Switching or Simplifying Antiretroviral Therapy

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

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Principles of Switching or Simplifying Antiretroviral Therapy

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 antiretroviral therapy in the setting of virologic suppression include managing or preventing short-term or long-term adverse effects, high pill burden, difficulties with food requirements, or problematic drug interactions.[1,2,3] Additional considerations may include pregnancy, cost, changes to insurance coverage, or a desire to match a partner's regimen. These reasons for switching an antiretroviral regimen are distinct from switching a regimen in the setting of virologic failure with documented antiretroviral resistance, which necessitates transitioning to a salvage regimen as guided by genotypic drug resistance testing.

Updating Antiretroviral Therapy to a Modern Regimen

One frequent reason that antiretroviral therapy switches are considered in clinical practice is to "update" a regimen that is no longer recommended as part of first-line or alternative antiretroviral therapy. In this situation, a 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 no longer be used in modern practice and should typically be updated to newer options in order to improve tolerability and reduce potential side effects. For example, certain protease inhibitors (PIs), including lopinavir-ritonavir, saquinavir, nelfinavir, indinavir, fosamprenavir, and tipranavir, should be replaced by boosted darunavir, boosted atazanavir, or a medication from another drug class. In addition, old nucleoside reverse transcriptase inhibitors (NRTIs)—zidovudine, didanosine, and stavudine—typically should be replaced by a newer NRTI or another medication from another medication class. In addition, most experts would also recommend updating older non-nucleoside reverse transcriptase (NNRTIs), such as nevirapine and 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 with optimizing and updating 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] Simplifying antiretroviral therapy may also have a significant economic impact, including lower copayments for the patient, particularly if the switch involves a reduction in the number of medications in the regimen.[11,12] By contrast, as more antiretroviral medications become available as generic preparations, a switch from an older medication (available as generic) to a new medication may increase the overall cost of the regimen; access to new medications and insurance coverage are important considerations before any antiretroviral therapy changes.

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: prior antiretroviral therapy regimens, past virologic failures, documented drug resistance, medication adherence, and past or current intolerance to antiretroviral medications. Any potential switch of antiretroviral therapy should assimilate a composite of all past drug resistance test results. Furthermore, it is essential to review a patient's active medication list for potential drug interactions (including herbal and over-the-counter medications) and consider food requirements, potential side effects, and cost or availability of the new regimen. 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, but that will compromise the efficacy of the new combination.

Validity of Antiretroviral Switch Studies

A number of clinical trials have examined the effects of switching antiretroviral therapy for patients with suppressed HIV RNA levels. Interpreting the results of antiretroviral therapy switch studies requires some caution, as these trials are often sponsored by industry and are frequently (though not always) designed as open-label trials, which may lead to bias against reporting adverse events. In addition, patients may enroll in these types of studies with a preference for randomization to the switch-therapy arm, which may lead to differential dropout from the control arm. Taken together, these factors may create a degree of inherent bias in switch trials. Despite these limitations, switch studies have generated abundant data, as well as a number of key lessons, that provide imperative clinical reminders when considering an antiretroviral therapy regimen change.

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. In recent years, an antiretroviral therapy switch to an INSTI-containing regimen has become highly clinically relevant, especially a switch to dolutegravir or bictegravir. Recent retrospective switch study data have found that such a switch may lead to an increase in weight and BMI for some individuals, particularly in the first 6 to 12 months after the switch.[13,14,15] Research into predictors, long-term consequences, and optimal management of such INSTI-associated weight change is ongoing. The following summaries outline several key prospective studies involving a switch to an INSTI that collectively show the virologic efficacy and potential benefits of such a switch. Switch studies relevant to the older, less frequently used INSTIs, raltegravir and elvitegravir, will not be included.

