup>56-59</sup> Clinical trials have not evaluated the use of coformulated cobicistat-boosted PI regimens as monotherapy or compared different PI/r monotherapy regimens. Based on the results from these studies, boosted-PI monotherapy **is not recommended (AI).** 

#### **Dolutegravir Monotherapy**

The strategy of switching patients with virologic suppression to DTG monotherapy has been evaluated in cohort studies, in clinical practice,<sup>60,61</sup> and in a randomized controlled trial.<sup>62</sup> This strategy has been associated with an unacceptable rate of virologic failure and subsequent development of INSTI resistance; therefore, a switch to DTG monotherapy **is not recommended** (AI).

#### **Boosted Atazanavir plus Raltegravir**

In a randomized study, patients with virologic suppression switched to a regimen consisting of ATV/r plus RAL or ATV/r plus TDF/FTC. The ATV/r plus RAL regimen switch was associated with higher rates of virologic failure and treatment discontinuation than the switch to ATV/r plus TDF/FTC.<sup>63</sup> A regimen consisting of ATV/r plus RAL **cannot currently be recommended (AI)**.

#### **Maraviroc plus Boosted Protease Inhibitor**

In a randomized controlled trial, patients with virologic suppression who were on a regimen of two NRTIs plus a boosted PI and who had only CCR5-tropic HIV (as detected by proviral DNA testing) were randomized to continue their current regimen or to switch to maraviroc (MVC) plus two NRTIs or to MVC plus a boosted PI. The boosted PI plus MVC regimen switch was associated with higher rates of virologic failure and treatment discontinuation than the other two regimens. Based on these results, a regimen consisting of a boosted PI and MVC **cannot be recommended (AI).**<sup>64</sup>

#### **Maraviroc plus Raltegravir**

In a nonrandomized pilot study, patients with virologic suppression were switched from their prescribed regimen to MVC plus RAL. This combination led to virologic relapse in 5 out of 44 patients.<sup>65</sup> Based on these study results, use of MVC plus RAL **is not recommended (AII).** 

# References

- 1. Eron JJ, Young B, Cooper DA, et al. Switch to a raltegravir-based regimen versus continuation of a lopinavir-ritonavir-based regimen in stable HIV-infected patients with suppressed viraemia (SWITCHMRK 1 and 2): two multicentre, double-blind, randomised controlled trials. *Lancet*. 2010;375(9712):396-407. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20074791.
- 2. Wirden M, Soulie C, Valantin MA, et al. Historical HIV-RNA resistance test results are more informative than proviral DNA genotyping in cases of suppressed or residual viraemia. *Journal of Antimicrobial Chemotherapy*. 2011;66(4):709-712. Available at: <u>https://academic.oup.com/jac/article/66/4/709/725741</u>.
- Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. *HEPATOLOGY*. 2018;67(4):1560-1599. Available at: https://aasldpubs.onlinelibrary.wiley.com/doi/10.1002/hep.29800.
- 4. Gallant JE, Daar ES, Raffi F, et al. Efficacy and safety of tenofovir alafenamide versus tenofovir disoproxil fumarate given as fixed-dose combinations containing emtricitabine as backbones for treatment of HIV-1 infection in virologically suppressed adults: a randomised, double-blind, active-controlled phase 3 trial. *Lancet HIV*. 2016;3(4):e158-165. Available at: <a href="http://www.ncbi.nlm.nih.gov/pubmed/27036991">http://www.ncbi.nlm.nih.gov/pubmed/27036991</a>.
- 5. Hagins D, Orkin C, Daar ES, et al. Switching to coformulated rilpivirine (RPV), emtricitabine (FTC) and tenofovir alafenamide from either RPV, FTC and tenofovir disoproxil fumarate (TDF) or efavirenz, FTC and TDF: 96-week results from two randomized clinical trials. *HIV Med*. 2018;19(10):724-733. Available at: <u>https://www.ncbi.nlm.nih.gov/pubmed/30101539</u>.
- Winston A, Post FA, DeJesus E, et al. Tenofovir alafenamide plus emtricitabine versus abacavir plus lamivudine for treatment of virologically suppressed HIV-1-infected adults: a randomised, double-blind, active-controlled, non-inferiority phase 3 trial. *Lancet HIV*. 2018;5(4):e162-e171. Available at: <u>https://www.ncbi.nlm.nih.gov/pubmed/29475804</u>.
- 7. Molina JM, Ward D, Brar I, et al. Switching to fixed-dose bictegravir, emtricitabine, and tenofovir alafenamide from dolutegravir plus abacavir and lamivudine in virologically suppressed adults with HIV-1: 48 week results of a randomised, double-blind, multicentre, active-controlled, phase 3, non-inferiority trial. *Lancet HIV*. 2018;5(7):e357-e365. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29925489.
- 8. Gilead Sciences. Biktarvy product label [package insert]. 2018. Available at: http://www.gilead.com/~/media/files/pdfs/medicines/hiv/biktarvy/biktarvy\_pi.pdf.
- 9. Sax PE, Rockstroh JK, Luetkemeyer AF, et al. Switching to bictegravir, emtricitabine, and tenofovir alafenamide in virologically suppressed adults with HIV. *Clin Infect Dis.* 2020. Available at: <u>https://www.ncbi.nlm.nih.gov/pubmed/32668455</u>.
- 10. Kityo C, Hagins D, Koenig E, et al. Switching to fixed-dose bictegravir, emtricitabine, and tenofovir alafenamide (B/F/TAF) in virologically suppressed HIV-1 infected women: a

