Switching or Simplifying Antiretroviral Therapy

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Module 3: Antiretroviral Therapy
Lesson 4: Switching or Simplifying Antiretroviral Therapy

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Background

Rationale for Switching or Simplifying Antiretroviral Therapy

There are many reasons why a patient may potentially benefit from a change in antiretroviral therapy, even when they have consistently suppressed HIV RNA levels. Common reasons to consider switching a regimen in the setting of virologic suppression include managing or preventing short-term or long-term adverse effects, reducing pill burden, and avoiding problematic drug interactions.[1,2,3] Additional considerations may include a need to change due to insurance requirements, optimizing the regimen for conception or pregnancy, or a patient preference to switch to a long-acting injectable regimen. These reasons for switching an antiretroviral regimen are distinct from changing antiretroviral therapy in the setting of virologic failure with documented antiretroviral resistance, which necessitates transitioning to a salvage regimen as guided by drug resistance testing. Nevertheless, even switches in the setting of long-term virologic suppression require careful clinical considerations to ensure the new regimen is safe and effective.

Updating Antiretroviral Therapy to a Modern Regimen

One common reason for antiretroviral therapy switches in clinical practice is to “update” an older regimen to a more modern option. In this situation, the regimen modification may benefit the person with HIV by reducing pill burden, eliminating food restrictions, and decreasing the risk for long-term adverse effects. Some older antiretroviral agents should always be replaced with a more modern, superior medication. For example, certain protease inhibitors (PIs), including fosamprenavir, indinavir, lopinavir-ritonavir, nelfinavir, and tipranavir, should be replaced by boosted darunavir or a medication from another drug class (often a second-generation integrase strand transfer inhibitor [INSTI]). Boosted atazanavir should generally also be changed to boosted darunavir or an INSTI. In addition, the old nucleoside reverse transcriptase inhibitor (NRTI) zidovudine should be replaced by a newer NRTI or another medication from another class. Furthermore, most experts would also recommend updating older NNRTIs, such as nevirapine or efavirenz, to a newer NNRTI or a medication from another drug class. If a patient is taking an antiretroviral regimen that includes one or more of the outdated medications noted above, clinicians should consider obtaining expert consultation to optimize the new antiretroviral regimen.

Switching Regimen to Reduce Pill Burden

Persons with HIV may request a change of antiretroviral therapy to reduce pill burden for the sake of convenience. If this change can be safely made with a high likelihood of maintaining virologic suppression, there may be long-term benefits associated with simplifying the antiretroviral regimen. Multiple studies have demonstrated that taking fewer pills translates to better adherence and higher rates of long-term virologic

control.[4,5,6,7,8] Furthermore, as the population of individuals living with HIV ages, they will increasingly need to take more medications for non-HIV-related conditions, leading to added polypharmacy and treatment complexity, thus increasing the benefit of simpler antiretroviral therapy combinations.[3,9,10]

Factors to Consider Before Switching or Simplifying Therapy

The principal goal of any antiretroviral therapy switch is to improve a patient's quality of life while maintaining virologic suppression.[1,3] Taking this overarching goal into consideration, a clinician contemplating a modification of antiretroviral therapy for a patient with consistently suppressed HIV RNA levels should consider multiple factors related to past history, including:

- Prior antiretroviral therapy regimens,
- Past virologic failures
- Past drug resistance test results (review every past resistance test result)
- Medication adherence and adherence barriers
- Past or current intolerance to antiretroviral medications.
- Active medication list (including herbal and over-the-counter medications)
- Potential changes in drug interactions (that may occur after the regimen switch)
- Food requirements with the new regimen
- Potential side effects with the new regimen
- Cost or availability of the new regimen.

Considering Past Virologic Failure and Drug Resistance

A history of virologic failure is particularly important when considering a switch from a regimen with an anchor drug that has a relatively higher genetic barrier to resistance to one with a relatively lower barrier to resistance, even if the individual has suppressed HIV RNA levels at the time the switch is considered. If considering a switch from an agent or regimen of relatively higher barrier to resistance to an agent or regimen of relatively lower barrier to resistance, it is imperative to ensure that there is no underlying resistance (to any component of the new regimen) that may have been overcome by the potency of the prior regimen (because such resistance could compromise the efficacy of the new combination). Any potential switch of antiretroviral therapy should assimilate a composite of all prior drug resistance test results. The most important points about past resistance to remember when considering an antiretroviral regimen switch are:

- All past resistance test results are relevant and should be taken into consideration (not just the most recent result).
- Some regimens have a relatively higher barrier to developing drug resistance (these include boosted protease inhibitors like boosted darunavir, and the second-generation INSTIs dolutegravir and bictegravir).
- Other options are considered to have a relatively lower barrier to drug resistance (such as elvitegravir, raltegravir, NNRTIs, and NNRTI combination tablets).
- In general, a person can switch from one high barrier to resistance medication to another high barrier to resistance medication, assuming there are no drug interaction issues or other contraindications (for example, a switch from once-daily boosted darunavir to dolutegravir is often acceptable).
- If switching from a regimen of relatively high barrier to resistance to a regimen of relatively lower barrier to resistance, it is imperative to ensure there are no drug resistance mutations that would compromise any part of the regimen, including the NRTI backbone (for example, switching dolutegravir to raltegravir or to an NNRTI). If prior resistance results are unavailable and the patient would benefit from the switch, expert consultation is recommended to help ensure the switch will maintain virologic suppression.
- If a person is taking a regimen that appears to be a salvage regimen, such as a regimen with more than three active antiretroviral agents (not including the pharmacokinetic booster), and past

resistance results are complex or not available, expert consultation is recommended prior to a switch or simplification of the therapy.

