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 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 various important clinical considerations to make sure the new regimen is safe and effective.

Updating Antiretroviral Therapy to a Modern Regimen

One frequent reason that antiretroviral therapy switches are considered 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. There are some older antiretroviral agents that should always be updated to 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. Further, most experts would also recommend updating older non-nucleoside reverse transcriptase (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 help 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 would potentially occur after the regimen switch)
- Food requirements with the new regimen
- Potential sides effects with the new regimen
- Cost or availability of the new regimen.

Considering Past Virologic Failure and Drug Resistance

A past history of virologic failure is particularly important when considering a switch from a regimen that has an anchor drug with 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 past 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 past resistance results are not available and the patient would benefit from the switch, expert consultation is suggested 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 making a switch or simplification to 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 with v 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** (Boosted PI plus two NRTIs to Bictegravir-Tenofovir alafenamide-Emtricitabine): Adults with virologic suppression were randomized to bictegravir-tenofovir alafenamide-emtricitabine or continue on 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** (Dolutegravir plus Abacavir-Lamivudine to Bictegravir-Tenofovir alafenamide-Emtricitabine): 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 rates were nearly identical in the two arms (94% in the bictegravir-tenofovir alafenamide-emtricitabine group versus 95% in the dolutegravir plus abacavir-lamivudine group maintain regimen.[12]
- **GS-380-1961** (Suppressive Antiretroviral Therapy to Bictegravir-Tenofovir alafenamide-Emtricitabine): 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 bictegravir-tenofovir alafenamide-emtricitabine group regimen) versus 95% in the group that maintained their baseline antiretroviral therapy regimen.[13]
- **GS-380-4030** (Dolutegravir plus either Tenofovir alafenamide-emtricitabine or Tenofovir DF-Emtricitabine to Bictegravir-Tenofovir alafenamide-Emtricitabine or Dolutegravir plus Tenofovir alafenamide-Emtricitabine): 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** (Suppressive Three-Drug ART to Bictegravir-Tenofovir alafenamide-Emtricitabine for Americans who Identify as Black): Adults with HIV in the United States who identified as Black or African American individuals (and with virologic suppression) were randomized to 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 based on an archived genotype at study entry.[15]

Switch to Dolutegravir

- **NEAT 022** (Boosted PI to Dolutegravir): 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** (Switch to Dolutegravir-Abacavir-Lamivudine): 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 remained comparable to those without NRTI resistance and treatment-emergent resistance was rare to absent.
- 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.[18,19,20] 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, two NRTIs (tenofovir alafenamide or tenofovir DF, along with emtricitabine or lamivudine), should be included in a regimen that also has an agent of 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. Multiple studies have evaluated a switch from efavirenz-based therapy to an alternate NNRTI to examine the impact on central nervous system side effects and lipid parameters.[21,22,23,24,25] 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.[26,27,28,29] 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** (Boosted PI or Boosted Elvitegravir or NNRTI to Doravirine): 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.[29] 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).[29] For those participants taking a boosted PI regimen at baseline, lipid parameters improved after the switch to doravirine.
- A5391 Do-IT (Switch from INSTI to Doravirine after Weight Gain). This multicenter, open-label, randomized trial randomized people with HIV and high body mass index (median 34.9 kg/m^2) 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. 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.

Switch to Rilpivirine

- **GS-366-1160** (Efavirenz to Rilpivirine): In this study, individuals with suppressed HIV RNA levels on efavirenz-tenofovir DF-emtricitabine were randomized to continue the current regimen or switch to rilpivirine-tenofovir alafenamide-emtricitabine.[30] 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.[30] 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** (Boosted PI to Rilpivirine): 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.[27] 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.[27]

Summary of Key Findings with NNRTI Switch Studies

The following summarizes key points when considering 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.[27,29,31] 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.[26,27]

- **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.[23,32]
- **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.[33] 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 rilpiviinr 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.[34] 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 doravirine-based ART, with either tenofovir alafenamide-emtricitabine or tenofovir DF-emtricitabine, did not produce clinically meaningful differences in weight change, fasting lipids, insulin resistance, fat mass, or bone mineral density.[34]

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 of a patient's regimen, with newer studies focused on switching tenofovir DF to tenofovir alafenamide. Multiple have shown that tenofovir alafenamide is safer in terms of renal and bone toxicity as compared to tenofovir DF. In addition, tenofovir alafenamide may be used in the setting of mild-to-moderate renal insufficiency (creatinine clearance as low as 30 mL/min). Further, tenofovir alafenamide combination tablets (coformulated with other antiretroviral medications) are smaller than equivalent tenofovir DF or abacavir coformulated tablets. For all of 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, therefore, will summarize 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 2-drug regimen will be discussed in more detail later in this lesson.