randomized, open-label, multicenter, active-controlled, phase 3, noninferiority trial. *J Acquir Immune Defic Syndr*. 2019;82(3):321-328. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31609930.

- 11. Mills AM, Cohen C, Dejesus E, et al. Efficacy and safety 48 weeks after switching from efavirenz to rilpivirine using emtricitabine/tenofovir disoproxil fumarate-based single-tablet regimens. *HIV Clin Trials*. 2013;14(5):216-223. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24144898.
- 12. Johnson M, Kumar P, Molina JM, et al. Switching to doravirine/lamivudine/tenofovir disoproxil fumarate (DOF/3TC/TDF) maintains HIV-1 virologic suppression through 48 weeks: results of the DRIVE-SHIFT trial. *J Acquir Immune Defic Syndr*. 2019;81(4):463-472. Available at: <u>https://www.ncbi.nlm.nih.gov/pubmed/30985556</u>.
- 13. Gatell JM, Assoumou L, Moyle G, et al. Switching from a ritonavir-boosted protease inhibitor to a dolutegravir-based regimen for maintenance of HIV viral suppression in patients with high cardiovascular risk. *AIDS*. 2017;31(18):2503-2514. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29112070.
- 14. Daar ES, DeJesus E, Ruane P, et al. Efficacy and safety of switching to fixed-dose bictegravir, emtricitabine, and tenofovir alafenamide from boosted protease inhibitor-based regimens in virologically suppressed adults with HIV-1: 48 week results of a randomised, open-label, multicentre, phase 3, non-inferiority trial. *Lancet HIV*. 2018;5(7):e347-e356. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29925490.
- 15. Arribas JR, DeJesus E, van Lunzen J, et al. Simplification to single-tablet regimen of elvitegravir, cobicistat, emtricitabine, tenofovir DF from multi-tablet ritonavir-boosted protease inhibitor plus coformulated emtricitabine and tenofovir DF regimens: week 96 results of STRATEGY-PI. *HIV Clin Trials*. 2017;18(3):118-125. Available at: <a href="https://www.ncbi.nlm.nih.gov/pubmed/28555519">https://www.ncbi.nlm.nih.gov/pubmed/28555519</a>.
- 16. Hodder S, Squires K, Kityo C, et al. Brief report: Efficacy and safety of switching to coformulated elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide (E/C/F/TAF) in virologically suppressed women. *J Acquir Immune Defic Syndr.* 2018;78(2):209-213. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29481486.
- 17. Palella FJ, Jr., Fisher M, Tebas P, et al. Simplification to rilpivirine/emtricitabine/tenofovir disoproxil fumarate from ritonavir-boosted protease inhibitor antiretroviral therapy in a randomized trial of HIV-1 RNA-suppressed participants. *AIDS*. 2014;28(3):335-344. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24670520.
- 18. Pozniak A, Markowitz M, Mills A, et al. Switching to coformulated elvitegravir, cobicistat, emtricitabine, and tenofovir versus continuation of non-nucleoside reverse transcriptase inhibitor with emtricitabine and tenofovir in virologically suppressed adults with HIV (STRATEGY-NNRTI): 48 week results of a randomised, open-label, phase 3b non-inferiority trial. *Lancet Infect Dis.* 2014;14(7):590-599. Available at: <a href="http://www.ncbi.nlm.nih.gov/pubmed/24908550">http://www.ncbi.nlm.nih.gov/pubmed/24908550</a>.
- 19. Arribas JR, Pialoux G, Gathe J, et al. Simplification to coformulated elvitegravir, cobicistat, emtricitabine, and tenofovir versus continuation of ritonavir-boosted protease inhibitor with

