

Optimizing Antiretroviral Therapy in the Setting of Viral Suppression

Updated: October 27, 2026

Reviewed: October 27, 2026

Key Considerations and Recommendations

- Many people with HIV and ongoing HIV viral suppression can be successfully transitioned to alternative regimens and maintain viral suppression.
- 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, drug–disease interactions, pill burden, pregnancy, cost, stigma or inconvenience from taking oral medications, or the desire to simplify a regimen may prompt regimen optimization.
- It is critical to review a person’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 switch to any regimen that has been shown to be highly effective in people who are ARV-naïve **(AI)** or to regimens extensively researched in optimization studies.
- For regimen optimization in the setting of existing NRTI resistance, there are two main options:
 - In many situations, a regimen containing two NRTIs (TAF or TDF plus FTC or 3TC) can be used along with a fully active drug with a high resistance barrier, such as DTG, BIC, or boosted DRV.
 - An NRTI-sparing regimen studied in the setting of therapy optimization can be utilized if no resistance to the agents is present.
- Monotherapy with any ARV medication has been associated with drug resistance and higher rates of virologic failure than multidrug ARV regimens; therefore, monotherapy as a switch strategy **is not recommended (AI)**.
- Discontinuation of HBV antivirals in a person with chronic HBV may cause serious hepatocellular injury resulting from HBV reactivation hepatitis; thus, anti-HBV therapy should not be stopped in people with HBV/HIV **(AII)**.
- When planning a regimen switch for a person with a history of resistance or intolerance to two or more drug classes, consultation with an HIV specialist is recommended in most cases **(AIII)**.
- During the first 3 months after an ARV regimen switch, close monitoring is recommended to ensure understanding of the new regimen and to assess adherence, tolerability, safety, and maintenance of viral suppression **(AIII)**.

Rating of Recommendations: A = Strong; B = Moderate; C = Weak

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

Key: 3TC = lamivudine; ARV = antiretroviral; BIC = bictegravir; DRV = darunavir; DTG = dolutegravir; FTC = emtricitabine; HBV = hepatitis B virus; NRTI = nucleoside reverse transcriptase inhibitor; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

With currently available antiretroviral therapy (ART), most people with HIV can achieve and maintain HIV viral suppression, the primary goal of HIV treatment. However, people with HIV may need or want to change their antiretroviral (ARV) regimen while virally suppressed for a variety of reasons. When optimizing ART in the setting of viral suppression, several key principles should be considered. The reasons for and principles of ART optimization are discussed below.

Reasons to Consider Regimen Optimization in the Setting of Viral Suppression

- To reduce pill burden and/or dosing frequency
- To switch to a regimen with a higher barrier to the development of resistance
- To enhance tolerability and/or decrease short- or long-term toxicity (see [Common and/or Severe Adverse Effects Associated With Antiretroviral Medications](#) for a more in-depth discussion of toxicities)
- To prevent or mitigate drug–drug interactions (see the [Liverpool HIV Drug Interaction Checker](#))
- To minimize food requirements or drug–food interactions
- To minimize drug–disease interactions, such as in the setting of renal or cardiovascular disease
- To decrease potential stigma or disclosure concerns (e.g., by switching to long-acting [LA] injectable cabotegravir [CAB]/rilpivirine [RPV])
- To allow optimal use of ART when pregnancy is desired or may occur (see the [Perinatal Guidelines](#))
- To reduce costs borne by the person with HIV and/or to comply with formulary requirements (see [Cost Considerations and Antiretroviral Therapy](#))

General Principles and Considerations for 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 (defined as the inability to maintain suppression of viral replication to HIV RNA levels <200 copies/mL) with the emergence of new resistance mutations, the person may require a more complex and/or less tolerated regimen.

Review Antiretroviral Treatment and Drug-Resistance Histories Before Optimization

Before switching from an effective ARV regimen, it is critical to thoroughly assess a person's full ARV history, including virologic responses, cumulative resistance test results, inferred resistance (as discussed below), and any past ARV-related intolerances, toxicities, or adverse reactions **(AI)**.

A review of cumulative resistance test results and clinical and virologic responses to prior regimens is essential when designing a new regimen, especially in people with a history of virologic failure or pretreatment drug resistance. If a person 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 person was on the suppressive regimen. Cumulative resistance test results refer to all previous and currently available results from standard genotype, proviral DNA genotype, and phenotype 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 person's most recent drug-resistance test—can be archived in the HIV reservoir and re-emerge under the appropriate selective drug pressure.

Resistance can often be inferred from the ARV history. For people with documented virologic failure on a regimen that includes drugs with lower barriers to resistance—such as a non-nucleoside reverse transcriptase inhibitor (NNRTI), lamivudine (3TC), emtricitabine (FTC), elvitegravir (EVG), or raltegravir (RAL)—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 from a regimen with a relatively high barrier to resistance—such as those that include dolutegravir (DTG), bictegravir (BIC), or boosted darunavir (DRV)—to one with a lower barrier to resistance.¹ In most instances, consultation with an HIV specialist is recommended when planning a regimen switch for a person with a history of resistance or intolerance to two or more drug classes (**AIII**).