Switch to Tenofovir Alafenamide

- **Study 109** (Tenofovir DF to Tenofovir alafenamide): The GS-109 switch study examined the outcomes of switching adults from tenofovir DF-containing antiretroviral therapy to a tenofovir alafenamide-containing regimen.[35] 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.[35] In total, 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.[35] Overall, participants who were switched to elvitegravir-cobicistat-tenofovir alafenamide-emtricitabine had noninferior virologic responses compared with those in the no-switch group.[35] 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** (Tenofovir DF to Tenofovir alafenamide): 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).[36] 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.[36] The group that switched to tenofovir alafenamide-emtricitabine experienced greater improvements in median eGFR as compared to the tenofovir DF-emtricitabine group (+8.4 mL/min versus +2.8 mL/min, a statistically significant difference).[36] Furthermore, markers of proximal tubule dysfunction improved in the tenofovir alafenamide-emtricitabine group and did not change in the emtricitabine-tenofovir DF group; bone mineral density improved in the tenofovir alafenamide-emtricitabine group whereas it worsened in the tenofovir DF-emtricitabine group.[36]
- **GS-366-1216**: In this randomized controlled trial, investigators enrolled individuals with suppressed HIV RNA levels for at least 6 months on a rilpivirine-tenofovir DF-emtricitabine, creatinine clearance above 50 mL/min, and no genotypic resistance to the study drugs.[37] Participants (total of 630) were randomized equally to continue the baseline regimen or switch to rilpivirine-tenofovir alafenamide-emtricitabine (each with matching placebo).[37,38] 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.[37]

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 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 presence of coinfections with hepatitis B virus.
- 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 off 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 possibly, the regimen could be switched 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 take into account 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 hepatitis B. 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 taken into account.

Simplifying Therapy to An Oral Two-Drug Regimen

In recent years, a number of 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, reduce medication-related adverse effects, and possibly lower costs.[3] The United States Food and Drug Administration (FDA) has approved the following two-drug oral regimens as maintenance regimens in persons with suppressed HIV RNA levels: oral dolutegravir-rilpivirine and oral dolutegravir-lamivudine. In addition, the two-drug regimen dolutegravir-lamivudine is also approved for use as initial antiretroviral therapy for individuals who meet certain specified parameters. Note that none of these two-drug regimens are considered appropriate treatment for chronic hepatitis B. The following summarizes the FDA maintenance therapy indications for the oral two-drug regimens.

- **Dolutegravir-rilpivirine**: To replace the current antiretroviral regimen in 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.

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** (Dolutegravir plus Rilpivirine): 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 (HIV RNA below 50 copies/mL for at least 12 months) on a standard three- or four-drug antiretroviral regimen.[39] Participants also had to have negative hepatitis B surface antigen, no history of virologic failure, and were required to take their first or second antiretroviral regimen only. The 513 individuals who switched to the two-drug regimen of dolutegravir plus rilpivirine had the same virologic suppression rate at 48 weeks as compared to the 511 individuals who continued current therapy (95% versus 95%). No instances of integrase resistance occurred, though one patient in the dolutegravir plus rilpivirine arm was found to have a significant NNRTI resistance mutation at the time of failure.[39,40]

Dolutegravir-Lamivudine

- **TANGO** (Dolutegravir-Lamivudine): In the open-label, phase 3 TANGO trial, investigators randomized adults who had suppressed HIV RNA levels on a three- or four-drug regimen to remain on the regimen or to switch to a two-drug regimen of fixed-dose dolutegravir-lamivudine.[41] Participants who enrolled were required to be taking a three- or four-drug antiretroviral regimen that included tenofovir alafenamide for at least 3 months, and they needed to have an HIV RNA level less than 50 copies/mL for longer than 6 months.[41] After 48 weeks, the two study groups had similar rates of virologic suppression (HIV RNA less than 50 copies/mL): 93.2% in the dolutegravir-lamivudine group and 93.0% in the group that remained on the three- or four-drug regimen.[41,42] Participants were followed for

144 weeks, and the results remained similar, with noninferior virologic efficacy demonstrated for those who switched to dolutegravir-lamivudine.[42]

