Optimizing Antiretroviral Therapy in the Setting of Viral Suppression

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Key Considerations and Recommendations
• Advances in antiretroviral (ARV) treatment and a better understanding of HIV drug resistance have made it possible to consider switching a person with HIV from an effective ARV regimen to an alternative ARV regimen in some situations. • The fundamental principle of ARV regimen optimization is to maintain viral suppression without jeopardizing future treatment options. • Adverse events, drug–drug or drug–food interactions, pill burden, pregnancy, cost, stigma, 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 likely switch to any regimen that has been shown to be highly effective in people who are ARV-naive (AI) or to NRTI-sparing options extensively researched in switch studies, such as dolutegravir (DTG) plus rilpivirine (RPV) (AI) or long-acting cabotegravir plus rilpivirine (LA CAB/RPV) (AI). • For regimen optimization in the setting of existing nucleoside reverse transcriptase inhibitor (NRTI) resistance, if an NRTI is to be included in the new regimen, two NRTIs (tenofovir alafenamide [TAF] or tenofovir disoproxil fumarate [TDF] plus emtricitabine [FTC] or lamivudine [3TC]) should be included, along with a fully active drug with a high resistance barrier, such as DTG (AII), bictegravir (BIC) (BIII), or boosted darunavir (BIII). Alternatively, as noted above, an NRTI-sparing regimen (such as DTG/RPV [AI] or LA CAB/RPV [AI]) is possible if there is no evidence of prior integrase strand transfer inhibitor (INSTI) or RPV resistance. • Monotherapy with either a boosted protease inhibitor or an INSTI 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 chronic hepatitis B virus (HBV)/HIV coinfection, HBV-active drugs that are potent and have a high barrier to resistance (i.e., TAF, TDF, or entecavir) should be used (AII). 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 person with a history of resistance to two or more drug classes (AIII). • Close monitoring to assess tolerability, viral suppression, adherence, and safety is recommended during the first 3 months after a regimen switch (AIII).
Rating of Recommendations: A = Strong; B = Moderate; C = Weak *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 optimization—a switch in therapy to improve certain aspects of therapy—clinicians must keep several key principles in mind to maintain viral suppression while addressing the concerns with the current regimen.

Reasons to Consider Regimen Optimization in the Setting of Viral Suppression

- To simplify a regimen by reducing pill burden and/or dosing frequency
- To enhance tolerability and/or decrease short- or long-term toxicity (see Table 20 and Table 21 in the Adverse Effects of Antiretroviral Agents section for a more in-depth discussion of toxicities)
- To prevent or mitigate drug–drug interactions (see Drug–Drug Interactions)
- To eliminate food requirements
- To switch to a long-acting (LA) injectable regimen for convenience, 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 ARV regimen optimization is to maintain viral suppression without jeopardizing future treatment options. If a regimen switch results in virologic failure with the emergence of new resistance mutations, the person may require a more complex and/or a less tolerated regimen.

Careful Review of Antiretroviral Treatment and Drug-Resistance History Before Optimization

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

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. In people 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 person's most recent drug-resistance test—can be archived in the HIV reservoir and reemerge under the appropriate selective drug pressure. Resistance often can be inferred from the ARV history. For people with documented failure on a regimen that includes drugs with relatively low barriers to resistance—such as a non-nucleoside reverse transcriptase inhibitor (NNRTI), elvitegravir (EVG), raltegravir (RAL), lamivudine (3TC), or emtricitabine (FTC)—a clinician should assume that there is resistance to these drugs, so-called *inferred resistance*. When uncertain about prior resistance, it is generally not advisable to switch from a suppressive ARV regimen, unless the new regimen is likely to be at least as active against potential resistant virus as the current suppressive regimen. This principle is particularly applicable when switching ARV-experienced individuals from a regimen with a

relatively high barrier to resistance—such as those that include pharmacologically boosted protease inhibitors (PIs), dolutegravir (DTG), or bictegravir (BIC)—to one with a lower barrier to resistance.[1] The Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel) recommends that clinicians consult an HIV specialist when contemplating optimization for a person with a history of resistance to two or more drug classes **(AIII).**

If optimization is considered in people with suppressed viral loads who do not have prior drug resistance data, proviral DNA genotypic resistance testing can be considered. For those who have no prior virologic failures and who are on their first or second regimen, or 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 any or all 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 person'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).