Monitoring after Antiretroviral Switch or Simplification

After switching or simplifying an antiretroviral regimen, it is important to plan for close follow-up during the first 3 months after the regimen change. This follow-up should include confirming the patient is taking the new combination appropriately, evaluating for medication tolerance, and obtaining an HIV RNA level within 4 to 8 weeks after the regimen change.[1]

Switching to an Integrase Strand Transfer Inhibitor

Integrase strand transfer inhibitors (INSTIs) have become the preferred and most widely used anchor drugs in antiretroviral regimens. The use of dolutegravir and bictegravir has expanded in clinical settings due to excellent tolerability, high barrier to resistance, minimal drug interactions, and convenient once-daily dosing. The following summaries outline several key prospective studies involving patients who were switched to an INSTI-based regimen that contained either bictegravir or dolutegravir. Switch studies relevant to the older, less frequently used INSTIs, raltegravir and elvitegravir, will not be included. These switch studies all involved individuals who had already achieved virologic suppression.

Switch to Bictegravir-Tenofovir alafenamide-Emtricitabine

- **GS-380-1878**: Adults with virologic suppression were randomized to bictegravir-tenofovir alafenamide-emtricitabine or to continue on a boosted PI. Participants in the bictegravir-tenofovir alafenamide-emtricitabine switch group plus maintained noninferior virologic efficacy as compared to continuing the boosted-PI regimen at 48 weeks, with virologic suppression in 92% versus 89%, respectively.[11]
- **GS-380-1844**: Adults taking dolutegravir plus abacavir-lamivudine were randomized to maintain their antiretroviral regimen or switch to bictegravir-tenofovir alafenamide-emtricitabine.[12] Rates of virologic suppression were nearly identical in the two arms: 94% in the bictegravir-tenofovir alafenamide-emtricitabine group versus 95% in the group that remained on dolutegravir plus abacavir-lamivudine.[12]
- **GS-380-1961**: Adult nonpregnant women with virologic suppression were randomized to maintain their antiretroviral regimen or switch to bictegravir-tenofovir alafenamide-emtricitabine.[13] The virologic suppression rates were equivalent in the two groups: 96% in the group switched to bictegravir-tenofovir alafenamide-emtricitabine versus 95% in the group that maintained their baseline antiretroviral therapy regimen.[13]
- **GS-380-4030**: Adults with at least 6 months of virologic suppression while taking dolutegravir plus either tenofovir alafenamide-emtricitabine or tenofovir DF-emtricitabine were randomized in a 1:1 ratio to switch to either bictegravir-tenofovir alafenamide-emtricitabine or dolutegravir plus tenofovir alafenamide-emtricitabine.[14] The virologic suppression rates were similar in those who switched to bictegravir-tenofovir alafenamide-emtricitabine compared with those on dolutegravir combination therapy (93.3% versus 91.1%, respectively), including among participants with archived NRTI resistance.[14] Weight gain was greater among those switching from tenofovir DF to tenofovir alafenamide rather than being clearly attributable to bictegravir versus dolutegravir.[14]
- **BRAAVE-2020**: Adults with HIV in the United States who identified as Black or African American individuals (and with virologic suppression) were randomized 2:1 to switch to bictegravir-tenofovir alafenamide-emtricitabine or continue their baseline regimen (2 NRTIs plus a third antiretroviral medication). The switch group had noninferior virologic suppression, including participants with an M184V/I resistance mutation. as determined by an archived genotype at study entry.[15]

Switch to Dolutegravir

- **NEAT 022**: In this trial, adults who were at least 50 years of age (and/or had a Framingham score of 10% or greater) were switched from a ritonavir-boosted PI to dolutegravir.[16] All participants had routinely suppressed HIV RNA levels while taking a boosted PI and two NRTIs, and none had documented NRTI resistance mutations.[16] After 48 weeks, 98% of individuals in the boosted PI arm maintained virologic suppression compared to 95% in the dolutegravir switch arm (a non-statistically significant difference). Notably, lipid parameters and cardiovascular risk improved in the switch arm.[16]
- **STRIIVING**: In the open-label STRIIVING study, investigators enrolled 551 adults with HIV who had suppressed HIV RNA levels and examined the consequences of switching to a fixed-dose combination of dolutegravir-abacavir-lamivudine (switch group) versus continuing current therapy (maintenance

group).[17] All participants were required to have suppressed HIV RNA levels while taking their first or second antiretroviral therapy regimen, a negative HLA-B*5701 assay, and no history of virologic failure. Participants were taking a broad range of antiretroviral therapy regimens at study enrollment. Analysis at week 24 showed similar rates of virologic suppression in the switch group (85%) and the maintenance group (88%).[17]

Summary of Key Findings with INSTI Switch Studies

Several key findings have emerged from the INSTI switch studies involving a switch to a bictegravir- or dolutegravir-based regimen.