Switch to Bictegravir

- **GS-380-1878** (Boosted PI plus two NRTIs to Bictegravir-Tenofovir alafenamide-Emtricitabine): In this trial, investigators evaluated the virologic impact of a change from a regimen with a ritonavir-boosted PI to the single-tablet regimen of bictegravir-tenofovir alafenamide-emtricitabine.[16] All participants had sustained suppressed HIV RNA for at least 6 months while taking a boosted PI plus two NRTIs. Participants were excluded if they had a history of virologic failure or prior treatment with an INSTI. No participant had documented NRTI resistance mutations.[16] A total of 577 individuals were randomized to continue the boosted PI plus two NRTIs or switch to bictegravir-tenofovir alafenamide-emtricitabine. After 48 weeks, 89% of individuals in the boosted PI arm maintained virologic suppression compared to 92% in the bictegravir-tenofovir alafenamide-emtricitabine switch arm (a difference that was not statistically significant, thus demonstrating noninferiority for the switch strategy).[16]
- **GS-380-1844** (Dolutegravir plus Abacavir-Lamivudine to Bictegravir-Tenofovir alafenamide-Emtricitabine): In this phase 3 trial, 561 adults with HIV and virologic suppression on dolutegravir plus abacavir-lamivudine were randomized to maintain their antiretroviral regimen or switch to bictegravir-tenofovir alafenamide-emtricitabine.[17] All participants had sustained suppressed HIV RNA for at least 3 months, and none had a history of virologic failure.[17] At week 48 of the study, the virologic suppression rates were equivalent—94% in the bictegravir-tenofovir alafenamide-emtricitabine group (switch regimen) versus 95% in the dolutegravir plus abacavir-lamivudine group (maintain regimen).[17]
- **GS-380-1961** (Suppressive Antiretroviral Therapy to Bictegravir-Tenofovir alafenamide-Emtricitabine): In this trial, 470 adult nonpregnant women with HIV who had virologic suppression were randomized to maintain their antiretroviral regimen or switch to bictegravir-tenofovir alafenamide-emtricitabine.[18] All participants had sustained suppressed HIV RNA for at least 3 months while taking one of the following three regimens: elvitegravir-cobicistat-tenofovir alafenamide-emtricitabine, elvitegravir-cobicistat-tenofovir DF-emtricitabine, or ritonavir-boosted atazanavir plus tenofovir DF-emtricitabine.[18] At week 48 of the study, the virologic suppression rates were equivalent—96% in the bictegravir-tenofovir alafenamide-emtricitabine group (switch regimen) versus 95% in the maintain regimen group.[18]
- **GS-380-4030** (Dolutegravir plus either Tenofovir alafenamide-emtricitabine or Tenofovir DF-Emtricitabine to Bictegravir-Tenofovir alafenamide-Emtricitabine or Dolutegravir plus Tenofovir alafenamide-Emtricitabine): In this randomized, double-blind, active-controlled trial, 565 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.[15] After 48 weeks of treatment, the bictegravir combination was noninferior to the dolutegravir combination, with 93.3% and 91.1%, respectively, maintaining an HIV RNA level below 50 copies/mL.[15] At study entry, approximately 25% of participants had NRTI resistance, and both

regimens demonstrated similar efficacy in the setting of the M184V/I NRTI mutation (or any NRTI mutation). Virologic failure infrequently occurred in both arms; three individuals in the study met the criteria for resistance testing (all in the dolutegravir arm), but no emergent drug resistance occurred.[15] Weight gain was greater for individuals who switched from tenofovir DF to tenofovir alafenamide and did not differ significantly between bictegravir and dolutegravir.[15]

- **BRAAVE-2020** (Suppressive Three-Drug ART to Bictegravir-Tenofovir alafenamide-Emtricitabine for Americans who Identify as Black): For this randomized, phase 3b, open-label study, adults in the United States who identified as Black or African American and who had virologic suppression on two NRTIs plus a third antiretroviral medication were enrolled and randomized to continue their baseline regimen or switch to bictegravir-tenofovir alafenamide-emtricitabine.[19] Of 495 participants who were randomized and treated, 10% had an M184V/I mutation at entry.[19] After 24 weeks of follow-up, the bictegravir combination was found to be noninferior to the continued baseline antiretroviral therapy regimen (96% with suppressed viral load in the bictegravir arm and 95% in participants who continued their baseline antiretroviral regimen), with low proportions found to have HIV RNA greater than 50 copies/mL at 24 weeks and low rates of virologic failure in both groups.[19] No participant in the trial developed new drug resistance, and both arms maintained high virologic efficacy rates regardless of any prior NRTI resistance.