Considerations for HBV/HIV Coinfection

For People With HBV/HIV Coinfection

When switching an ARV regimen in a person with active hepatitis B virus (HBV)/HIV coinfection (hepatitis B surface antigen [HBsAg] positive), tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF) (generally given with 3TC or FTC) should be continued as part of the new regimen. Both TDF and TAF are active against HBV and can be used as HBV monotherapy. Although 3TC and FTC are active against HBV, their use as monotherapy against HBV infection **is not recommended (AII)** because emergent HBV resistance to these drugs is highly likely. If TAF or TDF cannot be used, entecavir—a potent antiviral with a high HBV resistance barrier—should be used to treat HBV alongside a fully suppressive ARV regimen **(AII).** Entecavir should not be used without an active ARV regimen to prevent the development of the HIV M184V resistance mutation. Discontinuation of HBV antivirals may lead to reactivation of HBV, which can result in serious hepatocellular damage and death. Refer to the Hepatitis B Virus/HIV Coinfection section for specific recommendations.

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

People with HIV and unknown or nonimmune HBV status should be screened for HBV infection before switching an ARV regimen to one that does not include TAF or TDF plus 3TC or FTC (e.g., DTG/rilpivirine [RPV], DTG/3TC, LA cabotegravir [CAB]/RPV). If a person with HIV shows no evidence of chronic HBV infection (i.e., negative for hepatitis B surface antibody [HBsAg]) and is not immune to HBV (i.e., negative for HBsAb), vaccination should be initiated while considering the ARV switch (including in those with isolated hepatitis B core antibody [HBcAb]).

People with HIV and prior exposure to HBV infection without evidence of chronic infection (i.e., negative HBsAg, positive HBcAb, and either positive or negative HBsAb) are likely at low risk (<1%) of HBV reactivation and even lower risk of HBV reactivation-associated hepatitis, despite the discontinuation of NRTIs. However, there are no published studies to confidently estimate risk in this

population. Within this group, those with positive HBsAb 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.[3] See more information in the Hepatitis B Virus Infection section in the Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents With HIV.

For people previously exposed to HBV, alanine aminotransferase (ALT) should be monitored for 6 months (e.g., at the time of HIV viral load follow-up visits) after switching from ART that includes tenofovir (TDF or TAF) to one that does not include either of these drugs. An increase in ALT levels 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 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 interactions exist. For example, oral rilpivirine (RPV) and atazanavir (ATV) interact with acid-lowering agents, and many ARV drugs may interact with drug transporters or drugs that are inhibitors, inducers, or substrates of cytochrome P450 (CYP) enzymes (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 been previously managed with dose adjustments, will need to be reevaluated in the context of the new ARV regimen.

Assessment for Pregnancy or Pregnancy Potential

People of childbearing potential should have a pregnancy test before switching ART. If a person with HIV is found to be pregnant or desires pregnancy, clinicians should refer to the Perinatal Guidelines for recommendations on the safety and efficacy of ARV use at the time of conception or during pregnancy. All pregnancies that occur while an individual is receiving ART should be reported to the Antiretroviral Pregnancy Registry.

Monitoring After Switching Antiretroviral Therapy

After a treatment switch, people with HIV should be evaluated closely for 3 months (e.g., a clinic visit or telephone call 1 to 2 weeks after the change and a viral load test to check for rebound viremia 4 to 12 weeks after the switch) **(AIII).** The purpose of this close monitoring is to ensure the person clearly understands their prescribed ART regimen, assess medication tolerance, and conduct targeted laboratory testing when there are preexisting laboratory abnormalities or if there are potential concerns with the new regimen. For example, if 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 after the ART change. In the absence of any new complaints, laboratory abnormalities, or evidence of viral rebound over the first 2 to 3 months, clinical and laboratory monitoring may resume on a regularly scheduled basis (see Laboratory Testing for Initial Assessment and Monitoring).