- **SALSA** (Dolutegravir-Lamivudine): The phase 3, randomized, open-label SALSA trial compared outcomes with switching to a two-drug dolutegravir-lamivudine regimen versus continuing a standard baseline antiretroviral regimen.[43] 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.[43] All participants were taking a standard three-drug regimen with two NRTIs plus either an NNRTI, INSTI, or boosted PI.[43] They were randomized 1:1 to either continue the baseline regimen or switch to dolutegravir-lamivudine daily.[43] Overall, 493 individuals were randomized, and, after 48 weeks, the proportion of participants with virologic suppression was similar between the two arms, and zero participants developed virologic failure.[43]

Boosted Protease Inhibitor plus Lamivudine

- **DUAL-GESIDA** (Boosted Darunavir plus Lamivudine): Participants in this trial were taking ritonavir-boosted darunavir plus either abacavir-lamivudine or tenofovir DF-emtricitabine for at least 2 months and had HIV RNA level below 50 copies/mL for at least 6 months.[44] In addition, enrollment required no resistance mutations that would affect darunavir or lamivudine, and negative hepatitis B surface antigen. Participants were randomized 1:1 to continue the baseline regimen or transition to dual maintenance therapy with ritonavir-boosted darunavir plus lamivudine. At 48 weeks, 89% (112 of 126) participants in the dual therapy arm had HIV RNA below 50 copies/mL compared with 93% (114 of 123) participants in the triple therapy arm (a statistically non-significant difference). Virologic failure occurred in four individuals in the dual treatment arm and two in the triple therapy arm.
- **OLE** (Boosted Lopinavir plus Lamivudine or Emtricitabine): This randomized, open-label trial enrolled 250 adults with suppressed HIV RNA for at least 6 months on a regimen of lopinavir-ritonavir plus two NRTIs and compared continuation of this regimen to a switch to dual therapy (with twice-daily lopinavir-ritonavir plus lamivudine).[45] Entry criteria also included negative hepatitis B surface antigen status and no history of antiretroviral drug resistance or virologic failure on their pre-entry antiretroviral regimen. In an intent-to-treat analysis at 48 weeks, participants switching to lopinavir-ritonavir plus lamivudine had noninferior virologic responses when compared with those who continued lopinavir-ritonavir plus two NRTIs (88% versus 87%).[45]
- [Trial] SALT (Boosted Atazanavir plus Lamivudine): This randomized, open-label study recruited 286 adults with suppressed HIV RNA levels for at least 6 months on various antiretroviral regimens, no history of treatment failure or antiretroviral resistance, no antiretroviral regimen switch within the prior 4 months, and documented hepatitis B infection negativity.[46] Participants were randomized to switch to ritonavir-boosted atazanavir plus lamivudine or to ritonavir-boosted atazanavir plus two NRTIs. Based on 48-week viral load responses, the dual treatment regimen was found to be noninferior to the three-drug regimen.[46]

Boosted Protease Inhibitor plus a Second Anchor Drug

- **DUALIS** (Boosted Darunavir plus Dolutegravir): In this phase 3b randomized trial, investigators enrolled individuals with suppressed HIV RNA levels while taking boosted darunavir plus 2 NRTIs and randomized them to either continue their regimen (n = 133) or switch to the two-drug combination of boosted darunavir plus dolutegravir (n = 131).[47] At week 48, 86.3% of individuals who switched to the two-drug combination maintained a suppressed HIV RNA level, as compared to 87.9% of those who continued the three-drug combination regimen, which met the criteria for noninferiority.[47]
- **MARCH** (Boosted Protease Inhibitor plus Maraviroc): In this study, investigators randomized adults taking two NRTIs plus a boosted PI (with HIV RNA levels below 200 copies/mL for at least 24 weeks) to switch to maraviroc plus a boosted PI (n = 157), switch to maraviroc plus two NRTIs (n = 156), or continue their current regimen (n = 82).[48] Individuals enrolled in the study had no known antiretroviral drug resistance and had R5-tropic HIV. Those patients in the study who switched to dual therapy with maraviroc plus a boosted PI had inferior virologic responses (77%) compared with those who continued their three-drug boosted-PI regimen (92%) or switched to maraviroc plus two NRTIs

(95%).[48]

- **PROBE-2**: (Boosted Darunavir Plus Rilpivirine): For this randomized, open-label trial, investigators enrolled adults with HIV and suppressed HIV RNA levels for at least 6 months while taking standard, three-drug antiretroviral therapy.[49] A total of 160 participants were randomized to switch to darunavir-cobicistat plus rilpivirine for dual antiretroviral maintenance treatment either at the beginning of the study or after 24 weeks.[49] After 48 weeks of follow-up, at which time all participants were taking the dual antiretroviral therapy combination, overall high rates of virologic suppression were observed with zero cases of virologic failure in the early switch group and two cases in the late switch group (though neither had treatment-emergent drug resistance).[49]