- Overall, these trials show that switching to bictegravir-tenofovir alafenamide-emtricitabine maintains high rates of virologic suppression in carefully selected, virologically suppressed individuals, including those with archived NRTI resistance, such as M184V/I. Across these studies, virologic suppression rates were comparable to those in the absence of NRTI resistance, and treatment-emergent resistance was rare.
- The STRIVING study showed a switch to dolutegravir-abacavir-lamivudine was not equivalent to continuing a boosted-PI regimen in carefully selected patients with a negative HLA-B*5701 test and no prior history of prior virologic failure, drug resistance, multiple past antiretroviral therapy regimens, or hepatitis B coinfection.[17] This switch is rarely done in clinical practice now.
- Studies that have evaluated a switch to bictegravir-tenofovir alafenamide-emtricitabine or dolutegravir plus tenofovir alafenamide-emtricitabine have documented high levels of virologic efficacy for both of these options, regardless of history of virologic failure or pre-existing NRTI resistance-associated mutations, such as M184V/I.[18,20] The high efficacy of these combinations is attributed to the relatively high potency and barrier to resistance of the bictegravir and dolutegravir components, along with a reduction in viral replicative capacity that occurs with use of tenofovir alafenamide (or tenofovir DF) and emtricitabine in the setting of certain NRTI mutations. Recent recommendations suggest that for individuals with NRTI resistance, the switch regimen should include two NRTIs (tenofovir alafenamide or tenofovir DF, in combination with emtricitabine or lamivudine) plus an agent with a relatively high barrier to resistance (dolutegravir, bictegravir, or boosted darunavir).[1]

Switching to a Non-Nucleoside Reverse Transcriptase Inhibitor

Multiple studies have assessed the outcome of switching individuals to various NNRTI agents, including switches from one NNRTI to another NNRTI or from alternate anchor agents to an NNRTI. In particular, many studies have evaluated switching from an efavirenz-based therapy to an alternate NNRTI to examine the impact on central nervous system side effects and lipid parameters.[21,22,23] Although doravirine and rilpivirine are not part of first-line recommended antiretroviral regimens for treatment-naïve individuals in the United States, these agents may serve as alternative NNRTI medications and may be utilized in switch regimens following intolerability or complications of a PI- or INSTI-based antiretroviral regimen.[24,25,26,27] In particular, a switch to doravirine- or rilpivirine-based antiretroviral therapy may offer a treatment simplification or an improvement in tolerability for certain persons with HIV, though unique drug interactions with these agents, especially rilpivirine, should be considered. Therefore, the following summarizes key studies that involve a switch to doravirine or rilpivirine.

Switch to Doravirine

- **DRIVE SHIFT**: In this open-label switch trial, individuals with suppressed HIV RNA levels taking two NRTIs plus either a boosted PI, cobicistat-boosted elvitegravir, or an NNRTI were randomized to continue their current regimen or switch to doravirine-lamivudine-tenofovir DF.[27] After 24 weeks, 94% of participants who switched to the doravirine-anchored regimen maintained a suppressed HIV RNA, as compared to 95% who remained on their baseline regimen (a non-significant difference).[27] Among participants who were taking a boosted PI regimen at baseline, lipid parameters improved after the switch to doravirine.
- **Do-It Trial (ACTG 5391)**: This multicenter, open-label, randomized trial randomized people with HIV and high body mass index (median 34.9 kg/m²) who were virologically suppressed on a non-boosted INSTI (bictegravir, dolutegravir, or raltegravir) plus tenofovir alafenamide-emtricitabine to continue the regimen, switch the INSTI to doravirine while continuing tenofovir alafenamide-emtricitabine, or switch to doravirine plus tenofovir DF-emtricitabine.[28] At 48 weeks, the estimated mean weight change was −0.47% with doravirine plus tenofovir-emtricitabine, −2.73% with doravirine plus tenofovir DF-emtricitabine, and −1.84% with continued non-boosted INSTI plus tenofovir alafenamide-emtricitabine.[28] The regimen changes did not result in clinically meaningful differences in change in weight change.[28]

Switch to Rilpivirine

- **GS-366-1160**: In this study, individuals with suppressed HIV RNA levels on efavirenz-tenofovir DF-emtricitabine were randomized to continue their current regimen or switch to rilpivirine-tenofovir alafenamide-emtricitabine.[29] After 48 weeks, 90% of the participants in the rilpivirine-tenofovir alafenamide-emtricitabine arm maintained virologic suppression compared to 92% in the efavirenz-tenofovir DF-emtricitabine arm.[29] Significant improvements in bone mineral density and renal proximal tubule wasting were seen in the group randomized to the new regimen, likely due to the switch from tenofovir DF to tenofovir alafenamide.
- **SPIRIT**: This randomized, open-label trial enrolled individuals with sustained virologic suppression on a boosted PI-based regimen and compared switching to the single-tablet regimen of rilpivirine-tenofovir DF-emtricitabine versus maintaining the current PI-based treatment.[25] The rates of virologic suppression at 24 weeks were comparable (90%) in the two arms; lipid levels and gastrointestinal side effects improved for those individuals who switched to rilpivirine-based therapy.[25]

Summary of Key Findings with NNRTI Switch Studies

The following summarizes key points to consider when switching to an NNRTI-based regimen.