emtricitabine and tenofovir in adults with virologically suppressed HIV (STRATEGY-PI): 48 week results of a randomised, open-label, phase 3b, non-inferiority trial. *Lancet Infect Dis*. 2014;14(7):581-589. Available at: <u>http://www.ncbi.nlm.nih.gov/pubmed/24908551</u>.

- 20. van Wyk J, Ajana F, Bisshop F, et al. Efficacy and safety of switching to dolutegravir/lamivudine fixed-dose 2-drug regimen vs continuing a tenofovir alafenamide-based 3- or 4-drug regimen for maintenance of virologic suppression in adults living with human immunodeficiency virus type 1: phase 3, randomized, noninferiority TANGO study. *Clin Infect Dis.* 2020;71(8):1920-1929. Available at: <a href="https://www.ncbi.nlm.nih.gov/pubmed/31905383">https://www.ncbi.nlm.nih.gov/pubmed/31905383</a>.
- 21. Taiwo BO, Marconi VC, Berzins B, et al. Dolutegravir plus lamivudine maintains human immunodeficiency virus-1 suppression through week 48 in a pilot randomized trial. *Clin Infect Dis.* 2018;66(11):1794-1797. Available at: <a href="https://www.ncbi.nlm.nih.gov/pubmed/29293895">https://www.ncbi.nlm.nih.gov/pubmed/29293895</a>.
- 22. Joly V, Burdet C, Landman R, et al. Dolutegravir and lamivudine maintenance therapy in HIV-1 virologically suppressed patients: results of the ANRS 167 trial (LAMIDOL). *J Antimicrob Chemother*. 2019;74(3):739-745. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30476165.
- 23. Llibre JM, Brites C, Cheng CY, et al. Efficacy and safety of switching to the 2-drug regimen dolutegravir/lamivudine versus continuing a 3- or 4-drug regimen for maintaining virologic suppression in adults living with HIV-1: week 48 results from the phase 3, non-inferiority SALSA randomized trial. *Clin Infect Dis.* 2022. Available at: https://pubmed.ncbi.nlm.nih.gov/35235656.
- 24. Maggiolo F, Gulminetti R, Pagnucco L, et al. Lamivudine/dolutegravir dual therapy in HIVinfected, virologically suppressed patients. *BMC Infect Dis*. 2017;17(1):215. Available at: <u>https://www.ncbi.nlm.nih.gov/pubmed/28302065</u>.
- 25. Borghetti A, Baldin G, Lombardi F, et al. Efficacy and tolerability of lamivudine plus dolutegravir as a switch strategy in a multicentre cohort of patients with suppressed HIV-1 replication. *HIV Med.* 2018. Available at: <u>https://www.ncbi.nlm.nih.gov/pubmed/29573320</u>.
- 26. Sculier D, Wandeler G, Yerly S, et al. Efficacy and safety of dolutegravir plus emtricitabine versus standard ART for the maintenance of HIV-1 suppression: 48-week results of the factorial, randomized, non-inferiority SIMPL'HIV trial. *PLoS Med.* 2020;17(11):e1003421. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33170863.
- 27. Pulido F, Ribera E, Lagarde M, et al. Dual therapy with darunavir and ritonavir plus lamivudine vs triple therapy with darunavir and ritonavir plus tenofovir disoproxil fumarate and emtricitabine or abacavir and lamivudine for maintenance of human immunodeficiency virus type 1 viral suppression: randomized, open-label, noninferiority DUAL-GESIDA 8014-RIS-EST45 trial. *Clin Infect Dis.* 2017;65(12):2112-2118. Available at: <a href="https://pubmed.ncbi.nlm.nih.gov/29020293">https://pubmed.ncbi.nlm.nih.gov/29020293</a>.
- 28. Perez-Molina JA, Rubio R, Rivero A, et al. Dual treatment with atazanavir-ritonavir plus lamivudine versus triple treatment with atazanavir-ritonavir plus two nucleos(t)ides in virologically stable patients with HIV-1 (SALT): 48 week results from a randomised, open-