Specific Regimen Optimization Considerations

As with the recommendation for people who are starting ART, the use of a 2- or 3-drug ARV regimen (as discussed below) is generally recommended when switching ART in people with suppressed viral loads **(AI).** People 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 people who have not been on ART **(AI).** People 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 integrase strand transfer inhibitor (INSTI) has been explored in several trials or cohort studies.[4-7] Both INSTI[8] and boosted PI[9] 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;[10,11] therefore, ARV monotherapy as a maintenance strategy is **not recommended (AI).**

Optimization Strategies With Good Supporting Evidence for People Without Known Drug Resistance

Many clinical trials have enrolled participants with stable, suppressed viral loads without known underlying drug resistance and switched them to another regimen. Most of these studies demonstrated maintenance of viral suppression, some of which 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, particularly when the switch is to a drug with a low barrier to resistance.[1] In the two SWITCHMRK studies, those 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 explained by underlying NRTI resistance, a setting where viral suppression can generally be maintained by drugs with a high barrier to resistance, such as boosted PIs, but is less likely to maintain viral suppression when switched 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 underlying resistance.

Three-Drug Regimens

Within-Class Switches

Within-class switches (e.g., switching from one INSTI to another INSTI) may be prompted by adverse events or the availability of ARVs in the same class that offer a better safety profile, reduced dosing frequency, higher barrier to resistance, 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. Below are examples of within-class switch strategies that are proven to be effective in clinical trials or are likely to be effective in those without underlying drug resistance:

- From TDF[12,13] or abacavir (ABC)[14] to TAF
- From RAL or elvitegravir/cobicistat (EVG/c)[15] to BIC or DTG
- From DTG[16-18] to BIC or BIC to DTG

- From efavirenz to RPV,[13,19] doravirine (DOR),[20] or RPV to DOR

Between-Class Switches

Between-class switches (e.g., switching from a boosted PI to an INSTI) 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 examples of between-class switches that have been proven to be effective in clinical trials or are likely to be effective in those without underlying drug resistance:

- From a boosted PI to a second-generation INSTI (e.g., DTG,[21] BIC[22])
- From a boosted PI to RPV[23] or DOR[20]
- From an NNRTI to a second-generation INSTI[24,25] or a boosted PI

Two-Drug Regimens

Some two-drug ARV regimens are effective in maintaining HIV virologic control in people who initiated therapy with three-drug regimens and achieved sustained virologic suppression for at least 3 months. However, none of the two-drug regimens are effective as treatment for HBV and are therefore not recommended for people with HBV coinfection. In people with HBV who cannot take TAF or TDF, these regimens can be considered if used with a potent, high barrier-to-resistance anti-HBV active medication (i.e., entecavir) **(AII).** See the section above on HBV considerations during optimization. The following are examples of successful strategies studied in clinical trials for switching from 3- to 2-drug regimens in people with suppressed HIV.

Dolutegravir Plus Rilpivirine

Two Phase 3 trials, SWORD-1 and SWORD-2, demonstrated noninferior efficacy of switching to a 2-drug regimen of DTG with RPV compared to continuing a first or second ARV regimen in individuals with suppressed HIV-RNA without prior virologic failure.[26] Individuals were excluded from the study if they had active HBV infection (unless the person was also on a specific HBV active regimen), 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. 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 3-drug ARV regimen to DTG plus 3TC or FTC as a maintenance strategy in people with ongoing virologic suppression and no history of prior virologic failure or resistance to these agents was noninferior to continuing a 3-drug therapy in a large randomized clinical trial (TANGO),[27] in smaller clinical trials,[28-30] and in observational studies[31-33] **(AI).** 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.[34]