The next-generation sequencing genotypic resistance assay that analyzes proviral DNA, sometimes called an archived genotype, can be considered for people with viral suppression, particularly if complex or semi-complex pre-existing resistance is suspected. In individuals with no history of virologic failure who are receiving their first or second ARV regimen, or in those with available genotypic resistance results from prior virologic failures, proviral DNA genotypic testing is unlikely to provide additional clinically useful information and **is not recommended (AIII)**, even if a baseline genotype is not available.

However, in individuals with a history of multiple virologic failures whose prior ARV treatment history or genotypic resistance test results are unavailable at the time of virologic failure, proviral DNA genotypic testing may be considered (**CIII**). Results from proviral DNA genotypes should be interpreted with caution, as these assays might miss some or all previously existing drug-resistance mutations.² Furthermore, it is unclear if all mutations identified are relevant to subsequent regimen selection. The usefulness of these assays in the clinic is still under investigation and has yet to be fully determined (see the [Drug-Resistance Testing](#) section).

Antiretrovirals No Longer Recommended for Optimization in the Setting of Viral Suppression

The ARV medications nevirapine and oral zidovudine, which can cause serious adverse effects, are no longer recommended by the Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel) and are not suitable for optimizing ART in the setting of viral suppression. Certain protease inhibitors (PIs) (lopinavir and atazanavir [ATV]), first-generation integrase strand transfer inhibitors (INSTIs) (EVG, RAL), and the NNRTI efavirenz also have disadvantages, including higher pill burden, higher rate of toxicity, and, in some cases, a lower barrier to resistance, and therefore are no longer recommended for optimizing ART in the setting of viral suppression. See the [What to Start: Nucleoside Reverse Transcriptase Inhibitor Options as Part of Initial Therapy](#) and [What to Start: Non-Nucleoside Reverse Transcriptase Inhibitor-Based Regimens as Initial Antiretroviral Therapy](#) sections for more details.

Considerations Regarding Hepatitis B Virus (HBV) and HIV

HBV Screening for People With No History of HBV/HIV Coinfection

People with HIV who are not known to have chronic HBV infection (i.e., not known to have positive hepatitis B surface antigen [HBsAg]) should have HBV serology (HBsAg, hepatitis B surface antibody [anti-HBs], and hepatitis B core antibody [anti-HBc]) performed within 3 months before switching to an ARV regimen that does not include tenofovir alafenamide (TAF) or tenofovir disoproxil fumarate (TDF). If a person with HIV shows no evidence of chronic HBV infection (i.e., negative for HBsAg) and is not immune to HBV (i.e., anti-HBs <10 mIU/mL), vaccination should be

initiated while considering the ARV switch (including in those with isolated anti-HBc and those previously vaccinated for HBV). See the [Hepatitis B Virus Infection](#) and [Immunizations for Preventable Diseases in Adults and Adolescents With HIV](#) sections in the Adult OI Guidelines for details.

Managing People With Chronic HBV Infection (HBsAg Positive)

Tenofovir-based ARV regimens are effective against both HIV and HBV infection. When switching an ARV regimen in a person with HBV/HIV (i.e., HBsAg positive), anti-HBV therapy should be continued and, if feasible, (TDF or TAF) with (3TC or FTC) should be continued as components of the new ARV regimen **(All)**.

There are several effective oral and injectable ARV regimens that do not include tenofovir. When using one of these regimens, the HBV treatment options include adding TDF, TAF, or entecavir to the ARV regimen. TDF, TAF, or entecavir may be used as the only HBV-active antiviral in this setting based on their efficacy for the treatment of HBV in people without HIV. TDF or TAF are preferred over entecavir given their higher barrier to HBV resistance. If TAF or TDF cannot be used or it is desired to avoid TAF and TDF, entecavir is the alternative to treat HBV, given together with a fully suppressive ARV regimen **(All)**. Entecavir should not be used in people with HIV without a fully suppressive ARV regimen, given the risk of development of the HIV M184V resistance mutation in this setting.³ Entecavir **should not be used** in individuals with 3TC-resistant HBV. See the [Hepatitis B Virus/HIV Coinfection](#) section for additional important details regarding entecavir use and dosing for treatment of HBV.

Although 3TC and FTC are active against HBV, the use of 3TC or FTC as monotherapy against HBV infection **is not recommended (All)** due to the risk of emergent HBV resistance to these drugs.

