Optimizing Antiretroviral Therapy in the Setting of Viral Suppression

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Key Considerations and Panel's 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 regimen to an alternative regimen in some situations. • The fundamental principle of 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 a regimen switch. • 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)**. • A long-acting ARV regimen, such as the combination of injectable cabotegravir and rilpivirine, 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 **(AI)**. • 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 **(AII)**. Using lamivudine or emtricitabine as the only drug in a regimen with HBV activity **is not recommended (AII)**, 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 = Optional* ***Rating of Evidence***: *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 such a switch, 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 Adverse Effects of Antiretroviral Agents and Table 24 for a more in-depth discussion of possible toxicities)
- To prevent or mitigate drug-drug interactions (see Drug-Drug Interactions)
- To eliminate food or fluid requirements
- To switch to a long-acting injectable (LAI) 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 Perinatal

Guidelines)

- To reduce costs (see Cost Considerations and Antiretroviral Therapy)

General Principles of Regimen Optimization

Maintain Viral Suppression

The fundamental principle of 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 expensive 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 re-emerge 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), one 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 away 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.[1] 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.[2] 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 Drug-Resistance Testing).

Optimization in a Person with Hepatitis B Virus Coinfection

When switching an ARV regimen in a patient with hepatitis B virus (HBV)/HIV coinfection, tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF) should be continued as part of the new regimen, unless these

drugs are contraindicated, in which case, another first-line HBV antiviral is recommended. Both TDF and TAF are active against HBV.[3] 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 can emerge. If TDF or TAF cannot be used as part of the ARV regimen, refer to Hepatitis B Virus/HIV Coinfection for recommendations. In patients with no documented history of or immunity to HBV infection, repeat HBV serology and re-vaccination if needed should be considered 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) interacts with acid-lowering agents, and many ARV drugs may interact with rifamycin antibiotics (see Drug-Drug Interactions). 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 previously been managed with dose adjustments, will need to be re-evaluated in the context of the new ARV regimen.

Assessment for Pregnancy or Pregnancy Potential

Persons 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 Perinatal Guidelines for recommendations on the safety and efficacy of ARV use at the time of conception or during pregnancy. Recent debates about the use of integrase strand transfer inhibitors (INSTIs) pre-conception or during pregnancy are discussed further in the Perinatal Guidelines as well as in the "What to Start" section of those guidelines. All pregnancies that occur while a woman is receiving ART should be reported to the Antiretroviral Pregnancy Registry.

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, 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 had pre-existing 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. 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 sup-

pression; 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.[1] 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 (AEs) 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[4, 5] or abacavir (ABC)[6] to TAF
- From RAL to DTG
- From DTG,[7-9] EVG/c,[10] or RAL to BIC
- From Efavirenz (EFV) to RPV[5, 11] or doravirine (DOR).[12]

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,[13] BIC,[14] or EVG[15, 16])
- Replacing a boosted PI with RPV[17] or DOR[12]
- Replacing an NNRTI with an INSTI[18, 19]
- Replacing a boosted PI with the CCR5 antagonist maraviroc (MVC).[20] MVC is effective only in those in whom no CXCR-4-using virus (i.e., X4, dual-mixed tropic) is detected in plasma. Special consideration must be given before considering a switch, because these patients have undetectable plasma HIV RNA. At a minimum, this should include ensuring that no X4 or dual or mixed tropic virus has been identified in the past. If a prior tropism assay has not been performed, consideration can be given to performing a test for viral tropism from proviral DNA, recognizing that this strategy has not been thoroughly validated (see Co-receptor Tropism Assays).[20-22]

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 at least 3 to 6 months of virologic suppression 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 have adequate anti-HBV activity, these regimens are not recommended for individuals with HBV coinfection, unless the patient is also on an HBV active regimen **(AIII)**. Also see the above section 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 enrolled 1,024 participants with viral suppression for ≥1 year (defined by no HIV RNA >50 copies/mL in the past 6 months, and no more than one instance of HIV RNA 50 to 200 copies/mL in the 6 to 12 months before enrollment) who were on their first or second regimen, had no history of virologic failure, and no documented evidence of any major drug-resistance mutations.[23] Participants were randomized to remain on their combination ARV regimen or to switch to a regimen of once-daily DTG plus RPV (early-switch arm). Viral suppression was maintained in 95% to 96% of the participants in both arms at 48 weeks. At 52 weeks, those who were randomized to remain on their current regimens were allowed to switch to DTG plus RPV (late-switch arm). At 100 weeks, 89% of participants in the early-switch arm and 93% of those in the late-switch arm maintained HIV RNA <50 copies/mL.[24] DTG plus RPV is available as a coformulated single-tablet regimen and is a reasonable option when the use of NRTIs is not desirable. DTG plus RPV should be given only to patients who do not have chronic HBV infection (unless the patient is also on an HBV active regimen), have no evidence of resistance to either DTG or RPV, and have no significant drug-drug interaction that might reduce the concentration of either drug **(AI)**.