Switch to Dolutegravir

- **NEAT 022** (Boosted PI to Dolutegravir): In this trial, investigators enrolled individuals with HIV who were at least 50 years of age and/or had a Framingham score of 10% or greater, with the goal of analyzing the efficacy and impact of a change from a ritonavir-boosted PI to dolutegravir.[20] All participants had routinely suppressed HIV RNA levels while taking a boosted PI and two NRTIs, and none had documented NRTI resistance mutations.[20] A total of 415 individuals were randomized to continue two NRTIs plus a boosted PI, or switch to the same two NRTIs plus dolutegravir.[20] 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.[20] After 48 weeks, participants initially randomized to continue the boosted PI also switched to dolutegravir, thus allowing investigators to compare a group that switched immediately (immediate switch group) to one that switched at 48 weeks (delayed switch group).[21,22] Evaluation at week 96 demonstrated that in both groups, the switch to dolutegravir from a boosted PI led to only small increases in weight that stabilized over time, a reduction in lipids and estimated cardiovascular risk, and no increase in incident hypertension.[21,22,23]
- **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).[24] 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%).[24] After 24 weeks, all participants switched to dolutegravir-abacavir-lamivudine.[24] The 48-week data showed that 83% and 92% of participants from the early switch and late switch groups, respectively, maintained virologic suppression.[24] Adverse events and treatment discontinuations for side effects were more frequent in those who switched to the dolutegravir-containing single-tablet regimen, though overall reported treatment satisfaction was higher in this arm.[24]

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.

- Many experts expected that a switch to dolutegravir-abacavir-lamivudine, as in the STRIIVING study, would exhibit superior efficacy compared to continuing current therapy because prior trials demonstrated the superiority of dolutegravir-anchored combinations over other first-line regimens in treatment-naïve patients. There are several possible reasons why the switch was not superior in this trial: many participants may have already been taking INSTI-based regimens or single-tablet regimens, a switch from tenofovir DF to abacavir may have decreased the potency of the NRTI backbone, or the trial may have been too small to detect superior virologic efficacy in one arm. The central conclusion of the study is that carefully selected patients with negative HLA-B*5701 testing can switch or simplify therapy to dolutegravir-abacavir-lamivudine if they do not have a history of prior virologic failure, drug resistance, multiple past antiretroviral therapy regimens, or hepatitis B coinfection. Similarly, the NEAT 022 and GS-380-1878 studies demonstrated that individuals taking two NRTIs plus a boosted PI are likely to maintain virologic suppression after a switch to the same two NRTIs plus dolutegravir or bictegravir, and the switch may improve serum lipid levels and reduce cardiovascular risk.
- More recently, studies have evaluated a switch to bictegravir-tenofovir alafenamide-emtricitabine or dolutegravir plus tenofovir alafenamide-emtricitabine, and these trials 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.[25,26,27] 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

A number of studies have assessed the outcome of switching individuals to various NNRTI agents, including switches from one NNRTI to another NNRTI (within-class switches) or from alternate anchor agents to an NNRTI (between-class switches). Multiple switch 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.[28,29,30,31,32] Although doravirine, etravirine, 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.[33,34,35,36] 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. The following summarizes key studies that involve a switch to doravirine or rilpivirine. Since clinicians rarely switch to etravirine, the switch studies involving etravirine will not be addressed in detail.[29,37,38]

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 enrolled and randomized to either continue their current regimen or switch to doravirine-lamivudine-tenofovir DF.[36] After 24 weeks, 94% (419 of 447) of participants who switched to the doravirine-anchored regimen maintained a suppressed HIV RNA, as compared to 95% (211 of 223) who remained on their baseline regimen (a non-significant difference).[36] At 48 weeks, 91% (406 of 447) of the individuals taking the doravirine regimen had an HIV RNA level below 50 copies/mL, which was not significantly different from the week 24 data for the group who continued their baseline regimen.[36] For those participants taking a boosted PI regimen at baseline, lipid parameters improved after the switch to doravirine.