Discontinuation of HBV antivirals in a person with chronic HBV may cause serious hepatocellular injury resulting from HBV reactivation hepatitis; thus, anti-HBV therapy should not be stopped in people with HBV/HIV **(All)**. Refer to the [Hepatitis B Virus/HIV Coinfection](#) section for specific recommendations.

Monitoring After Regimen Switch in People With Positive Anti-HBc and Negative HBsAg

People with HIV and prior exposure to HBV infection (i.e., anti-HBc positive) without evidence of chronic infection (i.e., negative HBsAg) are likely at low risk (<2%) of HBV reactivation and even lower risk of HBV reactivation–associated hepatitis, despite the discontinuation of nucleoside reverse transcriptase inhibitors (NRTIs).^{4,5} However, no published studies have confidently estimated risk in this population. Within this group, those with positive anti-HBs are at the lowest risk for HBV reactivation, although HBV reactivation has been described when HBV-active therapy is withdrawn as part of an ART regimen in this situation.⁶ See more information in the [Hepatitis B Virus Infection](#) section in the Adult OI Guidelines.

For people with positive anti-HBc and negative HBsAg who switch to a tenofovir-sparing ARV regimen, alanine aminotransferase (ALT) should be monitored every 1 to 3 months for the first 6 months and every 6 months thereafter, as recommended in the [Hepatitis B Virus Infection](#) section of the Adult OI Guidelines. An increase in ALT level should prompt HBV DNA testing to assess for the reactivation of HBV. The presence of HBV reactivation would require the immediate addition of TAF, TDF, or entecavir to the ARV regimen.

Assessment of 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 interactions exist. For example, oral RPV and ATV interact with acid-lowering agents, oral absorption of INSTIs can be reduced by the presence of polyvalent cations, and many ARV drugs may interact with drug transporters or drugs that are inhibitors, inducers, or substrates of cytochrome P450 (CYP) enzymes (see the [Liverpool HIV Drug Interaction Checker](#)). In addition to new drug interactions, the discontinuation of some ARV drugs may necessitate adjusting the dosage of concomitant medications. For example, discontinuation of pharmacokinetic (PK) boosters (ritonavir or cobicistat) may alter the concentration 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 of Pregnancy or Pregnancy Potential

If a woman with HIV is found to be pregnant or desires pregnancy, clinicians should refer to the [Perinatal Guidelines](#) for recommendations on ART selection and the safety and efficacy of ARV use at the time of conception and during pregnancy. All pregnancies that occur while a woman is receiving ART should be reported to the [Antiretroviral Pregnancy Registry](#).

Monitoring After Optimizing Antiretroviral Therapy

After a treatment switch, people with HIV should be evaluated closely for 3 months (e.g., monitor for tolerability and viral load for rebound.) **(AIII)**. The purpose of this close monitoring is to ensure the person clearly understands their newly prescribed ART regimen, to assess medication tolerance, and to conduct targeted laboratory testing when there are pre-existing laboratory abnormalities or if there are potential concerns with the new regimen. For example, if a lipid abnormality prompted the ARV change or is a concern with the new regimen, fasting cholesterol subsets and triglycerides should be assessed within 3 months of the ART change. In the absence of any new complaints, laboratory abnormalities, or evidence of HIV viral rebound over the first 2 to 3 months, clinical and laboratory monitoring may resume on a regularly scheduled basis (see the [Laboratory Testing for Initial Assessment and Monitoring of People With HIV](#) section).

Specific Regimen Optimization Considerations

As with the recommendation for people who are starting ART for the first time, the use of a two- or three-drug ARV regimen (as discussed below) is generally recommended when switching ART in people with suppressed viral loads **(AI)**. **Monotherapy is not recommended (AI)** in the treatment of HIV; this includes monotherapy with either a boosted PI or a second-generation INSTI.^{7–10} Both INSTI¹¹ and boosted PI¹² monotherapy have been associated with higher rates of virologic failure than combination regimens. In addition, INSTI monotherapy has been associated with the development of resistance.^{13,14}

Optimization Strategies for People With No or Limited Drug Resistance

People who have no history of resistance mutations or virologic failure can likely switch to any two- or three-drug regimen with demonstrated efficacy in people without prior ART experience **(AI)** (see [What to Start](#)). In addition, several regimens not used in initial therapy have been studied specifically in the setting of therapy optimization (as discussed below). Several regimens with established efficacy in treatment-naïve populations have also demonstrated effectiveness for ART optimization in

people with no or limited resistance, including BIC/FTC/TAF,¹⁵⁻¹⁷ DTG with (TAF or TDF) plus (3TC or FTC),¹⁸ and DTG/3TC (discussed below).