label, non-inferiority trial. *Lancet Infect Dis*. 2015;15(7):775-784. Available at: <u>https://pubmed.ncbi.nlm.nih.gov/26062881</u>.

- 29. Fabbiani M, Gagliardini R, Ciccarelli N, et al. Atazanavir/ritonavir with lamivudine as maintenance therapy in virologically suppressed HIV-infected patients: 96 week outcomes of a randomized trial. *J Antimicrob Chemother*. 2018;73(7):1955-1964. Available at: <u>https://pubmed.ncbi.nlm.nih.gov/29668978/</u>
- 30. Arribas JR, Girard PM, Landman R, et al. Dual treatment with lopinavir-ritonavir plus lamivudine versus triple treatment with lopinavir-ritonavir plus lamivudine or emtricitabine and a second nucleos(t)ide reverse transcriptase inhibitor for maintenance of HIV-1 viral suppression (ole): a randomised, open-label, non-inferiority trial. *Lancet Infect Dis.* 2015;15(7):785-792. Available at: <a href="https://pubmed.ncbi.nlm.nih.gov/26062880">https://pubmed.ncbi.nlm.nih.gov/26062880</a>.
- 31. Spinner CD, Kümmerle T, Schneider J, et al. Efficacy and safety of switching to dolutegravir with boosted darunavir in virologically suppressed adults with HIV-1: a randomized, open-label, multicenter, phase 3, noninferiority trial: the DUALIS study. *Open Forum Infect Dis.* 2020;7(9):ofaa356. Available at: <u>https://pubmed.ncbi.nlm.nih.gov/32965277</u>.
- 32. Capetti AF, Cossu MV, Orofino G, et al. A dual regimen of ritonavir/darunavir plus dolutegravir for rescue or simplification of rescue therapy: 48 weeks' observational data. BMC Infect Dis. 2017;17(1):658. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28964268.
- 33. Wheeler J, Chan S, Harrigan PR, Becker M, Kasper K, Keynan Y. Dolutegravir with boosted darunavir treatment simplification for the transmitted HIV thymidine analog resistance in Manitoba, Canada. *Int J STD AIDS*. 2018;29(5):520-522. Available at: <a href="https://www.ncbi.nlm.nih.gov/pubmed/29513131">https://www.ncbi.nlm.nih.gov/pubmed/29513131</a>.
- 34. Flexner C, Owen A, Siccardi M, Swindells S. Long-acting drugs and formulations for the treatment and prevention of HIV infection. *Int J Antimicrob Agents*. 2021;57(1):106220. Available at: <u>https://www.ncbi.nlm.nih.gov/pubmed/33166693</u>.
- 35. Castillo-Mancilla J, Rana A. The LATITUDE study: long-acting therapy to improve treatment success in daily life. 2018. Available at: <a href="https://clinicaltrials.gov/ct2/show/NCT03635788">https://clinicaltrials.gov/ct2/show/NCT03635788</a>
- 36. The Food and Drug Administration. Cabenuva [package insert]. 2021. Available at: <u>https://gskpro.com/content/dam/global/hcpportal/en\_US/Prescribing\_Information/Cabenuva/</u> <u>pdf/CABENUVA-PI-PIL-IFU2-IFU3.PDF</u>.
- 37. Swindells S, Andrade-Villanueva JF, Richmond GJ, et al. Long-acting cabotegravir and rilpivirine for maintenance of HIV-1 suppression. *N Engl J Med*. 2020;382:1112-1123. Available at: https://www.nejm.org/doi/full/10.1056/NEJMoa1904398.
- 38. Orkin C, Arasteh K, Hernandez-Mora MG, et al. Long-acting cabotegravir and rilpivirine after oral induction for HIV-1 infection. *N Engl J Med*. 2020;382:1124-1135. Available at: <a href="https://www.nejm.org/doi/full/10.1056/NEJMoa1909512">https://www.nejm.org/doi/full/10.1056/NEJMoa1909512</a>.