Switch to Rilpivirine

- **GS-366-1160**& (Efavirenz to Rilpivirine): In this study, 875 individuals with suppressed HIV RNA levels on efavirenz-tenofovir DF-emtricitabine were enrolled and randomized in 1:1 fashion to either continue the current regimen or switch to rilpivirine-tenofovir alafenamide-emtricitabine.[39] After 48 weeks, 90% (394 of 438) of the participants in the rilpivirine-tenofovir alafenamide-emtricitabine arm maintained virologic suppression compared to 92% (402 of 437) of the individuals in the efavirenz-tenofovir DF-emtricitabine arm.[39] 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. Lipids were not significantly different between the two arms, which may be because two agents were switched: efavirenz to rilpivirine, which may lead to decreases in some lipid parameters, and tenofovir DF to tenofovir alafenamide, which may cause increases in lipids.[39]
- **SPIRIT** (Boosted PI to Rilpivirine): This randomized, open-label trial enrolled 476 individuals with sustained virologic suppression on a boosted PI-based regimen and compared switching to the rilpivirine-based single-tablet regimen of rilpivirine-tenofovir DF-emtricitabine versus maintaining the current PI-based treatment.[34] The study had strict entry criteria, including suppression of HIV RNA levels for at least 6 months on a regimen of two NRTIs plus a boosted PI, no history of virologic failure, taking only a first or second antiretroviral regimen, and no resistance to NRTIs or any study drugs.[34] The rates of virologic suppression at 24 weeks were comparable between the arm that switched to rilpivirine-tenofovir DF-emtricitabine (94%) and the arm that continued two NRTIs plus a boosted PI (90%); lipid levels and gastrointestinal side effects improved for those individuals who switched to rilpivirine-based therapy.[34]

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.[34,36,37] 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.[33,34]
- **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.[30,40]
- **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.[41] Based on available data, most experts agree that a baseline HIV RNA level greater than 100,000 copies/mL does not preclude a switch to rilpivirine-based therapy if the following criteria are met: (1) there is no history of virologic failure, (2) the HIV RNA levels have been suppressed below 50 copies/mL for at least 6 months, and (3) there is no resistance to emtricitabine, rilpivirine, or tenofovir DF (or tenofovir alafenamide).
- **Concerns for Long Efavirenz Half-Life**: When switching an individual from an NNRTI, such as efavirenz, to an alternate agent, it is important to consider that some NNRTIs have a long half-life and the potential to induce metabolism of other medications. With a change from efavirenz to rilpivirine, there were initial concerns that the induction effect would hamper virologic outcomes, though data suggest this is not the case and the induction effect on rilpivirine is not clinically significant.[30].
- **Switch to Doravirine Following INSTI-Associated Weight Gain**: Doravirine has been found to have relatively neutral effects on weight.[42] 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. At this time, the short- and long-term effects of such a switch on weight and on cardiometabolic parameters have not been confirmed. Investigations into the effects of such a switch are currently being studied in a randomized clinical trial.

Within-Class Nucleoside Reverse Transcriptase Inhibitor Switches

A switch from older NRTIs, such as zidovudine or stavudine, to tenofovir DF or tenofovir alafenamide might be employed in order to reduce long-term toxicity risk. A switch from abacavir to tenofovir DF or tenofovir alafenamide is most often considered if a patient has a cardiac complication or is considered to be a significant risk for ischemic cardiovascular disease. A switch from tenofovir DF to either abacavir or tenofovir alafenamide may be considered in persons who develop renal insufficiency or have bone mineral density loss.[43]

Trials Involving Within-Class NRTI 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 older studies focused on switching to tenofovir DF or abacavir and newer studies focused on switching to tenofovir alafenamide. The following summarizes within-class NRTI switches, with an emphasis on larger, prospective trials involving more contemporary NRTIs.

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.[44] 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.[44] 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.[44] Overall, participants who were switched to elvitegravir-cobicistat-tenofovir alafenamide-emtricitabine had noninferior virologic responses compared with those in the no-switch group.[44] 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).[45] 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.[45] 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).[45] 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.[45]
- **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.[46] Participants (total of 630) were randomized equally to continue the baseline regimen or switch to rilpivirine-tenofovir alafenamide-emtricitabine (each with matching placebo).[46,47] 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.[46]
- **EMERALD**: In this phase 3 trial, researchers enrolled adults with well-controlled HIV on a boosted protease inhibitor plus tenofovir DF-emtricitabine and then randomized them in a 2:1 ratio to either