Dolutegravir plus Lamivudine or Emtricitabine

A switch from three-drug regimens to DTG plus (3TC or FTC) as maintenance strategy in patients with virologic suppression has been examined in a large randomized clinical trial (TANGO),[25] in three small clinical trials,[26, 27] and in observational studies[28-30] with good success.

The Phase 3 TANGO study enrolled participants who were on their first ARV regimen with HIV RNA <50 copies/mL for ≥6 months. Participants were randomized to switch to open-label DTG plus 3TC (n = 369) or to continue their TAF-based triple therapy (n = 372). The participants had no history of virologic failure or evidence of resistance to DTG or 3TC and did not have HBV coinfection. At Week 48, switching to DTG plus 3TC was non-inferior to continuing the current regimen, with 93% of participants in both arms maintaining HIV RNA <50 copies/mL. No unexpected AEs were identified as related to DTG or 3TC.[25] Switching to a DTG plus 3TC regimen can be a good option for individuals who have no evidence of resistance to either drug and do not have HBV coinfection, unless the patient is also on an HBV active regimen **(AI)**.

Ritonavir-Boosted Protease Inhibitor plus Lamivudine

A ritonavir-boosted protease inhibitor (PI/r) plus 3TC may be a reasonable option when the continued use of TDF, TAF, or ABC is contraindicated or not desirable. Growing evidence indicates that a PI/r-based regimen plus 3TC can maintain viral suppression in patients who initiated triple-drug therapy, achieved sustained viral suppression for ≥1 year, and have no evidence of or risk for drug resistance to either the PI/r or 3TC. However, these regimens have a higher pill burden and are less well tolerated than the above-mentioned dual combinations. These regimens are not suitable for individuals with active HBV infection, unless the patient is also on an HBV active regimen. To date, no published clinical trials have evaluated cobicistat-boosted PI with 3TC as dual therapy, but clinically, these regimens are reasonable. Examples of boosted PI plus 3TC regimens that have been shown to be effective in clinical trials include the following:

- ATV/r plus 3TC **(CI)**[31, 32]
- Darunavir/ritonavir (DRV/r) plus 3TC **(BI)**[33]
- LPV/r plus 3TC **(CI)**[34]

Boosted Darunavir plus Dolutegravir

An open-label, Phase 3b, non-inferiority clinical trial randomized 263 participants who were on boosted DRV plus two NRTIs to continue on the same regimen or switch to boosted DRV plus DTG (study recruitment was stopped prematurely due to slow recruitment). At 48 weeks, the study demonstrated that switching to DTG plus boosted DRV was non-inferior to continuing triple therapy. In both arms, approximately 87% of participants maintained

viral suppression at HIV RNA <50 copies/mL, and both groups had comparable rates of AEs.[35] Because of the small sample size of this study, the regimen of boosted DRV plus DTG is recommended only in the absence of other alternative options **(CI)**. Similar results were observed in two small observational studies (13 participants and 56 participants).[36, 37] This regimen is not suitable for individuals with active HBV infection, unless the patient is also on an HBV active regimen.

Long-Acting Antiretroviral Therapy

In recent years, 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 that is given intravenously, was approved for use in combination with optimized background therapy in heavily treatment-experienced patients (see Virologic Failure). In January 2021, LAI formulations of the INSTI cabotegravir (CAB) and the NNRTI RPV were approved by the Food and Drug Administration (FDA). This combination is indicated as a complete regimen for the treatment of HIV in adults to replace a current, stable ARV regimen in those with sustained (e.g., 3 to 6 months) virologic suppression (HIV-1 RNA <50 copies/mL), with no history of treatment failure, and no known or suspected resistance to either CAB or RPV.[38] Multiple other long-acting ARV medications and/or drug delivery systems are being studied.[39]

Long-acting ARV medications provide the convenience of reduced dosing frequency and may be beneficial or improve the 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 6 months at baseline. Thus, these therapies are recommended for similar populations that are consistently engaged in care. The Panel awaits data from ongoing clinical trials in patients with suboptimal adherence and poor viremic control to assess the safety and efficacy of the regimen in these patients.[40]

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 pharmacokinetic 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. Development of HIV drug resistance after a long-acting medication dose has been documented in at least one HIV pre-exposure prophylaxis (PrEP) trial in a patient who contracted HIV more than 2 months after the prior long-acting dose of RPV. Like other optimization strategies, the general principles of regimen optimization apply.