- 39. Rizzardini G, Overton ET, Orkin C, et al. Long-acting injectable cabotegravir + rilpivirine for HIV maintenance therapy: week 48 pooled analysis of phase 3 ATLAS and FLAIR trials. *J Acquir Immune Defic Syndr*. 2020;85(4):498-506. Available at: <u>https://www.ncbi.nlm.nih.gov/pubmed/33136751</u>.
- 40. Swindells S, Lutz T, Van Zyl L, et al. Week 96 extension results of a phase 3 study evaluating long-acting cabotegravir with rilpivirine for HIV-1 treatment. *AIDS*. 2022;36(2):185-194. Available at: <u>https://pubmed.ncbi.nlm.nih.gov/34261093</u>.
- 41. Overton ET, Richmond G, Rizzardini G, et al. Long-acting cabotegravir and rilpivirine dosed every 2 months in adults with HIV-1 infection (ATLAS-2M), 48-week results: a randomised, multicentre, open-label, phase 3b, non-inferiority study. *Lancet*. 2021;396(10267):1994-2005. Available at: https://pubmed.ncbi.nlm.nih.gov/33308425.
- 42. Jaeger H, Overton ET, Richmond G, et al. Long-acting cabotegravir and rilpivirine dosed every 2 months in adults with HIV-1 infection (ATLAS-2M), 96-week results: a randomised, multicentre, open-label, phase 3b, non-inferiority study. *Lancet HIV*. 2021;8(11):e679-e689. Available at: https://pubmed.ncbi.nlm.nih.gov/34648734.
- 43. Orkin C, Bernal Morell E, Tan DHS, et al. Initiation of long-acting cabotegravir plus rilpivirine as direct-to-injection or with an oral lead-in in adults with HIV-1 infection: week 124 results of the open-label phase 3 FLAIR study. *Lancet HIV*. 2021;8(11):e668-e678. Available at: https://pubmed.ncbi.nlm.nih.gov/34656207.
- 44. Cutrell AG, Schapiro JM, Perno CF, et al. Exploring predictors of HIV-1 virologic failure to long-acting cabotegravir and rilpivirine: a multivariable analysis. *Aids*. 2021;35(9):1333-1342. Available at: <u>https://pubmed.ncbi.nlm.nih.gov/33730748</u>.
- 45. Overton ET, Richmond G, Rizzardini G, et al. Long-acting cabotegravir+rilpivirine every 2 months: ATLAS-2M week 152 results. Presented at: Conference on Retroviruses and Opportunistic Infections (CROI); 2022. Virtual. Available at: <u>https://www.croiconference.org/abstract/long-acting-cabotegravir-rilpivirine-every-2-months-atlas-2m-week-152-results.</u>
- 46. Patel P, Thiagarajah S, Ford S, et al. Cabotegravir pharmacokinetic tail in pregnancy and neonatal outcomes. Presented at: Conference on Retroviruses and Opportunistic Infections; 2020. Boston, Massachusetts. Available at: <u>https://www.croiconference.org/abstract/cabotegravir-pharmacokinetic-tail-in-pregnancyand-neonatal-outcomes</u>.
- 47. Patel P, Ford SL, Baker M, et al. Pregnancy outcomes and pharmacokinetics in pregnant women living with HIV exposed to long-acting cabotegravir and rilpivirine in clinical trials. *Open Forum Infectious Diseases*. 2021;8(Supplement\_1):S534-S534. Available at: https://doi.org/10.1093/ofid/ofab466.1080.
- 48. Acosta RK, Willkom M, Andreatta K, et al. Switching to bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) from dolutegravir (DTG)+F/TAF or DTG+F/tenofovir disoproxil fumarate (TDF) in the presence of pre-existing NRTI resistance. *J Acquir Immune Defic Syndr*. 2020;85(3):363-371. Available at: <u>https://www.ncbi.nlm.nih.gov/pubmed/32701823</u>.