switch to darunavir-cobicistat-tenofovir alafenamide-emtricitabine or continue their pre-enrollment regimen.[48] After 52 weeks, participants initially randomized to continue their baseline regimen also switched to darunavir-cobicistat-tenofovir alafenamide-emtricitabine, such that all participants were then taking this single-tablet, tenofovir alafenamide-containing regimen.[49] A total of 1,080 individuals enrolled and continued in the study for 96 weeks, at which point analyses showed that virologic suppression was maintained at a relatively high rate (90.7% in the early switch arm and 93.8% in the late switch arm), with only rare virologic failures (less than 2%) in both groups and no treatment-emergent resistance mutations were reported.[48,49] In both groups, following the switch from tenofovir DF to tenofovir alafenamide, markers of renal tubular wasting improved, as did bone mineral density, but there were small increases in serum lipid parameters. Changes in weight were not statistically significant in this trial.[48,49]

Switch to Tenofovir DF

- **SWEET** (Zidovudine-Lamivudine to Tenofovir DF-Emtricitabine): In this randomized, open-label trial involving 234 adults with suppressed HIV RNA levels on a regimen of efavirenz plus zidovudine-lamivudine, investigators randomized the participants to continue the same regimen or replace the zidovudine-lamivudine backbone with tenofovir DF-emtricitabine (there were 117 individuals randomized in each arm).[50] At 48 weeks, participants in the two arms had similar rates of HIV RNA levels of less than 50 copies/mL (85% in those who continued zidovudine-lamivudine versus 88% in those who switched to tenofovir DF-emtricitabine). Participants who switched to tenofovir DF-emtricitabine had improved hemoglobin, lower total cholesterol and triglyceride levels, and preserved or restored limb fat after 48 weeks.[50]
- **SWIFT** (Abacavir-Lamivudine to Tenofovir DF-Emtricitabine): Investigators randomized 311 adults with suppressed HIV RNA levels (for at least 3 months) while taking a regimen of abacavir-lamivudine plus a boosted PI to switch the abacavir-lamivudine backbone to tenofovir DF-emtricitabine or maintain the current regimen.[51] At week 48, the proportion of participants with HIV RNA less than 50 copies/mL was similar in the switch to tenofovir DF-emtricitabine arm and in the maintain abacavir-lamivudine arm (86% and 83%), but the switch group had fewer virologic failures (3% versus 11%) and improved lipid parameters. This study, however, was limited by a low rate of participants who were taking boosted darunavir; boosted darunavir has been shown to be effective when combined with abacavir-lamivudine for either initial antiretroviral therapy or as a switch strategy, even at high viral loads.[52,53]

Switch to Abacavir

- [Trial] ASSURE (Emtricitabine-Tenofovir DF to Abacavir-Lamivudine): In this trial, investigators randomized adults with suppressed HIV RNA on a regimen of tenofovir DF-emtricitabine plus ritonavir-boosted atazanavir to either maintain current therapy (97 participants) or switch to abacavir-lamivudine plus unboosted atazanavir (199 participants). Results demonstrated maintenance of virologic suppression with improvements in bone and renal markers 24 weeks after the switch.[54]
- **STEAL** (Other NRTIs to Tenofovir DF-Emtricitabine or Abacavir-Lamivudine): In this randomized, open-label trial, investigators enrolled 357 adults taking older NRTIs and randomized them to switch the existing NRTI backbone to tenofovir DF-emtricitabine or abacavir-lamivudine.[55] At week 96 after the switch, virologic failure occurred in 4% (7 of 178) of the participants in the tenofovir DF-emtricitabine group and in 6% (10 of 179) of those in the abacavir-lamivudine group (intent-to-treat analysis). Participants who switched to tenofovir DF-emtricitabine had more favorable lipid profiles and experienced fewer serious non-AIDS cardiovascular events when compared with those in the abacavir-lamivudine group.[55]

Summary and Recommendations for Within-Class NRTI Switches

Tenofovir alafenamide is a newer NRTI agent that, per the above switch trials and other studies, is safer in terms of renal and bone toxicity as compared to tenofovir DF. Another advantage over tenofovir DF is that

tenofovir alafenamide may be used in the setting of mild-to-moderate renal insufficiency (creatinine clearance as low as 30 mL/min). Data suggest that tenofovir alafenamide is also an effective option for patients coinfected with HIV and hepatitis B. In addition, tenofovir alafenamide combination tablets (coformulated with other antiretroviral medications) are smaller than similar tenofovir DF coformulated tablets. For all of these reasons, most clinicians nowadays have a low threshold to switch tenofovir DF or abacavir to tenofovir alafenamide, especially if the patient has any evidence of intolerability or side effects, or significant risk factors for renal disease or osteoporosis (in the setting of tenofovir DF use), or ischemic cardiovascular disease (in the setting of abacavir use).