Boosted Protease Inhibitor Plus Lamivudine

A boosted PI plus 3TC is a reasonable 2-drug optimization option in individuals without resistance who are suppressed on a current regimen and who do not have active HBV infection. Pill burden and potential drug interactions are limitations compared to the above 2-drug regimens. Several regimens using a boosted PI plus 3TC have been shown to be effective in clinical trials, including darunavir/ritonavir (DRV/r) **(BI),**[35] darunavir/cobicistat (DRV/c) **(BIII),** atazanavir/ritonavir (ATV/r) **(CI),**[36,37] and LPV/r **(CI).**[38] 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 the standard of care for HBV treatment because of a high risk of emerging resistance.[34]

Boosted Darunavir Plus Dolutegravir

An open-label, Phase 3b, noninferiority clinical trial evaluated the continuation of DRV/r plus two NRTIs versus a switch to DRV/r plus DTG; the switched regimen was noninferior.[39] Because of the small sample size of this study, the regimen of DRV/r plus DTG is recommended only in the absence of other alternative options but can be considered in particular for individuals with resistance and/or intolerance to 3TC (or FTC), ABC, and TDF (or TAF) **(CI).** Similar results were observed in two small observational studies.[40,41] 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).

Long-Acting Intramuscular Cabotegravir Plus Rilpivirine

Long-acting ARV medications provide the convenience of reduced dosing frequency and may improve quality of life for individuals with pill fatigue or concerns about disclosure of HIV status or stigma associated with daily oral medication. Long-acting (LA) intramuscular (IM) injectable formulations of the INSTI cabotegravir (CAB) and the NNRTI RPV are approved by the U.S. Food and Drug Administration (FDA) to be given once monthly or every 2 months as a complete regimen for individuals ≥12 years old with sustained (e.g., ≥3 months) virologic suppression (HIV-1 RNA <50 copies/mL) on a stable ARV regimen, with no history of treatment failure, and with no known or suspected resistance to either CAB or RPV.[42-44]

Panel's Recommendation

The Panel recommends that monthly or every 2-month LA CAB/RPV can be used to replace an existing oral ARV regimen in people with HIV who fulfill all of the following criteria **(AI)**:

- Sustained viral suppression for at least 3 months
- No history of documented or suspected resistance to either CAB or RPV
- No active HBV infection (unless also receiving TAF, TDF, or entecavir)
- Not pregnant or actively planning pregnancy
- Not receiving medications with significant drug interactions with oral (during lead-in or bridging therapy) or injectable CAB or RPV (see Tables 24b and Table 24d)

Oral lead-in therapy with CAB and RPV is optional and can be done based on provider–patient discussion.

Clinical Trial Data

Two Phase 3 clinical trials (ATLAS and FLAIR) randomized almost 1,200 participants with HIV-1 and viral suppression on oral ART to receive once-monthly LA CAB/RPV or to continue their oral ARV regimens.[45,46] Participants could not have prior resistance to INSTIs or NNRTIs (except the K103N mutation), previous virologic failure (ATLAS trial), or active or occult HBV infection. Both studies used a 1-month oral lead-in of once-daily CAB 30 mg with RPV followed by injectable LA CAB/RPV monthly (loading dose x 1 followed by maintenance dosing). In the intention to treat the exposed population, HIV RNA >50 copies/mL at Week 48 occurred in 11 (1.9%) participants in the IM arms and 10 (1.7%) participants in the oral therapy arms (combining data from both studies) demonstrating that long-acting therapy was noninferior to continued oral therapy.[47] Virologic failure was rare; however, when it occurred, resistance to INSTIs, NNRTIs, or both was common.

The ATLAS-2M study compared LA CAB 600 mg/RPV 900 mg every 8 weeks (n = 522) versus LA CAB 400 mg/RPV 600 mg every 4 weeks (n = 523) in ART-experienced adults.[48] At 48 and 96 weeks, every 8-week dosing was noninferior to every 4-week dosing (HIV RNA ≥50 copies/mL; 2% vs. 1% at 48 weeks).[49,50]

In the SOLAR study, 687 individuals who were virologically suppressed on BIC/FTC/TAF were randomized 2:1 to either switch to LA CAB/RPV every 2 months or remain on BIC/FTC/TAF.[51] At 48 weeks LA CAB/RPV was virologically noninferior to continued BIC/FTC/TAF with 1% versus <1% virologic failure, respectively. There was also no difference in viral suppression with or without oral lead-in when initiating LA CAB/RPV therapy. Based on these data and other existing data, oral lead-in therapy is now considered optional (see the CABENUVA FDA drug label).