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 ART regimens in those with viral suppression, particularly when the switch is to a drug with a low barrier to resistance.¹ In the two SWITCHMRK studies, individuals with viral suppression on two NRTIs plus lopinavir/ritonavir (LPV/r) were switched to two NRTIs plus RAL. The studies found that individuals with a history of previous virologic failure had a higher risk of failure after switching to the RAL-based regimen. This finding is likely due to underlying NRTI resistance that was not recognized before the switch. In this setting, viral suppression can generally be maintained by switching to drugs with a high barrier to resistance, such as boosted PIs or second-generation INSTIs combined with two NRTIs. However, maintaining viral suppression is less likely when switching to a drug with a low barrier to resistance, such as RAL.

The strategies listed below support these observations and principles of optimizing therapy and include a discussion about switching ART regimens in those with no or limited underlying resistance. As discussed earlier, before switching from an effective ARV regimen, it is critical to thoroughly assess a person's full ARV history, including virologic responses, cumulative resistance test results, inferred resistance (as discussed below), and any past ARV-related intolerances, toxicities, or adverse reactions **(AI)**.

Within-Class Switches

Within-class switches may be prompted by adverse events or the availability of ARVs in the same class that offer benefits such as a better safety profile, reduced dosing frequency or pill burden, higher barrier to resistance, or no requirement for PK boosting. Within-class switches usually maintain viral suppression, provided there is no drug resistance to the new ARV. In the modern era, common within-class switches include within NRTIs, NNRTIs, and INSTIs. People on older boosted PI-based therapy can also commonly be switched to boosted DRV. When considering a regimen switch in a person with prior virologic failure, switching from a regimen with a high resistance barrier to one with a lower resistance barrier is generally not recommended. Between-class switches, as discussed next, are also commonly utilized in therapy optimization.

Between-Class Switches

Between-class switches (e.g., switching from a boosted PI to an INSTI) are generally safe in people without known resistance. In general, such switches should be avoided if any doubt exists about the activity of the new agent or the other agents in the regimen. In the current era, between-class switches are most common with the NNRTI, PI, and INSTI classes. Other common switches include from therapy containing NRTIs to NRTI-sparing therapy. These switches should also take into consideration, when appropriate, that switching from a high-resistance-barrier medication to a low-resistance-barrier medication, in the setting of prior virologic failure, is generally not recommended as previously discussed.

Two-Drug Oral Regimens

Several two-drug ARV regimens are effective in maintaining HIV virologic control in people who initiated therapy with two- or three-drug regimens and achieved sustained viral suppression for at least 3 months. However, none of these two-drug regimens are effective as treatment for HBV and are therefore **not recommended** on their own for people with HBV coinfection (see the [Hepatitis B Virus/HIV Coinfection](#) section). Individuals with active HBV infection would also need to be on a

potent HBV drug with a high barrier to resistance (i.e., TAF, TDF, or entecavir) **(AII)**. See the section above on HBV considerations during optimization. The following are examples of successful strategies studied in clinical trials for switching to two-drug regimens in people with viral suppression.

Dolutegravir Plus Rilpivirine

Two Phase 3 trials, SWORD-1 and SWORD-2, demonstrated noninferior efficacy of switching to a two-drug regimen of DTG with RPV compared with continuing a first or second ARV regimen in individuals with suppressed HIV RNA without prior virologic failure.¹⁹ Individuals were excluded from the study if they had active HBV infection (unless the person was also on a specific HBV-active agent), resistance to DTG or RPV, or significant drug interactions. DTG/RPV is suitable for use in people with an isolated K103N resistance mutation and in those with NRTI resistance.²⁰ Individuals with active HBV infection need to be on a potent HBV drug with a high barrier to resistance (i.e., TAF, TDF, or entecavir).

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 people with ongoing viral suppression and no history of prior virologic failure or resistance to these agents was noninferior to continuing a three-drug regimen in a large randomized clinical trial (TANGO)^{21,22} and in multiple smaller clinical trials.²³⁻²⁸ Individuals with active HBV infection need to be on a potent HBV drug with a high barrier to resistance (i.e., TAF, TDF, or entecavir). 3TC or FTC monotherapy is not considered standard of care for HBV treatment because of a high risk of emerging resistance.²⁹

Limited prospective and observational cohort data are available on the use of DTG/3TC in people with a history of M184V/I mutations, based either on historical RNA resistance testing and/or proviral DNA resistance testing.³⁰⁻³³ Although some early data are promising, more clinical outcome data are needed to determine whether specific factors—including duration of pre-switch viral suppression, when the M184V/I was detected, the method of M184V/I detection (i.e., RNA versus proviral DNA genotyping), or other factors—impact the effectiveness of DTG/3TC as a switch strategy in people with HIV with historical M184V/I mutations.³⁴ Currently, the Panel **does not recommend** the use of DTG/3TC in people with historical M184V/I mutations **(BIII)**.