- **Switch from Boosted PI to NNRTI**: In general, a switch from a boosted protease inhibitor-based regimen to doravirine or rilpivirine is associated with improved lipid parameters.[25,27,30] A switch or simplification of boosted PI-based regimens to doravirine- or rilpivirine-based therapy may be an option for select patients, but this type of regimen change has a significant risk of virologic failure if the patient has taken multiple regimens in the past, has previously experienced virologic failure, or has resistance mutations, such as a pre-switch M184V/I that compromise the NRTI backbone of the new regimen.[24,25]
- **Switch from Efavirenz to Rilpivirine**: Several studies have shown that patients can safely switch within the NNRTI class from efavirenz to rilpivirine, with equivalent virologic suppression and improved central nervous system side effects.[22,31]
- **Switch to Rilpivirine if Baseline HIV RNA Greater than 100,000 copies/mL**: For antiretroviral treatment-naïve persons, rilpivirine-based therapy carries a higher risk of virologic failure if the pretreatment HIV RNA level is 100,000 copies/mL or higher.[32] In contrast, a baseline HIV RNA level greater than 100,000 copies/mL does not preclude a switch to rilpivirine-based therapy if the HIV RNA levels have been suppressed below 50 copies/mL for at least 6 months, and there is no known or suspected resistance to rilpivirine or other agents combined with rilpivirine in the switch regimen, such as emtricitabine, tenofovir alafenamide, or tenofovir DF.
- **Switch to Doravirine Following INSTI-Associated Weight Gain**: Doravirine has been found to have relatively neutral effects on weight.[28] For this reason, some clinicians consider switching to a doravirine-based regimen following weight gain associated with taking an INSTI; this switch often also includes switching tenofovir alafenamide to tenofovir DF. The A5391 Do-IT trial showed that switching from a non-boosted INSTI with tenofovir alafenamide-emtricitabine to a doravirine-based regimen, did not produce clinically meaningful differences in weight change, fasting lipids, insulin resistance, fat mass, or bone mineral density.[28]

Nucleoside Reverse Transcriptase Inhibitor Switches

Multiple studies have examined the efficacy and safety of switching the nucleoside (or nucleotide) reverse transcriptase inhibitor (NRTI) backbone agents in a patient's regimen, with more recent studies focusing on switching tenofovir DF to tenofovir alafenamide. These studies have shown that tenofovir alafenamide is safer than tenofovir DF, with respect to renal and bone toxicity. In addition, tenofovir alafenamide may be used in the setting of mild-to-moderate renal insufficiency (creatinine clearance as low as 30 mL/min). For these reasons, most clinicians favor tenofovir alafenamide over tenofovir DF or abacavir, assuming there are no cost or coverage barriers, drug interactions, or other concerns about the switch. The following summaries focus on within-class NRTI switches to tenofovir alafenamide. Another strategy that is becoming more common is a switch that reduces the number of NRTIs in the regimen (such as a switch from an anchor drug with two NRTIs to dolutegravir-lamivudine or doravirine-islatravir) or a switch to a regimen that avoids NRTIs altogether, such as dolutegravir-rilpivirine or long-acting injectable cabotegravir-rilpivirine; these switches to a two-drug regimen will be discussed in more detail later in this lesson.

Switch to Tenofovir Alafenamide

- **Study 109**: The GS-109 switch study examined the outcomes of switching adults from tenofovir DF-containing antiretroviral therapy to a tenofovir alafenamide-containing regimen.[33] Participants in this study were required to have HIV RNA less than 50 copies/mL for at least 48 weeks on a tenofovir DF-containing regimen, which had to be their first regimen, and to have an estimated glomerular filtration rate (eGFR) above 50 mL/min.[33] A total of 1,436 participants taking tenofovir DF and emtricitabine in combination with boosted atazanavir (n = 601), efavirenz (n = 376), or elvitegravir-cobicistat (n = 459) were randomized 2:1 to switch to elvitegravir-cobicistat-tenofovir alafenamide-emtricitabine or remain on their current therapy.[33] Overall, participants who were switched to elvitegravir-cobicistat-tenofovir alafenamide-emtricitabine had noninferior virologic responses compared with those in the no-switch group.[33] Switching to tenofovir alafenamide led to improvements in markers of renal proximal tubulopathy and bone mineral density, though all lipid levels (total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides) increased.
- **GS-311-1089**: In this randomized, double-blind, double-dummy, active-controlled study, investigators enrolled individuals with HIV RNA below 50 copies/mL on a regimen consisting of tenofovir DF-emtricitabine plus a third agent to either maintain their current regimen (n = 330) or switch to tenofovir alafenamide-emtricitabine plus the same third agent (n = 333).[34] At 48 weeks, a similar proportion of participants had HIV RNA below 50 copies/mL (94% in the tenofovir alafenamide-emtricitabine arm and 93% in the tenofovir DF-emtricitabine arm).[34] The group that switched to tenofovir alafenamide-emtricitabine experienced a statistically significant improvement in median eGFR compared to the tenofovir DF-emtricitabine group (+8.4 mL/min versus +2.8 mL/min, a statistically significant difference).[34] Furthermore, markers of proximal tubule dysfunction improved in the tenofovir alafenamide-emtricitabine group and did not change in the emtricitabine-tenofovir DF group.[34] Bone mineral density improved in the tenofovir alafenamide-emtricitabine group, whereas it worsened in the tenofovir DF-emtricitabine group.[34]
- **GS-366-1216**: In this randomized controlled trial, investigators enrolled individuals with suppressed HIV RNA levels for at least 6 months on rilpivirine-tenofovir DF-emtricitabine, creatinine clearance above 50 mL/min, and no genotypic resistance to the study drugs.[35] Participants (total of 630) were randomized equally to continue the baseline regimen or switch to rilpivirine-tenofovir alafenamide-emtricitabine (each with a matching placebo).[35,36] After 48 weeks, 94% of 316 participants in the tenofovir alafenamide arm and 94% of 313 in the tenofovir DF arm had HIV RNA below 50 copies/mL, demonstrating noninferior virologic efficacy of the regimen switch.[35]

Summary and Recommendations for Within-Class NRTI Switches

The following summarizes key points and recommendations about NRTI backbone changes.