Lastly, the Cabotegravir and Rilpivirine Efficacy and Safety (CARES) trial, an open-label trial conducted in Africa, randomized people with HIV and viral suppression to receive LA CAB/RPV every 8 weeks or to continue with their oral ARV regimen. At 48 weeks, 246 of 255 (96%) in the LA CAB/RPV arm and 250 of 257 (97%) in the oral ARV arm maintained HIV RNA <50 copies/mL. Two LA CAB/RPV participants had virologic failure at Week 48 and developed high-level resistance to both CAB and RPV.[52]

Adverse Effects

The most common adverse events associated with LA CAB/RPV are injection site reactions (ISRs) which occurred in more than 80% of participants at least once. ISRs reduce in frequency over time, occurring in about 10% to 30% of participants 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 have also been reported.[49,53]

Practical Considerations When Using Long-Acting Injectable Cabotegravir and Rilpivirine

When prescribing LA CAB/RPV, clinicians should refer to the FDA product label[42] for guidance with the following practical considerations:

- Injection techniques, including injection sites and needle length in people with body mass index >30 kg/m^2

- Several drugs, particularly those interacting with CYP3A or uridine diphosphate glucuronosyltransferase 1A1, are contraindicated with CAB and RPV (oral and/or IM) due to significant drug interactions (Drug–Drug Interaction Tables 24b and 24d).
- Management strategies for missed doses of IM injections and use of oral bridging therapy

HIV Viral Load and Drug-Resistance Testing Monitoring

HIV viral load monitoring should be performed 4 to 8 weeks after a switch to LA CAB/RPV. HIV viral load also should be checked in people with unplanned missed visits and delayed dosing of LA CAB/RPV. When viremia develops during LA therapy, resistance testing, including integrase resistance testing, should be performed. Follow-up dosing in people with missed doses should not be delayed while awaiting viral load and resistance test results. In a pooled analysis from FLAIR, ATLAS, and ATLAS-2M, confirmed virologic failure was more common in the setting of baseline, proviral, RPV resistance-associated mutations; HIV-1 subtype A6 (rare in the United States); higher baseline body mass index; and lower week-8 trough RPV concentration.[54] However, some recent studies did not observe worse outcomes in people with a high body mass index (Opera Cohort and CARES Study).[55,56] In the setting of confirmed virologic failure on LA CAB/RPV, resistance to NNRTIs and INSTIs is common.[57-59]

Pregnancy Considerations

Initiation of LA CAB/RPV is not recommended during pregnancy. Clinicians should refer to the Perinatal Guidelines for recommendations in managing people who become pregnant or are planning pregnancy while receiving LA CAB/RPV. Health care providers are strongly encouraged to register people with HIV who become pregnant while receiving LA CAB/RPV in the Antiretroviral Pregnancy Registry.

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

There are emerging data on the use of LA CAB/RPV in people with a history of adherence challenges. The open-label Long-Acting Therapy to Improve Treatment Success in Daily Life (LATITUDE [ACTG A5359]) Study enrolled people who had HIV viremia, challenges in taking daily oral ART, and no evidence of CAB or RPV resistance.[60] After adherence support and conditional financial incentive, participants who were able to achieve viral suppression were randomized to monthly LA CAB/RPV or to continue on the oral regimen. Study randomization was stopped early by the Data Safety Monitoring Board because of lower rates of virologic failure in individuals randomized to LA CAB/RPV than those staying on oral therapy (see the Virologic Failure section for more discussion).

Optimization Strategies for People With Viral Suppression and a History 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.