Boosted Darunavir Plus Lamivudine or Emtricitabine

A boosted PI plus 3TC or FTC is a reasonable two-drug optimization option in individuals without resistance who are suppressed on a current regimen and do not have resistance to 3TC/FTC or the boosted PI. Currently, the Panel **does not recommend** the use of a boosted PI with 3TC or FTC in people with historical M184V/I mutations **(BIII)**.³⁵⁻³⁷ Higher pill burden and potential drug interactions are limitations compared with most of the other two-drug regimens. Boosted DRV is the PI of choice for this combination.³⁸ Earlier trials supported the use of ATV/ritonavir^{39,40} or LPV/r with 3TC.⁴¹ These PIs have a higher pill burden, a higher side effect profile, and are generally less well tolerated than boosted DRV; thus, they are no longer recommended. Individuals with active HBV infection need to be on a potent HBV drug with a high barrier to resistance (e.g., TAF, TDF, or entecavir). 3TC or FTC monotherapy is not considered the standard of care for HBV treatment because of a high risk of emerging resistance.²⁹

Boosted Darunavir Plus Dolutegravir

An open-label, Phase 3b noninferiority clinical trial evaluated a switch to DRV/ritonavir (DRV/r) plus DTG versus the continuation of DRV/r plus two NRTIs; the DRV/r plus DTG regimen was noninferior.⁴² Similar results were observed in an observational study of those with NRTI

resistance.⁴³ The combination of boosted DRV plus DTG can be considered for individuals when resistance or intolerance to NRTIs and/or NNRTIs limits other treatment options. Individuals with active HBV infection need to be on a potent HBV drug with a high barrier to resistance (i.e., TAF, TDF, or entecavir). Additional information on the use of boosted DRV plus DTG in treatment-experienced people with ARV resistance is located below (see [Data From Virologic Failure Studies Inform Optimization With NRTI Resistance](#)).

Doravirine Plus Islatravir

Doravirine (DOR) in combination with islatravir (ISL), a new NRTI that specifically blocks translocation, has demonstrated efficacy as a switch strategy in two large Phase 3 studies of more than 1,000 people who were virally suppressed without DOR resistance, prior virologic failure, or active HBV infection. In one study, participants switched from BIC/FTC/TAF,⁴⁴ and in the other study, individuals switched from a stable two- or three-drug ART regimen.⁴⁵ At Week 48, DOR 100 mg/ISL 0.25 mg was noninferior to the baseline regimen for maintenance of viral suppression, with <2% of DOR/ISL-treated participants having HIV RNA ≥ 50 copies/mL. Contrary to earlier studies with higher doses of ISL, no CD4 T lymphocyte (CD4) cell count or total lymphocyte count declines were noted, and there were no differences in CD4 count changes between treatment arms. Additionally, no differences were observed in weight change between arms in either study. At virologic failure, five of seven individuals on DOR/ISL had no resistance.

The combination of DOR/ISL can be used in people with ongoing viral suppression and no history of prior virologic failure or resistance to DOR or ISL. There are insufficient data to recommend the use of DOR/ISL as a switch strategy in treatment-experienced patients who have known or suspected NRTI and/or NNRTI resistance that could compromise the activity of ISL and/or DOR, including the presence of M184I/V mutations. Individuals with active HBV infection need to be on a potent HBV drug with a high barrier to resistance (i.e., TAF, TDF, or entecavir).

Coadministration of DOR/ISL with 3TC or FTC is **contraindicated**, as significant decreases in intracellular islatravir-triphosphate concentrations may occur.⁴⁶ DOR/ISL should not be administered with drugs that are strong CYP3A inducers, as significant decreases in DOR concentrations may occur. For detailed information on drug–drug interactions with DOR and/or ISL, see the [Liverpool HIV Drug Interaction Checker](#).

Bictegravir Plus Lenacapavir

Two Phase 3 trials generated evidence for an oral BIC 75 mg/lenacapavir (LEN) 50 mg single-tablet regimen as an ART simplification strategy. Both trials excluded participants with known or suspected BIC or LEN resistance, active tuberculosis, or HBV infection. In the open-label ARTISTRY-1 study, 557 virally suppressed adults who were taking complex, multi-tablet regimens were randomized 2:1 to switch to once-daily BIC/LEN or continue baseline therapy.⁴⁷ In the double-blind ARTISTRY-2 trial, 577 adults with viral suppression on BIC/FTC/TAF were randomized 2:1 to switch to BIC/LEN or continue BIC/FTC/TAF.⁴⁸ In both trials, BIC/LEN demonstrated noninferior virologic efficacy compared with continuation of the baseline regimen; approximately 1% of participants in each arm in both trials had HIV RNA ≥ 50 copies/mL at Week 48. Safety profiles were similar between the study arms.