- 49. Hagins D, Kumar P, Saag M, et al. Switching to bictegravir/emtricitabine/tenofovir alafenamide in Black Americans with HIV-1: a randomized phase 3B, multicenter, openlabel study. *J Acquir Immune Defic Syndr.* 2021;88(1):86-95. Available at: https://pubmed.ncbi.nlm.nih.gov/34397746.
- 50. Aboud M, Kaplan R, Lombaard J, et al. Dolutegravir versus ritonavir-boosted lopinavir both with dual nucleoside reverse transcriptase inhibitor therapy in adults with HIV-1 infection in whom first-line therapy has failed (DAWNING): an open-label, non-inferiority, phase 3B trial. *Lancet Infect Dis.* 2019;19(3):253-264. Available at: <a href="https://www.ncbi.nlm.nih.gov/pubmed/30732940">https://www.ncbi.nlm.nih.gov/pubmed/30732940</a>.
- 51. Paton NI, Musaazi J, Kityo C, et al. Dolutegravir or darunavir in combination with zidovudine or tenofovir to treat HIV. *N Engl J Med*. 2021;385(4):330-341. Available at: <u>https://pubmed.ncbi.nlm.nih.gov/34289276</u>.
- 52. Huhn GD, Tebas P, Gallant J, et al. A randomized, open-label trial to evaluate switching to elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide plus darunavir in treatment-experienced HIV-1-infected adults. *J Acquir Immune Defic Syndr*. 2017;74(2):193-200. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27753684.
- 53. Bierman WF, van Agtmael MA, Nijhuis M, Danner SA, Boucher CA. HIV monotherapy with ritonavir-boosted protease inhibitors: a systematic review. *AIDS*. 2009;23(3):279-291. Available at: <u>http://www.ncbi.nlm.nih.gov/pubmed/19114854</u>.
- 54. Arribas JR, Clumeck N, Nelson M, Hill A, van Delft Y, Moecklinghoff C. The MONET trial: week 144 analysis of the efficacy of darunavir/ritonavir (DRV/r) monotherapy versusDRV/r plus two nucleoside reverse transcriptase inhibitors, for patients with viral load < 50 HIV-1 RNA copies/ml at baseline. *HIV Med*. 2012;13(7):398-405. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22413874.
- 55. Ciaffi L, Koulla-Shiro S, Sawadogo AB, et al. Boosted protease inhibitor monotherapy versus boosted protease inhibitor plus lamivudine dual therapy as second-line maintenance treatment for HIV-1-infected patients in sub-Saharan Africa (ANRS12 286/MOBIDIP): a multicentre, randomised, parallel, open-label, superiority trial. *Lancet HIV*. 2017. Available at: <a href="https://www.ncbi.nlm.nih.gov/pubmed/28566227">https://www.ncbi.nlm.nih.gov/pubmed/28566227</a>.
- 56. Guiguet M, Ghosn J, Duvivier C, et al. Boosted protease inhibitor monotherapy as a maintenance strategy: an observational study. *AIDS*. 2012;26(18):2345-2350. Available at: <a href="http://www.ncbi.nlm.nih.gov/pubmed/22695301">http://www.ncbi.nlm.nih.gov/pubmed/22695301</a>.
- 57. Karlstrom O, Josephson F, Sonnerborg A. Early virologic rebound in a pilot trial of ritonavirboosted atazanavir as maintenance monotherapy. *J Acquir Immune Defic Syndr*. 2007;44(4):417-422. Available at: <u>http://www.ncbi.nlm.nih.gov/pubmed/17159658</u>.
- 58. Katlama C, Valantin MA, Algarte-Genin M, et al. Efficacy of darunavir/ritonavir maintenance monotherapy in patients with HIV-1 viral suppression: a randomized openlabel, noninferiority trial, MONOI-ANRS 136. *AIDS*. 2010;24(15):2365-2374. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20802297.