- Situations may arise that warrant consideration of (1) a switch from one NRTI backbone to another NRTI backbone, (2) a switch from a regimen that includes two NRTIs to a regimen with one NRTI, or (3) a switch to an NRTI-sparing regimen. Whenever one of these switches is considered, the specific choice should be based on prior antiretroviral history, prior HIV drug resistance data, drug interactions, drug-food interactions, and the presence of hepatitis B virus (HBV) coinfection.
- Any switch to abacavir requires screening with HLA-B*5701 prior to the switch, and abacavir should not be used if the HLA-B*5701 test is positive. In current clinical care, use of abacavir has declined markedly, and switching to abacavir is uncommon. More often, consideration is given to switching from abacavir to tenofovir alafenamide. Reasons that abacavir has fallen out of favor include the HLA-B*5701 testing requirement, plus accumulating data showing that abacavir affects platelet activity and raises risk for major adverse cardiovascular events.
- Individuals taking tenofovir DF who develop nephrotoxicity or reduced bone mineral density should switch to tenofovir alafenamide or, if appropriate, to dolutegravir-lamivudine, doravirine-islatravir, or an NRTI-sparing regimen. In this situation, a switch from tenofovir DF to abacavir could also be considered, but would not be preferred.
- Since tenofovir DF and tenofovir alafenamide are preferred medications for HBV treatment, a switch from either of these agents to abacavir, dolutegravir-lamivudine, doravirine-islatravir, or to an NRTI-sparing regimen should consider the person's HBV status. If a person has HBV infection, they should continue tenofovir DF or tenofovir alafenamide, since both of those antiretrovirals are also active against HBV. If the individual cannot take tenofovir DF or tenofovir alafenamide for any reason, expert consultation is recommended to ensure adequate treatment for the HIV-HBV coinfection.
- A switch from older NRTIs to tenofovir alafenamide generally maintains virologic efficacy and may reduce risks of certain comorbidities, but this switch has been associated with weight gain in some individuals. Therefore, before switching to tenofovir alafenamide, the pros and cons of such a switch should always be considered and discussed with the patient.
- Tenofovir DF-lamivudine is now available in multiple generic formulations in the United States, so the lower cost of tenofovir DF and possible insurance restrictions with tenofovir alafenamide may need to be considered.

Simplifying Therapy to An Oral Two-Drug Regimen

In recent years, numerous studies have examined simplifying a standard three-drug oral antiretroviral regimen to a two-drug oral maintenance antiretroviral therapy for individuals who have persistently suppressed HIV RNA levels. The goals of this simplification strategy (from three drugs to two drugs) are to minimize the pill burden and reduce medication-related adverse effects.[3] The United States Food and Drug Administration (FDA) has approved the following single-tablet two-drug oral regimens for maintenance therapy in persons with suppressed HIV RNA levels: dolutegravir-rilpivirine, dolutegravir-lamivudine, and doravirine-islatravir. Note: none of these two-drug regimens are considered an appropriate treatment for chronic HBV. The following summarizes the FDA maintenance therapy indications for the oral two-drug regimens.

- **Dolutegravir-rilpivirine**: To replace the current antiretroviral regimen for those who are virologically suppressed (HIV RNA less than 50 copies/mL) on a stable antiretroviral regimen for at least 6 months with no history of treatment failure and no known substitutions associated with resistance to either dolutegravir or rilpivirine.
- **Dolutegravir-lamivudine**: For adults with no antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen with no history of treatment failure and no known substitutions associated with resistance to either dolutegravir or lamivudine.
- **Doravirine-islatravir**: To replace the current antiretroviral regimen for adults with suppressed HIV-1 RNA levels, no history of virologic failure, and no doravirine-associated drug resistance mutations.

Trials with Oral Two-Drug Maintenance Therapy

Trials in which patients are switched to dual maintenance therapy generally employ stringent inclusion criteria, similar to other modern switch studies. These criteria select for patients who have a history of excellent adherence to therapy and few (if any) virologic failures. The following summarizes published data on simplification to dual antiretroviral therapy (oral or injectable) versus continuing standard three-drug oral antiretroviral therapy.

Dolutegravir-Rilpivirine

- **SWORD-1** and **SWORD-2**: These two identical phase 3, randomized controlled trials evaluated the safety, efficacy, and tolerability of switching to dolutegravir plus rilpivirine in persons with virologic suppression on a standard three-drug antiretroviral regimen.[37] Exclusions included positive hepatitis B surface antigen or a history of virologic failure. Individuals who switched to the two-drug regimen had the same virologic suppression rate at 48 weeks compared to the group that continued current therapy (95% versus 95%, respectively).[37,38]

Dolutegravir-Lamivudine

- **TANGO**: In the open-label, phase 3 TANGO trial, investigators randomized adults who had suppressed HIV RNA levels on a three-drug regimen to switch to dolutegravir-lamivudine or remain on their baseline regimen.[39] After 48 weeks, the two study groups had similar rates of virologic suppression: 93.2% in the dolutegravir-lamivudine group and 93.0% in the group that remained on their baseline regimen.[39,40] Participants were followed for 144 weeks, and the results remained similar, with noninferior virologic efficacy demonstrated for those who switched to dolutegravir-lamivudine.[40]
- **SALSA**: The phase 3, randomized, open-label SALSA trial compared switching to a dolutegravir-lamivudine regimen versus continuing a standard baseline antiretroviral regimen.[41] Enrollees were adults with suppressed HIV RNA levels for at least 6 months, taking their first or second antiretroviral regimen, with no history of virologic failure.[41] All participants were taking a standard three-drug regimen with two NRTIs plus either an NNRTI, INSTI, or boosted PI.[41] After 48 weeks, the proportion

of participants with virologic suppression was similar between the two arms, and zero participants developed virologic failure.[41]