- Multiple situations may arise that warrant consideration of (1) a switch from one NRTI to another NRTI or (2) a switch from a regimen that includes one or more NRTIs 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, and drug-food interactions,
- Persons taking a regimen that includes didanosine, stavudine, or zidovudine should switch the regimen to a newer, safer, more effective regimen that does not include these older NRTIs.
- 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 addition, in some instances, the presence of an M184V resistance mutation should also be considered when switching to abacavir, since the presence of an 184V mutation may impact the likelihood of virologic success.
- Individuals taking tenofovir DF who develop nephrotoxicity or reduced bone mineral density should switch to tenofovir alafenamide, abacavir, or an NRTI-sparing regimen. Clinically, the most likely reason to switch from tenofovir DF to abacavir is the development of renal insufficiency. In this situation, switching from tenofovir DF to tenofovir alafenamide is also an important option, especially if the resistance profile suggests a switch to abacavir would be problematic.
- If a person is taking abacavir, and they develop a risk of cardiovascular disease, abacavir should, if possible, be switched to another agent.
- Since tenofovir DF and tenofovir alafenamide are preferred medications for HBV treatment, a switch from either of these agents to abacavir or to an NRTI-sparing regimen should take into account the person's HBV status.
- A switch from older NRTIs to tenofovir alafenamide generally maintains virologic efficacy and may reduce risks of certain comorbidities, but the use of tenofovir alafenamide, especially in combination with bictegravir or dolutegravir, 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.
- For persons with weight gain on a regimen containing tenofovir alafenamide, some experts would recommend changing tenofovir alafenamide to tenofovir DF, abacavir, or possibly an NRTI-sparing regimen. The pros and cons of a switch from tenofovir alafenamide (because of weight gain) should occur with shared decision-making.
- Tenofovir DF-lamivudine is now available in multiple generic formulations in the United States, so cost considerations and insurance restrictions may need to be taken into account when comparing tenofovir DF versus tenofovir alafenamide.

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.[56] 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.[56,57]

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.[58] 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.[58] 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.[58,59] Participants were followed for

144 weeks, and the results remained similar, with noninferior virologic efficacy demonstrated for those who switched to dolutegravir-lamivudine.[59]

- **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.[60] 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.[60] All participants were taking a standard three-drug regimen with two NRTIs plus either an NNRTI, INSTI, or boosted PI.[60] They were randomized 1:1 to either continue the baseline regimen or switch to dolutegravir-lamivudine daily.[60] 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.[60]

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.[61] 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).[62] 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%).[62]
- [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.[63] 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.[63]

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).[64] 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.[64]
- **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).[65] 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%).[65]

- **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.[66] 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.[66] 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).[66]

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.[47] 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).[47] 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.[47] Injection site reactions were common in the long-acting antiretroviral therapy group (86% experienced some reaction), though most were mild and short-lived.[47] 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.[67] Over time, the injection site reactions were noted to decrease in frequency.[67] 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.[68] 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.[68] Both strategies (direct-to-inject and oral lead-in) were found to be safe and well-tolerated overall.[68]
- **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).[69] 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.[69] 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.[69] Injection site reactions were common in the injectable antiretroviral therapy arm but generally mild; serious reactions were infrequent.[69] Among participants who continued long-acting therapy during an extension phase to 96 weeks, 98% (51 of 52) maintained virologic suppression.[70]
- **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.[71] 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.[71] Individuals who enrolled were then randomized to intramuscular cabotegravir and rilpivirine injections every 4 weeks (n = 523) or every 8 weeks (n = 522).[71] 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.[71] 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.[71] 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).[72] 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.[72] The following summarizes key recommendations for the use of injectable cabotegravir and rilpivirine as a two-drug maintenance antiretroviral therapy regimen.[1,72]

- 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.[73,74] It should be noted that this strategy is not approved by the FDA and is not recommended in the Adult and Adolescent ART 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

Step-Down Monotherapy

The concept of step-down monotherapy has been explored to minimize the number of antiretroviral medications and thereby minimize potential drug toxicity and costs. This concept has been examined with boosted protease inhibitors and dolutegravir—medications that have high antiviral potency and a very high genetic barrier to resistance. In addition, this concept has only been studied as step-down therapy in persons with persistently suppressed HIV RNA levels on a stable three-drug antiretroviral regimen. The following summarizes key clinical trials related to step-down monotherapy.