Summary and Recommendations with Oral Two-Drug Simplification

Taken together, available trial data suggest simplification to oral dual maintenance therapy may be a useful strategy for selected treatment-experienced individuals. 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 and dolutegravir-lamivudine; both of these combinations are available as a single-tablet once-daily option. In general, these two-drug simplification strategies should be used in carefully selected individuals who are not expected to have problems with adherence.
- 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 also positive, less robust data using other dual regimens, including (1) ritonavir-boosted protease inhibitor plus lamivudine and (2) dolutegravir plus boosted darunavir. All of these regimens require taking multiple pills daily. If using a boosted protease inhibitor two-drug regimen, darunavir is the preferred protease inhibitor to use.
- There are also ongoing clinical trials examining new dual therapy options, including studies involving the NNRTI doravirine, the capsid inhibitor lenacapavir, and the investigational agent islatravir.

Simplifying 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.

Trials with Two-Drug Injectable Cabotegravir and Rilpivirine Maintenance Therapy

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

- **FLAIR** (Monthly, Long-Acting Injectable Cabotegravir and Rilpivirine after Oral Lead-In): In this phase 3, randomized, open-label, noninferiority trial, antiretroviral-naïve adults were enrolled and started on oral dolutegravir-abacavir-lamivudine.[38] At 16 weeks, those participants with an HIV RNA level below 50 copies/mL were randomized to either (1) continue oral therapy (n = 283) or (2) switch to oral cabotegravir and rilpivirine for 1 month, followed by a monthly long-acting injectable cabotegravir and rilpivirine (n = 283).[38] 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), which met the criteria for noninferiority of the long-acting combination.[38] Injection site reactions were common in the long-acting antiretroviral therapy group (86% experienced some reaction), though most were mild and short-lived.[38] After 96 weeks of follow-up, findings were similar, with only 3% of participants in either study developing an HIV RNA above 50 copies/mL.[50] Over time, the injection site reactions were noted to decrease in frequency.[50] After 100 weeks in the study, participants receiving oral antiretroviral therapy could opt to switch to the long-acting, injectable therapy and could choose whether to take the oral lead-in.[51] After week 124, among participants who opted to switch to long-acting therapy, 99% (110 of 111) who chose a direct-to-inject strategy maintained suppressed HIV RNA levels as compared to 93% (113 of 121) of those who opted for an oral lead-in.[51] Both strategies (direct-to-inject and oral lead-in) were found to be safe and well-tolerated overall.[51]
- **ATLAS** (Switch to Monthly Injectable Cabotegravir and Rilpivirine): 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 (n = 308 in each group).[52] 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.[52] 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.[52] Injection site reactions were common in the injectable antiretroviral therapy arm but generally mild; serious reactions were infrequent.[52] Among participants who continued long-acting therapy during an extension phase to 96 weeks, 98% (51 of 52) maintained virologic suppression.[53]
- **ATLAS-2M** (Switch to Monthly or Bimonthly Cabotegravir and Rilpivirine): 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.[54] 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.[54] Individuals who enrolled were then randomized to intramuscular cabotegravir and rilpivirine injections every 4 weeks (n = 523) or every 8 weeks (n = 522).[54] 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.[54] There were 8 confirmed virologic failures in the every 8-week arm (2%) versus 2 confirmed virologic failures in the every 4-week arm (less than 1%); however, more confirmed virologic failure cases in the every 8-week arm were found to have pretreatment rilpivirine resistance-

associated mutations, which may have raised their risk for virologic failure.[54] Both dosing strategies were well-tolerated in the trial.

Summary and Recommendations with Injectable Cabotegravir and Rilpivirine

For some individuals, the option of switching to long-acting injectable cabotegravir and rilpivirine may be attractive to eliminate pill burden, drug-food interactions, and the potential need to have a safe, private place to store oral medications (for persons who do not want to disclose their HIV status to persons they are living with).[55] 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, and use of a regimen that does not have a high genetic barrier to resistance. 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.[55] The following summarizes key recommendations for the use of injectable cabotegravir and rilpivirine as a two-drug maintenance antiretroviral therapy regimen.[1,55]