Within-Class Switch From Dolutegravir to Bictegravir in the Setting of Limited 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, 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.[61] Results from this trial lend theoretical support to other optimization strategies that include a switch from one high-barrier drug to another in the setting of underlying NRTI genotypic resistance. This study also supports using drugs with a high barrier to resistance when only one, and possibly no NRTIs in the background regimen, need to be fully active. This is further supported by other lines of evidence, some of which are discussed below.

Data of Within and Between Class Switches to Bictegravir in the Setting of Limited Drug Resistance

The BRAAVE study was an open-label, optimization study for Black people with HIV and viral suppression for ≥12 months on a standard regimen of two NRTIs plus a third agent (INSTI, NNRTI, or PI). Individuals were randomized to switch to BIC/FTC/TAF or to remain on current therapy (although individuals on TDF were switched to TAF). Switching to BIC-based therapy was noninferior for maintaining viral suppression compared with continuing current oral therapy. Baseline regimens included 61% INSTI, 31% NNRTI, and 9% PI. Baseline resistance did not affect the outcomes of therapy. In particular, NRTI resistance was present in 14% of participants, with 10% harboring the M184V/I mutation.[62]

Switch From a Boosted Protease Inhibitor to Dolutegravir in Individuals With Viral Suppression and Prior First-Line NNRTI Plus NRTI Failure

The second-line switch to DTG (2SD) study was conducted at four sites in Kenya in a population of people with HIV who had prior first-line NNRTI plus NRTI regimen failure and achieved viral suppression on a current ritonavir-boosted PI-based regimen without undergoing genotypic resistance testing.[63] In this prospective, open-label trial, 795 participants with HIV 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. Grade 3 or 4 adverse events were similar in the two groups. This study was limited by the absence of genotypic resistance data demonstrating the amount of NRTI resistance present at the time of first-line NNRTI plus NRTI failure. Nevertheless, several related studies in similar settings have demonstrated that extensive NRTI and NNRTI resistance is expected in this situation, often including resistance to tenofovir and 3TC or FTC.[64-66] Accepting that substantial NRTI resistance was likely to be present in this study population, 2SD provided evidence that a person who is suppressed on a boosted PI-based regimen is likely to remain suppressed on a second-generation INSTI-based regimen 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 second-generation INSTIs plus TAF or TDF and FTC or 3TC.[64]

Data From Virologic Failure Studies Inform Optimization With NRTI Resistance in Clinical Practice

Several studies conducted in resource-limited countries where people with first-line NNRTI-based virologic failure and who have NRTI-resistance support treatment recommendations for optimizing ART in these settings (details in the Virologic Failure section). In the DAWNING study,[67] for individuals who failed 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 as 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 and 50% having a K65R mutation. 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.[64] At Week 96, TDF was superior to zidovudine when combined with 3TC.[68]

Although these were studies of ART use in the setting of initial NNRTI-based virologic failure, we expect 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 **(AII),** BIC **(BIII),** or boosted DRV (DRV/c or DRV/r) **(BIII).** The use of regimens without any fully active NRTIs **is not routinely recommended** when there are other viable treatment options. However, in some clinical situations—such as when prior resistance testing is not fully available, to avoid major drug–drug interactions, to keep regimens simpler, or for other reasons—a regimen with a fully active drug with a high resistance barrier plus two partially active NRTIs can be considered. Both tenofovir and cytidine analogs 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 an 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 and cumulative drug resistance profile should be undertaken. Consultation with a clinician with expertise in HIV drug resistance is recommended **(AIII).**

As described in the Optimization Strategies for People With Viral Suppression and a History 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 achieve suppression in those experiencing virologic failure and maintain suppression in the setting of optimization.[63,64] 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. In people with prior virologic failure(s) and/or limited prior resistance testing, proviral DNA genotypes can be considered. Clinicians should keep in mind that proviral DNA resistance mutations found will be useful, but some archived resistance mutations may not be found with this testing. Previous studies demonstrated that it is best to include at least 2 (preferably 3) 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.[69] In this setting, 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, and fusion inhibitors) or capsid inhibitors (e.g., lenacapavir), recognizing that entry and capsid inhibitors have primarily been studied and are indicated for those with virologic failure.

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