Trials with Boosted PI Monotherapy

In addition to examining a simplification to dual therapy, several trials have assessed simplifying combination antiretroviral therapy to single-drug monotherapy, generally with a boosted PI or dolutegravir. Note this strategy is not recommended in the Adult and Adolescent ART Guidelines due to high virologic failure rates, even when using medications with a high genetic barrier to resistance, such as boosted darunavir or dolutegravir.[1] The following summarizes available data for boosted PI maintenance monotherapy with either lopinavir-ritonavir or darunavir boosted with ritonavir.

- **MONET** (Darunavir boosted with Ritonavir): This trial enrolled 256 adults who were virologically suppressed for at least 6 months on triple antiretroviral therapy and then randomized them to switch to once-daily ritonavir-boosted darunavir monotherapy or triple therapy with once-daily ritonavir-boosted darunavir plus 2 investigator-chosen NRTIs.[75] After 144 weeks of follow-up, the percentage of patients with HIV RNA less than 50 copies/mL was 69% in the ritonavir-boosted darunavir monotherapy arm versus 74% in the triple antiretroviral therapy arm.[75] Later analysis showed that patients without hepatitis C virus coinfection and with a pre-trial HIV RNA level below 5 copies/mL by an ultrasensitive RNA assay were more likely to remain suppressed on boosted darunavir monotherapy. In addition, those who experienced virologic rebound after simplifying to boosted darunavir monotherapy were very likely to again achieve viral suppression when antiretroviral therapy was re-intensified with NRTIs.[76] Similar to the MONOI trial, resistance analysis of those who failed in the MONET trial showed the development of resistance-associated mutations was rare, even in those who failed boosted darunavir monotherapy.[77]
- **MONOI** (Darunavir boosted with Ritonavir): In this trial, investigators randomized 225 virologically suppressed individuals taking triple antiretroviral therapy that included ritonavir-boosted darunavir to maintain combination therapy or simplify to ritonavir-boosted darunavir monotherapy.[78,79] At 96 weeks, virologic efficacy rates were comparable (88% in the monotherapy arm and 84% in the combination therapy arm).[79] Post-hoc analysis demonstrated no significant darunavir-associated resistance mutations in any participant who failed therapy in this trial, and minority darunavir resistance mutations developed in only 1 person.[80]
- **OK04** (Lopinavir-Ritonavir): In this trial, adults taking a boosted PI plus 2 NRTIs with no history of virologic failure and with HIV RNA below 50 copies/mL for at least 6 months were randomized to continue current therapy (n = 98) or simplify to ritonavir-boosted lopinavir monotherapy (n = 100).[81] At 96 weeks, the percentage of participants without treatment failure (defined as HIV RNA increase to above 500 copies/mL) was 87% in the monotherapy arm and 78% in the combination therapy arm, but low-level viral rebound was more frequent in the monotherapy arm, and 12% of participants in this group reinitiated NRTIs for combination therapy due to low-level viral rebound.[81]
- **PIVOT** (Protease Inhibitor Monotherapy): The open-label PIVOT trial randomized 587 adults with suppressed HIV RNA levels for at least 6 months (and no regimen change in the previous 3 months) to either ongoing triple therapy or simplification to ritonavir-boosted PI monotherapy; the study protocol included close monitoring of the HIV RNA level and reintroduction of combination therapy for viral rebound.[82] Virologic rebound occurred in 35% of participants in the monotherapy arm and in 3% of those on triple therapy, but all patients with virologic rebound on the PI monotherapy had virologic

suppression if they restarted triple antiretroviral therapy.[82] At the end of the trial, only 58% of participants in the switch group were still taking monotherapy. Subsequent analysis determined several independent predictors of viral rebound after simplification to boosted PI monotherapy, including shorter time since first viral suppression, lower CD4 cell count nadir, lower pre-switch CD4 count, and non-White ethnicity.[83] In this trial, the specific PI agent used was not a predictor of failure.