- Long-acting injectable cabotegravir and rilpivirine is the only recommended and FDA-approved non-oral two-drug maintenance therapy option.
- Persons switching to an injectable cabotegravir and rilpivirine maintenance regimen should 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 or occult HBV infection (unless on separate treatment for HBV), and good adherence and engagement in care.
- 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) is different for every 1-month dosing versus every 2-month dosing.
- 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.
- 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.
- Injectable cabotegravir and rilpivirine is not recommended for use in pregnancy.
- 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.
- When using the injectable form of cabotegravir and rilpivirine, drug levels are not impacted by antacids, histamine-2 receptor blockers, or proton pump inhibitors. If an woman becomes pregnant (or is trying to conceive) while receiving cabotegravir and rilpivirine, this regimen should be switched to a *Preferred* or *Alternative* three-drug antiretroviral regimen as recommended for use in pregnancy per the Perinatal HIV Clinical Guidelines.
- Recently, there have been publications on the use of long-acting, injectable cabotegravir and rilpivirine for individuals who have detectable HIV RNA levels.[56,57] It should be noted that this strategy is not approved by the FDA and is not recommended in the Adult and Adolescent ARV Guidelines. Most experts recommend that persons with detectable HIV RNA levels should not receive treatment with cabotegravir and rilpivirine, except in extenuating circumstances, such as persons with advanced HIV and no feasible oral options (plus there is capacity for robust outreach and adherence support).

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 has 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 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 of relatively high barrier to resistance to one of 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

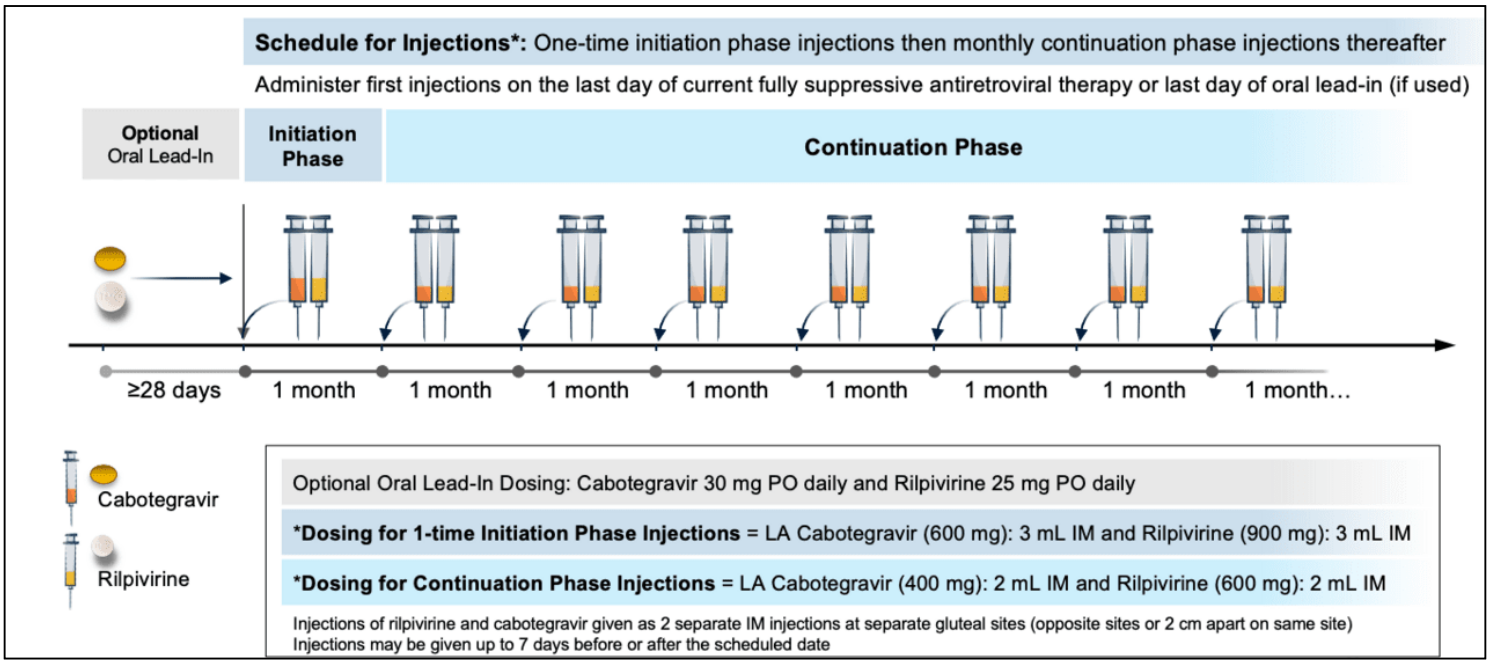

Figure 2 Every 2-Month Dosing Schedule of Injectable Cabotegravir and Rilpivirine, with Optional Oral Lead-In

Illustration: David H. Spach, MD