More than 90% of individuals receiving LAI medications in randomized clinical trials prefer these treatments over standard, daily oral therapy.[41] The patient satisfaction surveys may be biased because they were conducted in populations who consented to LAI clinical trials. Another potential advantage of LAI regimens is the ease of documenting adherence.

Cabotegravir plus Rilpivirine

CAB is a novel INSTI and 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) before initiation of the LAI regimen and as oral bridging in the event of planned missed injections.

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.[42, 43] 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, participants were ARV-naive at enrollment and needed to achieve HIV viral suppression by 16 to 20 weeks on an initial oral regimen of DTG/ABC/3TC. Participants were then randomized to LAI CAB and RPV once monthly versus continued oral therapy. Both studies used a one-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 (plus or minus 7 days).

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).[41] This demonstrated non-inferiority of LAI CAB and RPV compared to oral three-drug standard of care. Four to six percent of participants in each arm had no virologic data available per the FDA Snapshot algorithm. Virologic failure was rare; however, when it occurred, resistance to INSTIs, NNRTIs, or both was common, and it was more likely to occur in persons with HIV-1 subtype A1 who had an L74I substitution at baseline. Subtype A1 is not common in the United States.

The 48-week and 96-week results of the ATLAS-2M trial, which used every 8-week injections of CAB 600 mg IM with RPV 900 mg IM after a 4-week oral lead-in, showed non-inferiority compared to every 4-week injections,[44] but this dosing schedule has not received FDA approval. Results of longer-term follow-up of ATLAS-2M are awaited.

Adverse Events When Using Long-Acting CAB and RPV

AEs were more common in those 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 AEs 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. Hypersensitivity reactions, post-injection reactions, hepatotoxicity, and depressive disorders also have been reported.

Panel's Recommendation

The data from the ATLAS and FLAIR trials support that separate monthly ventrogluteal IM injections of CAB and RPV, after oral lead-in therapy, 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), who have good adherence and engagement in care, 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); 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 **(AI)**.

Practical Considerations When Using Long-Acting Injectable CAB and RPV

Practical considerations regarding the feasibility of monthly 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, 1½-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^2. 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 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 full prescribing information.

Management of Missed Doses of Long-Acting Injectable CAB and RPV

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 ≥12 months after the last dose.[38] Individuals who miss doses or discontinue therapy without starting an oral regimen are at increased risk of virologic failure with development of drug resistance. 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. 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. If long-acting CAB and RPV are continued, and it has been less than 2 months since the last injections, it is recommended to resume the prior dosing schedule with CAB 400 mg IM and RPV 600 mg IM once monthly. If injections are missed by more than 2 months, resuming administration with a loading dose, followed by monthly maintenance dosing, is recommended. When stopping therapy, transition to a suppressive oral regimen should occur within 4 weeks of the last IM doses.

Viral Load Monitoring

Viral load monitoring should be performed 4 to 8 weeks after a switch to long-acting CAB and RPV. HIV-RNA 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 doses should not be delayed while waiting for viral load and resistance test results. However, regimen changes should be prompted if resistance to CAB and/or RPV is discovered. In patients who develop resistance to CAB or RPV or both drugs, the regimen should be changed based on resistance test results (see Virologic Failure). Consultation with an expert in HIV drug resistance should be considered.

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, then appropriate treatment for HBV infection is needed (see Hepatitis B Virus/HIV Coinfection).

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

These regimens have not been studied in pregnancy; management of patients who become pregnant while on therapy will need close oversight. Health care providers are strongly encouraged to register people who become pregnant while receiving IM CAB and RPV with the Antiretroviral Pregnancy Registry. In clinical trials to date, participants who became pregnant were switched from IM CAB and RPV to an alternative ARV regimen for the remainder of their pregnancies.[45] Although numbers were small, no congenital anomalies, preterm birth, or drug-related maternal or neonatal adverse events have been reported to date in the four live births of infants from mothers who conceived while receiving IM CAB and RPV. In three of these four participants with available PK data, CAB concentrations remained therapeutic in two women with normal weight through delivery. The rate of decline in CAB concentrations in the third pregnant participant was faster than expected; this participant had a low BMI (15.3 kg/m^2) and may have had altered absorption from the long-acting depot injection site.