These findings support BIC/LEN as an effective simplification strategy for virally suppressed people with HIV, provided there is no known or suspected BIC or LEN resistance or clinically significant drug interactions precluding LEN use. Individuals with active HBV infection need to be on a potent HBV drug with a high barrier to resistance (i.e., TAF, TDF, or entecavir). Of note, initiation of BIC/LEN requires additional oral loading doses of LEN on Days 1 and 2. Loading doses must be repeated after a treatment interruption of more than 7 days. People with HIV should be counseled

about this requirement at initiation and follow up, and clinicians should reassess the appropriateness of this regimen after any treatment interruption that requires repeating the loading doses of LEN.

Long-Acting Intramuscular Cabotegravir Plus Rilpivirine

Use of LA CAB/RPV, administered intramuscularly every 1 or 2 months, with or without a 28-day or longer oral lead-in with these same agents, is a viable optimization strategy in individuals with HIV viral suppression for at least 3 months.⁴⁹⁻⁵¹ Growing data on the use of LA CAB/RPV in the setting of HIV viremia is discussed in the [Virologic Failure](#) section. Candidates for LA CAB/RPV should not have known or suspected resistance to either ARV medication. Drug interactions for both the oral lead-in, if used, and the long-term injections need to be considered (see the [Liverpool HIV Drug Interaction Checker](#)). Individuals with active HBV infection need to be on a potent HBV drug with a high barrier to resistance (i.e., TAF, TDF, or entecavir).

ATLAS and FLAIR were randomized clinical trials with almost 1,200 participants with HIV and viral suppression on oral ART. The studies compared continued oral therapy versus a switch to once-monthly LA CAB/RPV after a 28-day oral lead-in with these same agents.^{52,53} In the intention-to-treat analysis, HIV RNA >50 copies/mL at Week 48 occurred in 1.9% of participants in the LA CAB/RPV arms and 1.7% of participants in the oral therapy arms (combining data from both studies), demonstrating that LA therapy was noninferior to continued oral therapy.⁴⁹ In ATLAS-2M, every-8-week LA CAB/RPV was noninferior to every-4-week LA CAB/RPV in previously suppressed individuals.⁵⁴ In the 687-subject SOLAR study, LA CAB/RPV was noninferior to continued oral BIC/FTC/TAF. There was no difference in viral suppression with or without oral lead-in when initiating LA CAB/RPV therapy.⁵⁵ In the CARES trial, an open-label trial conducted in Africa that enrolled 501 participants, every-8-week LA CAB/RPV was noninferior to continued oral therapy.⁵⁶ In all of these studies, virologic failure was rare; however, when it occurred, resistance to INSTIs, NNRTIs, or both was common.^{52,57}

Practical Considerations When Using Long-Acting Injectable Cabotegravir and Rilpivirine

When prescribing LA CAB/RPV, clinicians should refer to the U.S. Food and Drug Administration product label⁵¹ for guidance with practical considerations, including needle length for those with body mass index (BMI) ≤ 30 kg/m² (1.5-inch needle) versus BMI >30 kg/m² (2-inch needle), as well as management strategies for planned or unexpected missed doses. HIV viral load monitoring should be performed 4 to 8 weeks after a switch to LA CAB/RPV or when returning to care after missed or delayed doses. When individuals are virally suppressed and continue on schedule with injections, viral load monitoring can then resume per current guidelines (see the [Laboratory Testing for Initial Assessment and Monitoring of People With HIV](#) section). Resistance testing, including integrase resistance testing, should be performed in the setting of HIV viremia >200 to 500 copies/mL, regardless of time since last injection.^{52-54,58-60}

Initiation of LA CAB/RPV **is not recommended** during pregnancy. Clinicians should refer to the [Perinatal Guidelines](#) for recommendations for managing women who become pregnant or are planning pregnancy while receiving LA CAB/RPV. Health care providers are strongly encouraged to register women with HIV who become pregnant while receiving LA CAB/RPV in the [Antiretroviral Pregnancy Registry](#).^{52-54,57-60}

Considerations Regarding Long-Acting Cabotegravir Plus Rilpivirine Use in People With a History of Adherence Challenges

There are accumulating data on the use of LA CAB/RPV in people who face challenges with adherence to oral medications. The open-label LATITUDE (ACTG A5359) study enrolled people who had HIV viremia, challenges in taking daily oral ART, and no evidence of CAB or RPV resistance.⁶¹ After adherence support and conditional financial incentives to achieve viral suppression with daily oral ART, participants who were virally suppressed were randomized to monthly LA CAB/RPV or continuing their oral regimen. Of note, despite the requirement for viral suppression before randomization, 24 of the 150 participants randomized to LA CAB/RPV had HIV RNA >200 copies/mL at randomization, including 8 with HIV RNA >10,000 copies/mL. The LATITUDE study was stopped early due to greater efficacy of the LA CAB/RPV regimen. Virologic failure was significantly less common in the LA CAB/RPV group compared to continued oral therapy. See the [Virologic Failure](#) section for more discussion on the use of LA CAB/RPV in people with viremia.