Doravirine-Islatravir

- **Trial 051**: This phase 3, randomized, open-label trial evaluated once-daily fixed-dose doravirine-islatravir in adults with HIV-1 who had maintained virologic suppression for at least 3 months on a stable oral two- or three-drug antiretroviral regimen.[42] Participants had no history of virologic treatment failure, no known doravirine resistance, and no active hepatitis B infection, and were randomized 2:1 to switch to doravirine-islatravir or continue baseline antiretroviral therapy.[42] At week 48, doravirine-islatravir maintained non-inferior virologic efficacy (HIV-1 RNA ≥50 copies/mL occurred in 1.4% versus 4.9% of participants, respectively), and virologic suppression was maintained in 95.6% versus 91.9%, respectively. [42]
- **Trial 052**: This phase 3, randomized, double-blind, trial enrolled adults who were virologically suppressed on bictegravir-tenofovir alafenamide-emtricitabine and had no history of treatment failure or known doravirine resistance.[43] Participants were randomized 2:1 to switch to once-daily, fixed-dose doravirine-islatravir or continue bictegravir-tenofovir alafenamide-emtricitabine.[43] At week 48, doravirine-islatravir was noninferior to continued bictegravir-tenofovir alafenamide-emtricitabine for the primary endpoint of HIV-1 RNA ≥50 copies/mL, which occurred in 1.5% versus 0.6% of participants, respectively; virologic suppression was maintained in 91.5% versus 94.2%, respectively.[43]

Summary and Recommendations with Oral Two-Drug Simplification

Taken together, available trial data suggest simplification to oral fixed-dose dual maintenance therapy may be a useful strategy for selected treatment-experienced individuals with virologic suppression. The following summarizes key recommendations.

- If simplifying to a two-drug oral maintenance regimen, the best available data (and only FDA-approved options) are dolutegravir-rilpivirine, dolutegravir-lamivudine, and doravirine-islatravir. These combinations are all available as a single-tablet once-daily option.
- Persons switching to an oral two-drug maintenance regimen should meet the following criteria: (1) suppressed HIV-1 RNA levels (less than 50 copies/mL) on a stable antiretroviral regimen for at least 3 to 6 months, (2) no history of treatment failure, and (3) no known substitutions associated with resistance to the individual components of the two-drug regimen.
- It is important to review a patient’s HBV status prior to switching to any of the two-drug maintenance regimens, since none of the commonly used two-drug maintenance regimens provide effective treatment for HBV.
- There are favorable, but less robust data using a boosted protease inhibitor plus a second drug, including studies with ritonavir-boosted protease inhibitor plus lamivudine, boosted darunavir plus dolutegravir, boosted darunavir plus rilpivirine, and boosted darunavir plus maraviroc. In addition, dolutegravir plus doravirine is another option clinicians can consider, but data are limited. None of the options mentioned are FDA-approved combinations, and all require taking multiple pills daily. In modern clinical practice, a switch to any of these options is infrequently done.
- There are also ongoing clinical trials examining new dual therapy options, including studies involving daily oral dosing with bictegravir-lenacapavir, weekly dosing with lenacapavir plus islatravir, and weekly dosing with ulonivirine plus islatravir.

Optimizing Therapy to Injectable Cabotegravir and Rilpivirine

A two-drug, long-acting, injectable regimen (cabotegravir plus rilpivirine) has been approved by the FDA as an option to replace standard oral antiretroviral therapy in certain individuals who have suppressed HIV RNA levels. This long-acting, parenteral two-drug option requires careful consideration of eligibility based on clinical, logistical, and cost/coverage factors. For some individuals, the option of switching to long-acting injectable cabotegravir and rilpivirine may be an attractive option.[44] There are, however, potential downsides, including a need for frequent clinic visits for intramuscular injections (two gluteal injections are required at each visit since the medications are given as separate injections), potential side effects from the injection, use of a regimen that does not have a high genetic barrier to resistance, and lack of activity against HBV. Further, due to the long-acting nature of these injectable medications, missed injection doses may lead to virologic failure with emergent NNRTI and/or INSTI resistance.[44]

Trials with Injectable Cabotegravir and Rilpivirine Maintenance Therapy

The following summarizes key phase 3 clinical trials with injectable cabotegravir plus rilpivirine.

- **FLAIR**: In this phase 3, randomized, open-label, noninferiority trial, antiretroviral-naïve adults were enrolled and started on oral dolutegravir-abacavir-lamivudine.[36] At 16 weeks, those participants with an HIV RNA level below 50 copies/mL were randomized to continue oral therapy or switch to monthly long-acting injectable cabotegravir and rilpivirine (after a 1-month oral lead-in).[36] After 48 weeks, a similar proportion of individuals in each arm of the trial had an HIV RNA level above 50 copies/mL (2.1% with injectable cabotegravir and rilpivirine therapy and 2.5% with continued oral antiretroviral therapy.[36]
- **ATLAS**: For this phase 3, open-label, noninferiority trial, investigators randomized persons with an HIV RNA level below 50 copies/mL for at least 6 months on standard three-drug oral antiretroviral therapy to continue their oral regimen or switch to monthly intramuscular long-acting injectable cabotegravir and rilpivirine (after a 1-month oral lead-in).[45] After 48 weeks, HIV RNA levels were less than 50 copies/mL in 92.5% of participants receiving injectable cabotegravir and rilpivirine and in 95.5% of those receiving oral therapy.[45] In addition, HIV RNA levels greater than 50 copies/mL were identified in 1.6% of individuals in the long-acting antiretroviral therapy arm and 1.0% in the oral antiretroviral therapy arm, a non-significant difference.[45]
- **ATLAS-2M**: This phase 3b, randomized, open-label trial was designed to compare two doses of long-acting, injectable cabotegravir and rilpivirine: 600 mg and 900 mg every 2 months versus 400 mg and 600 mg every 1 month.[46] Enrollees were taking standard oral antiretroviral therapy at baseline with suppressed HIV RNA levels and no history of virologic failure, or were participants from the ATLAS trial who completed 52 weeks of oral or long-acting therapy and had a suppressed HIV RNA level.[46] Individuals who enrolled were then randomized to intramuscular cabotegravir and rilpivirine injections every 4 weeks or every 8 weeks.[46] The investigators found that every 8-week dosing was non-inferior to every 4-week dosing (HIV RNA level above 50 copies/mL 2% versus 1%, respectively) after 48 weeks of treatment.[46]