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 other studies, as discussed below.

Within-Class Switch from One High-Resistance Barrier Drug to Another (e.g., from DTG to BIC [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. 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.[46]

Between-Class Switch from One High-Resistance Barrier Drug to Another (e.g., from a Boosted PI to a BIC- or DTG-Containing Regimen with at Least One Fully Active NRTI)

The GS 4030 study provides theoretical support for replacing a boosted PI-regimen with a BIC- or DTG-containing regimen, if at least one of the NRTIs in the regimen is fully active.[9, 46] Although no switch studies have tested this strategy, based on the GEMINI studies in treatment-naive patients, a DTG plus 3TC regimen **(when both ARVs are fully active)** is highly effective. In addition, the TANGO study (described above), demonstrated that in the setting of no underlying drug resistance, DTG plus 3TC, as the active NRTI, was a very effective switch strategy. In the DAWNING study,[47] in the setting of virologic failure with underlying NRTI resistance, DTG plus one fully active NRTI was more effective than LPV/r plus one fully active NRTI. Based upon standard optimization principles, if DTG plus two NRTIs, one of which is fully active, was effective in those with virologic failure, it also should be effective in those already virologically suppressed **(BIII)**.

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)**.

One randomized controlled trial conducted in this patient population is described below.

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.[48] 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. 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 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.[49-51] 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 most studies, resuming NRTIs in patients

who are experiencing low-level viral rebound has led to re-suppression.[52-55] No clinical trials have evaluated the use of coformulated cobicistat-boosted protease inhibitor 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,[56, 57] and in a randomized controlled trial.[58] 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 atazanavir/ritonavir (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.[59] 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 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)**.[60]

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 five out of 44 patients.[61] 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: https://academic.oup.com/jac/article/66/4/709/725741.

3. 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://www.ncbi.nlm.nih.gov/pubmed/29405329.

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: http://www.ncbi.nlm.nih.gov/pubmed/27036991.

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: https://www.ncbi.nlm.nih.gov/pubmed/30101539.

6. 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: https://www.ncbi.nlm.nih.gov/pubmed/29475804.

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. Biktarvy Product Label [package insert]. Gilead Sciences. 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: https://www.ncbi.nlm.nih.gov/pubmed/32668455.

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 (DOR/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: https://www.ncbi.nlm.nih.gov/pubmed/30985556.

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: https://www.ncbi.nlm.nih.gov/pubmed/28555519.

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: http://www.ncbi.nlm.nih.gov/pubmed/24908550.

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: http://www.ncbi.nlm.nih.gov/pubmed/24908551.

20. Pett SL, Amin J, Horban A, et al. Week 96 results of the randomized, multicentre Maraviroc Switch (MARCH) study. *HIV Med*. 2018;19(1):65-71. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28703491.

21. Vitiello P, Brudney D, MacCartney M, et al. Responses to switching to maraviroc-based antiretroviral therapy in treated patients with suppressed plasma HIV-1-RNA load. *Intervirology*. 2012;55(2):172-178. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22286889.

22. Bonjoch A, Pou C, Perez-Alvarez N, et al. Switching the third drug of antiretroviral therapy to maraviroc in aviraemic subjects: a pilot, prospective, randomized clinical trial. *J Antimicrob Chemother*. 2013;68(6):1382-1387. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23354282.

23. Llibre JM, Hung CC, Brinson C, et al. Efficacy, safety, and tolerability of dolutegravir-rilpivirine for the maintenance of virological suppression in adults with HIV-1: phase 3, randomised, non-inferiority SWORD-1 and SWORD-2 studies. *Lancet*. 2018;391(10123):839-849. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29310899.

24. Aboud M, Orkin C, Podzamczer D, et al. Efficacy and safety of dolutegravir-rilpivirine for maintenance of virological suppression in adults with HIV-1: 100-week data from the randomised, open-label, phase 3 SWORD-1 and SWORD-2 studies. *Lancet HIV*. 2019;6(9):e576-e587. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31307948.

25. 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: https://www.ncbi.nlm.nih.gov/pubmed/31905383.

26. 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: https://www.ncbi.nlm.nih.gov/pubmed/29293895.