- 59. Vernazza P, Daneel S, Schiffer V, et al. The role of compartment penetration in PImonotherapy: the atazanavir-ritonavir monomaintenance (ATARITMO) trial. *AIDS*. 2007;21(10):1309-1315. Available at: <u>http://www.ncbi.nlm.nih.gov/pubmed/17545707</u>.
- 60. Blanco JL, Rojas J, Paredes R, et al. Dolutegravir-based maintenance monotherapy versus dual therapy with lamivudine: a planned 24 week analysis of the DOLAM randomized clinical trial. *J Antimicrob Chemother*. 2018;73(7):1965-1971. Available at: <a href="https://www.ncbi.nlm.nih.gov/pubmed/29608685">https://www.ncbi.nlm.nih.gov/pubmed/29608685</a>.
- 61. Oldenbuettel C, Wolf E, Ritter A, et al. Dolutegravir monotherapy as treatment de-escalation in HIV-infected adults with virological control: DoluMono cohort results. *Antivir Ther*. 2017;22(2):169-172. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27588613.
- 62. Wijting I, Rokx C, Boucher C, et al. Dolutegravir as maintenance monotherapy for HIV (DOMONO): a phase 2, randomised non-inferiority trial. *Lancet HIV*. 2017;4(12):e547-e554. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29107562.
- 63. van Lunzen J, Pozniak A, Gatell JM, et al. Brief report: switch to ritonavir-boosted atazanavir plus raltegravir in virologically suppressed patients with HIV-1 infection: a randomized pilot study. *J Acquir Immune Defic Syndr*. 2016;71(5):538-543. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26605505.
- 64. Pett SL, Amin J, Horban A, et al. Maraviroc, as a switch option, in HIV-1-infected individuals with stable, well-controlled HIV replication and R5-tropic virus on their first nucleoside/nucleotide reverse transcriptase inhibitor plus ritonavir-boosted protease inhibitor regimen: week 48 results of the randomized, multicenter MARCH study. *Clin Infect Dis.* 2016;63(1):122-132. Available at: https://pubmed.ncbi.nlm.nih.gov/28703491.
- 65. Katlama C, Assoumou L, Valantin MA, et al. Maraviroc plus raltegravir failed to maintain virological suppression in HIV-infected patients with lipohypertrophy: results from the ROCnRAL ANRS 157 study. *J Antimicrob Chemother*. 2014;69(6):1648-1652. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24535278.