Summary and Recommendations with Injectable Cabotegravir and Rilpivirine

Recently, there have been multiple publications on the use of long-acting, injectable cabotegravir and rilpivirine for individuals who have detectable HIV RNA levels.[47,48,49,50,51] It should be noted that this strategy is not approved by the FDA. In the Adult and Adolescent ARV Guidelines, this strategy is discussed as an option to consider, but should be done in conjunction with robust outreach and support, and should only be done in extenuating circumstances, such as for a patient with advanced HIV who has not been successful with oral antiretroviral therapy despite significant efforts at adherence support or who absolutely cannot take oral therapy.[1,44]

- The injectable combination may be given every 1 or 2 months, with or without a 28-day lead-in of oral

preparations of cabotegravir and rilpivirine (Figure 1) and (Figure 2). Some individuals may prefer the oral lead-in phase to confirm tolerability before receiving injections, but a direct-to-inject approach is also reasonable and approved by the FDA if a person prefers to skip the oral lead-in. The dose of cabotegravir and rilpivirine (per injection) differs between the every 1-month and 2-month dosing schedules.

- Long-acting injectable cabotegravir and rilpivirine require administering each drug separately as an intramuscular gluteal injection, preferably as a ventrolateral gluteal injection. The injections should be at separate gluteal sites (opposite sites or 2 cm apart on the same site). The injections should be administered by a health care provider in a clinical setting. The drug levels of injectable cabotegravir and rilpivirine are not impacted by antacids, histamine-2 receptor blockers, or proton pump inhibitors.
- For persons with a body mass index (BMI) greater than 30 kg/m^2, the standard injection needle provided in the product packaging (23-gauge, 1½-inch) should be replaced with a longer 2-inch needle to ensure adequate medication reaches the muscle tissue.
- Persons switching to injectable cabotegravir and rilpivirine maintenance therapy should ideally meet the following criteria: HIV-1 RNA levels less than 50 copies/mL for at least 3 to 6 months on a stable antiretroviral regimen, no history of an antiretroviral treatment failure, no known or suspected resistance to either cabotegravir or rilpivirine, no active HBV infection (unless on separate treatment for HBV), and good adherence and engagement in care. As noted, more experience now exists with switching to this regimen in persons who do not have suppressed HIV RNA levels.
- A switch to injectable cabotegravir and rilpivirine maintenance therapy can be considered in persons with detectable HIV RNA levels if achieving suppressed HIV RNA levels is not realistic with oral therapy and there is no resistance to cabotegravir or rilpivirine. For these individuals, close follow-up and outreach support is recommended. In this situation, most experts recommend using injections every month until HIV RNA levels are less than 50 copies/mL, and then a transition to injections every 2 months can be considered.
- Injectable cabotegravir and rilpivirine have not been fully evaluated for use in pregnancy. Lower levels of cabotegravir and rilpivirine have been observed during pregnancy. If a woman becomes pregnant (or is trying to conceive) while receiving injectable cabotegravir and rilpivirine, expert consultation is advised to determine the best approach. If injectable cabotegravir and rilpivirine are used during pregnancy, maternal plasma HIV RNA levels should be monitored closely.
- If the injections are stopped, it is imperative to resume effective oral combination antiretroviral therapy because residual levels of the long-acting drugs remain in systemic circulation for as long as 12 months.

Simplifying Maintenance Therapy to Monotherapy

Although step-down maintenance monotherapy with a boosted protease inhibitor or dolutegravir is an interesting concept because of the high potency and very high genetic barrier to resistance with these medications, the available monotherapy data have been very disappointing, with consistently unacceptably high rates of virologic failure. Further, this approach with dolutegravir has been associated with significant development of integrase drug resistance. For these reasons, the Adult and Adolescent ARV Guidelines state that step-down monotherapy (with a boosted PI or dolutegravir) is not recommended.[1]