27. 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.

28. Maggiolo F, Gulminetti R, Pagnucco L, et al. Lamivudine/dolutegravir dual therapy in HIV-infected, virologically suppressed patients. *BMC Infect Dis*. 2017;17(1):215. Available at: https://www.ncbi.nlm.

nih.gov/pubmed/28302065.

29. 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: https://www.ncbi.nlm.nih.gov/pubmed/29573320.

30. 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.

31. 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: http://www.ncbi.nlm.nih.gov/pubmed/26062881.

32. 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: https://www.ncbi.nlm.nih.gov/pubmed/29668978.

33. Pulido F, Ribera E, Lagarde M, et al. Dual therapy with darunavir and ritonavir plus lamivudine versus triple therapy with darunavir and ritonavir plus tenofovir disoproxil fumarate and emtricitabine or abacavir and lamivudine for maintenance of HIV-1 viral suppression: randomised, open label, non-inferiority DUAL-GESIDA 8014-RIS-EST45 trial. *Clin Infect Dis.* 2017;65(12):2112-2118. Available at: http://www.ncbi.nlm.nih.gov/pubmed/29020293.

34. 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: http://www.ncbi.nlm.nih.gov/pubmed/26062880.

35. Spinner CD, Kummerle 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: https://www.ncbi.nlm.nih.gov/pubmed/32965277.

36. 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.

37. 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: https://www.ncbi.nlm.nih.gov/pubmed/29513131.

38. Cabenuva [package insert]. The Food and Drug Administration. 2021. Available at: https://gskpro.com/content/dam/global/hcpportal/en_US/Prescribing_Information/Cabenuva/pdf/CABENUVA-PI-PIL-IFU2-IFU3.PDF.

39. 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: https://www.ncbi.nlm.nih.gov/pubmed/33166693.

40. Castillo-Mancilla J, Rana A. The LATITUDE Study: Long-Acting Therapy to Improve Treatment SUccess in Daily LifE. 2018. Available at: https://clinicaltrials.gov/ct2/show/NCT03635788

41. 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: https://www.ncbi.nlm.nih.gov/pubmed/33136751.

42. 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.

43. 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: https://www.nejm.org/doi/full/10.1056/NEJMoa1909512.

44. Overton ET, Richmond GJ, Rizzardini G, et al. CABOTEGRAVIR + RILPIVIRINE EVERY 2 MONTHS IS NONINFERIOR TO MONTHLY: ATLAS-2M STUDY. Presented at: Conference on Retroviruses and Opportunistic Infections; 2020. Boston, Massachusetts. Available at: https://www.croiconference.org/abstract/cabotegravir-rilpivirine-every-2-months-is-noninferior-to-monthly-atlas-2m-study/.

45. 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: https://www.croiconference.org/abstract/cabotegravir-pharmacokinetic-tail-in-pregnancy-and-neonatal-outcomes/.

46. 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: https://www.ncbi.nlm.nih.gov/pubmed/32701823.

47. 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: https://www.ncbi.nlm.nih.gov/pubmed/30732940.

48. 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.

49. 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: http://www.ncbi.nlm.nih.gov/pubmed/19114854.

50. 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 versus DRV/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.

51. 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: https://www.ncbi.nlm.nih.gov/pubmed/28566227.

52. 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: http://www.ncbi.nlm.nih.gov/pubmed/22695301.

53. Karlstrom O, Josephson F, Sonnerborg A. Early virologic rebound in a pilot trial of ritonavir-boosted atazanavir as maintenance monotherapy. *J Acquir Immune Defic Syndr*. 2007;44(4):417-422. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17159658.

54. Katlama C, Valantin MA, Algarte-Genin M, et al. Efficacy of darunavir/ritonavir maintenance monotherapy in patients with HIV-1 viral suppression: a randomized open-label, noninferiority trial, MONOI-ANRS 136. *AIDS*. 2010;24(15):2365-2374. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20802297.

55. Vernazza P, Daneel S, Schiffer V, et al. The role of compartment penetration in PI-monotherapy: the Atazanavir-Ritonavir Monomaintenance (ATARITMO) Trial. *AIDS*. 2007;21(10):1309-1315. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17545707.

56. 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: https://www.ncbi.nlm.nih.gov/pubmed/29608685.

57. 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.

58. 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.

59. 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.

60. 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://www.ncbi.nlm.nih.gov/pubmed/27048747.

61. 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.