Optimization Strategies Specifically in the Setting of NRTI and/or NNRTI Resistance

Some existing data demonstrate the safety and efficacy of select within-class and between-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). These findings are further supported by data extrapolated from those experiencing virologic failure.

When High-Resistance-Barrier Medications Are Available

Results from several clinical trials support or lend theoretical support to optimization strategies for people with viral suppression that include a switch (1) from a low-barrier drug to a high-barrier drug (e.g., DTG, BIC, boosted DRV) or (2) from one high-barrier drug to another in the setting of underlying NRTI genotypic resistance.

The GS-US-380-4030 study enrolled 565 participants 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, switch to BIC was noninferior to continuing DTG. 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.⁶²

The BRAAVE study was an open-label, optimization study for Black people with HIV and viral suppression for ≥12 months on a standard regimen of two NRTIs plus a third agent (INSTI, NNRTI, or PI). NRTI resistance was present in 14% of participants, with 10% harboring the M184V/I mutation. Individuals were randomized to switch to BIC/FTC/TAF or 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.⁶³

The second-line switch to DTG (2SD) study was conducted at four sites in Kenya in people with HIV who had prior first-line NNRTI plus NRTI regimen failure and achieved viral suppression on an RTV-boosted PI-based regimen without undergoing genotypic resistance testing.⁶⁴ In this prospective, open-label trial, 795 participants were randomized 1:1 to switch the boosted PI to DTG or continue the current regimen. NRTIs were not switched, although a switch was allowed if clinically indicated. At Week 48, switching to DTG was noninferior to continuing a boosted PI, with about 5% of participants in each arm having viral rebound >50 copies/mL. In the 40 people with virologic

rebound, 20 in each arm, no resistance to DTG or PIs was found. This study was limited by the absence of genotypic resistance data at the time of NNRTI/NRTI failure. Studies in similar populations have demonstrated that extensive NRTI and NNRTI resistance is expected in this situation, including resistance to 3TC/FTC and tenofovir.⁶⁵⁻⁶⁷ It is therefore possible to infer that switching from one high-barrier drug to another is safe and effective during viral suppression in the setting of NRTI resistance. This is further supported by data showing that people with virologic failure and NRTI resistance can be successfully treated with a high-barrier drug (second-generation INSTI or boosted PI) plus TAF or TDF and FTC or 3TC.⁶⁵

Data From Virologic Failure Studies Inform Optimization With NRTI Resistance

Several studies conducted in resource-limited countries in people with first-line NNRTI-based virologic failure, and who have NRTI resistance, support treatment recommendations for optimizing ART in individuals with NRTI resistance (see the [Virologic Failure](#) section for details). In the DAWNING study,⁶⁸ which included individuals who were failing first-line NNRTI-based ART, DTG (84%) outperformed LPV/r (70%) for 48-week viral suppression (<50 copies/mL). Participants who had one active NRTI in their study regimen had similar virologic responses to those with two active NRTIs. In the NADIA study, participants failing first-line NNRTI-based therapy were randomized to either DTG or DRV/r combined with randomized NRTIs. At enrollment, resistance to NRTIs was common, with 86% of participants having an M184V mutation conferring resistance to 3TC and FTC, and 50% having a K65R mutation conferring resistance to TAF and TDF. At 48 weeks, DTG was noninferior to DRV/r, with both groups achieving viral suppression to <400 copies/mL in about 90% of participants. There were no differences in rates of viral suppression between participants with resistance to one or both NRTIs in their regimen compared to those with no NRTI resistance.⁶⁵ At Week 96, TDF/3TC was superior to zidovudine/3TC.⁶⁹

The D2EFT trial evaluated DRV/r plus DTG versus DRV/r plus two NRTIs in people with virologic failure on a first-line NNRTI-based regimen containing two NRTIs. Resistance to one or both NRTIs was common. At 96 weeks, 86% of 251 participants on DTG plus DRV/r achieved viral suppression (viral load <50 copies/mL) with no treatment-emergent resistance observed.⁷⁰ Several other observational studies have also demonstrated the efficacy of the combination of DTG with boosted DRV in those with ARV resistance when used in the setting of virologic failure or as treatment optimization in viral suppression.⁷¹⁻⁷⁶ The combination of DTG plus boosted DRV can be considered for individuals when resistance or intolerance to NRTIs and/or NNRTIs limits other treatment options. Individuals with active HBV infection need to be on a potent HBV drug with a high barrier to resistance (i.e., TAF, TDF, or entecavir).