Summary Points

- Even if a person with HIV has stable virologic suppression, there may be reasons to consider switching an antiretroviral therapy regimen switch, especially if the change is associated with increased medication tolerability and/or convenience.
- Certain older HIV antiretroviral regimens, such as those that contain stavudine, didanosine, and very old HIV protease inhibitors, should be changed due to long-term safety issues, even if the person had undetectable HIV RNA levels.
- Multiple factors should be considered before undertaking any modification of antiretroviral therapy, including past history of virologic failures and resistance, duration of virologic suppression, number of past regimens, prior medication intolerances, pill burden, drug interactions, food requirements, and insurance status.
- Assessing past treatment failures and resistance is especially important if the antiretroviral therapy regimen switch being considered involves transitioning from a regimen with a relatively high barrier to resistance to one with a relatively low barrier to resistance.
- Select patients (those without multiple past regimens, virologic failures, or resistance) may successfully switch from a boosted PI to any INSTI-based regimen. For individuals with a history of virologic failure and NRTI resistance who have suppressed viral loads on a boosted PI with 2 NRTIs, the new regimen should consist of dolutegravir (or bictegravir) with tenofovir alafenamide (or tenofovir DF) plus emtricitabine or lamivudine, in order to keep a consistent high barrier to resistance and prevent the emergence of further resistance.
- Individuals taking an efavirenz-based regimen can switch to rilpivirine without any modification of the rilpivirine dose and are likely to experience an improvement in neuropsychological adverse events and serum lipid levels. A switch to doravirine or INSTI-based combinations is also commonly considered in this scenario.
- A switch from a tenofovir DF- or abacavir-containing combination to a formulation that includes tenofovir alafenamide may reduce the risk of long-term renal or bone toxicity (in the setting of switching from tenofovir DF) and may reduce cardiovascular risk (if switching off abacavir). This switch may also lead to weight gain for some individuals.
- The FDA has approved the following two-drug regimens for maintenance antiretroviral therapy: oral dolutegravir-rilpivirine, oral dolutegravir-lamivudine, and long-acting injectable cabotegravir plus rilpivirine. These two-drug regimens should only be offered to persons with sustained suppressed HIV RNA levels, no resistance to either of the medications in the regimen, and no evidence of chronic HBV.
- Dual regimens that incorporate boosted darunavir, including darunavir plus ritonavir and the fixed-dose combination darunavir-cobicistat, appear promising as part of dual therapy when given with dolutegravir. Combining dolutegravir (or boosted darunavir) with doravirine also holds promise as maintenance antiretroviral therapy.
- Available data suggest that simplification to monotherapy is associated with unacceptably high rates of virologic failure, even with potent agents like boosted darunavir or dolutegravir; this strategy is not recommended.

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Figures

Figure 1 Monthly Dosing Schedule of Injectable Cabotegravir and Rilpivirine, with Optional Oral Lead-In

Illustration: David H. Spach, MD

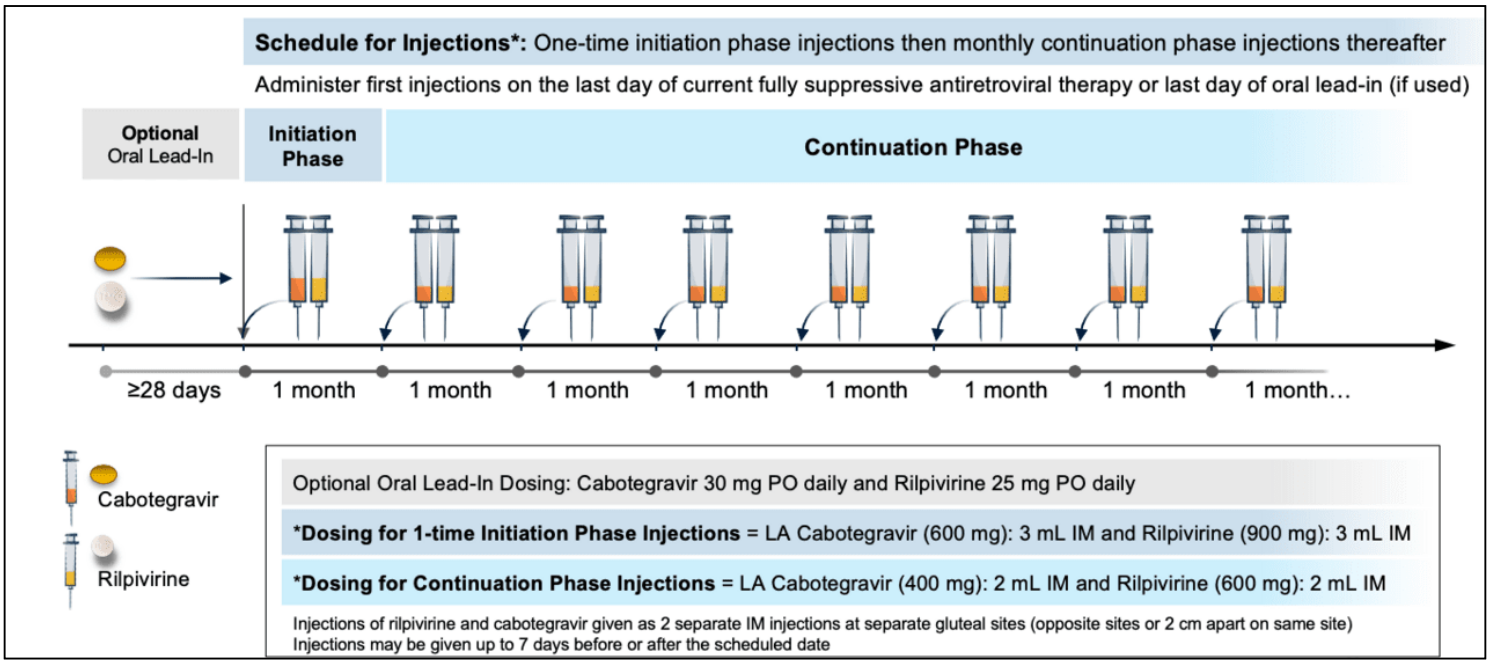

Figure 2 Every 2-Month Dosing Schedule of Injectable Cabotegravir and Rilpivirine, with Optional Oral Lead-In

Illustration: David H. Spach, MD