Although these were studies of ART use in the setting of initial NNRTI-based virologic failure, the Panel expects that regimens that are effective during viremia would also be effective in the setting of viral suppression in people 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 NRTI resistance, two NRTIs (TAF or TDF plus 3TC or FTC) should be included in the regimen with a fully active drug with a high resistance barrier, such as DTG, BIC, or boosted DRV (DRV/cobicistat or DRV/r). The use of regimens without any fully active NRTIs **is not routinely recommended** when other viable treatment options are available. However, in some clinical situations—such as when prior resistance testing is not fully available, to avoid major drug–drug interactions, or to simplify regimens—a regimen with a fully active drug with a high resistance barrier plus two partially active NRTIs can be considered. Both tenofovir (TAF and TDF) and 3TC and FTC may retain partial activity even when resistance is present.

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

Before optimizing the ARV regimen of a person with viral suppression who has a history of treatment failure and complex drug resistance, a careful review of the individual's full ARV history, including regimen failures, intolerances, and adverse reactions, as well as review of inferred and cumulative documented drug resistance, should be undertaken. Consultation with a clinician with expertise in HIV drug resistance is recommended **(AIII)**.

As described in the Optimization Strategies Specifically in the Setting of NRTI and/or NNRTI Resistance section above, any regimen that includes a fully active drug with a high barrier to resistance (e.g., DTG, BIC, or boosted DRV) plus two NRTIs (even if resistance is present) is likely to maintain suppression in the setting of optimization.^{64,65}

Bictegravir/Lenacapavir With a History of Complex Antiretroviral Resistance

The two-drug NRTI-sparing regimen BIC/LEN has been studied in people with complex ARV history and underlying drug resistance (e.g., NRTI, NNRTI, and/or PI resistance). The Phase 3 ARTISTRY-1 trial enrolled virally suppressed adults (median age of 60 years) receiving stable, complex ARV regimens, including many with extensive treatment histories and historical drug resistance. Among participants randomized to BIC/LEN, 67% had historical NRTI resistance, 55% NNRTI resistance, and 41% PI resistance. Complex regimens were defined as those that included an NNRTI or boosted PI plus at least one agent from a non-NRTI class, required more than one pill per day or twice-daily dosing, or combined parenteral and oral agents. Participants were taking a median of three ARV pills per day (range 2 to 11). Switching to once-daily, single-tablet oral BIC 75 mg/LEN 50 mg maintained viral suppression at a rate noninferior to continuation of the baseline regimen (proportion of participants with HIV RNA ≥ 50 copies/mL at 48 weeks was $\sim 1\%$ in both arms).⁴⁷

These findings support BIC/LEN as an effective simplification strategy for virally suppressed people with prior ARV resistance, provided there is no known or suspected BIC or LEN resistance or clinically significant drug interactions precluding BIC or LEN use. Individuals with active HBV infection need to be on a potent HBV drug with a high barrier to resistance (i.e., TAF, TDF, or entecavir). Of note, initiation of BIC/LEN requires additional oral loading doses of LEN on Days 1 and 2. Loading doses must be repeated after a treatment interruption of more than 7 days. People with HIV should be counseled about this requirement at initiation and follow up, and clinicians should reassess the appropriateness of this regimen after any treatment interruption that requires repeating the loading doses of LEN.

When High-Resistance-Barrier Medications Are Not Available

Reliably maintaining suppression when there is not a fully active drug with a high resistance barrier is more complicated and requires careful consideration before any switch is made. As noted above, in people who have experienced multiple prior failures and for whom prior ARV history or prior genotypic resistance test results obtained during an episode of virologic failure are not available, proviral DNA genotypic testing may be appropriate **(CIII)**. Clinicians should keep in mind that proviral DNA resistance mutations found can be helpful, but some or all archived resistance mutations may not be found with this testing. Previous studies demonstrated that it is best to include at least two (preferably three) fully active drugs in the setting of virologic failure if a fully active drug with a high resistance barrier is not included in the regimen due to resistance and/or intolerance.⁷⁷ In the setting of multiclass resistance that includes INSTI resistance, it will often require incorporating active drugs

in classes other than NRTIs, NNRTIs, PIs, and INSTIs, such as entry inhibitors (i.e., CCR5 antagonists, post-attachment inhibitors, attachment inhibitors) or capsid inhibitors (i.e., LA injectable LEN), recognizing that entry inhibitors and LA injectable LEN have primarily been studied and are indicated for those with virologic failure.

Knowledge Gaps

- More research is needed on the role of ARV optimization in slowing or reversing excessive ARV-associated weight gain across the age spectrum, from adolescents and young adults to older adults with HIV.
- Research is needed on the long-term virologic outcomes of specific ARV regimens in the setting of underlying viral resistance, such as DTG/3TC or DOR/ISL in people with historical M184V/I mutations.
- Research is needed on the role of the proviral DNA genotype in designing a new regimen in people with unknown ARV history and unknown resistance patterns.
- Research is needed on the safety and efficacy of other novel LA optimization strategies.
- More research is needed on managing people with anti-HBc positivity after switching to non-HBV-active therapy.
- Research is needed on the safety and efficacy of ART switch strategies for people with chronic kidney disease who are not yet on dialysis.

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