- **PROTEA** (Darunavir boosted with Ritonavir): In this randomized, controlled trial, investigators enrolled 137 adults with suppressed HIV RNA levels on a first-line triple antiretroviral therapy regimen and switched the regimen to either once-daily ritonavir-boosted darunavir monotherapy or triple therapy with two NRTIs plus once-daily ritonavir-boosted darunavir.[84] At week 96, fewer individuals in the ritonavir-boosted darunavir monotherapy arm had HIV RNA less than 50 copies/mL than the participants in the triple antiretroviral therapy arm (75% versus 85%).

Trials with Dolutegravir Monotherapy

Although there has also been an interest in simplification to dolutegravir monotherapy, concern has been raised regarding the ethics and design of dolutegravir monotherapy studies completed to date, and preliminary data reveals concern regarding this strategy due to the risk of failure and development of integrase resistance.[85] The following summarizes the major clinical studies that have examined dolutegravir monotherapy.

- **DOLAM** (Dolutegravir Monotherapy): In this multi-center, open-label trial, investigators randomized persons with HIV and suppressed HIV RNA levels on a three-drug antiretroviral regimen to either remain on the current regimen, switch to dolutegravir-lamivudine dual therapy, or switch to dolutegravir monotherapy.[86] Eligibility required HIV RNA levels less than 50 copies/mL for at least 12 months, nadir CD4 count greater than 200 cells/mm^3, no prior virologic failure, no HIV drug resistance to dolutegravir or lamivudine, and negative hepatitis B surface antigen.[86] A total of 91 participants enrolled, and after 24 weeks, 6.5% (2 of 31) of the participants receiving dolutegravir monotherapy developed virologic failure, and both had significant integrase resistance.[86] The investigators concluded that an unacceptable risk of viral failure occurred with dolutegravir monotherapy (with development of integrase inhibitor cross-resistance mutations), and this arm of the trial was stopped.[86]
- **DoluMono** (Dolutegravir Monotherapy): In this retrospective, single-center, cohort study, investigators evaluated a switch to dolutegravir for maintenance therapy in 31 individuals taking three-drug antiretroviral therapy with a routinely suppressed HIV RNA level (less than 50 copies/mL for at least 6 months).[87] Subjects enrolled were also required to have no evidence of active hepatitis B replication, no history of INSTI failure, and no known INSTI resistance.[87] After 24 weeks, 94% (29 of 31) participants who switched to dolutegravir monotherapy maintained an HIV RNA level of less than 50 copies/mL.[87] Among the two failures, one discontinued dolutegravir, and the other developed resistance to dolutegravir with significant new resistance-associated mutations (Q148H and G140S).[87]
- **DOMONO** (Dolutegravir Monotherapy): In this randomized, open-label, multi-center trial, investigators compared dolutegravir step-down monotherapy versus continued standard maintenance combination antiretroviral therapy in adults with suppressed HIV RNA levels (less than 50 copies/mL).[88] Entry criteria included nadir CD4 count greater than 200 cells/mm^3, HIV RNA peak of less than 100,000 copies/mL, no baseline HIV drug resistance, and no previous virologic failure.[88] For the first 24 weeks, 51 subjects immediately switched to dolutegravir monotherapy, and 53 remained on standard maintenance therapy. At week 24, virologic suppression to a level less than 200 copies/mL was maintained in 98% (49 of 50) subjects in the dolutegravir group and in 100% (53 of 53) in the combination antiretroviral therapy group. After 24 weeks, 46 of the 53 participants on standard maintenance therapy who were still enrolled crossed over to the dolutegravir monotherapy arm.[88] When 77 of the 96 subjects had reached week 48 in the study, 8 had developed virologic failure, including 2 before week 24 and 6 after week 24. Analysis of the virologic failures revealed that 3 individuals receiving dolutegravir had developed integrase inhibitor resistance mutations. Due to

virologic failure and dolutegravir resistance, the trial was stopped early.[88] The study investigators concluded that the genetic barrier of dolutegravir monotherapy is not sufficient to support dolutegravir monotherapy.

Summary and recommendations for 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 ART 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

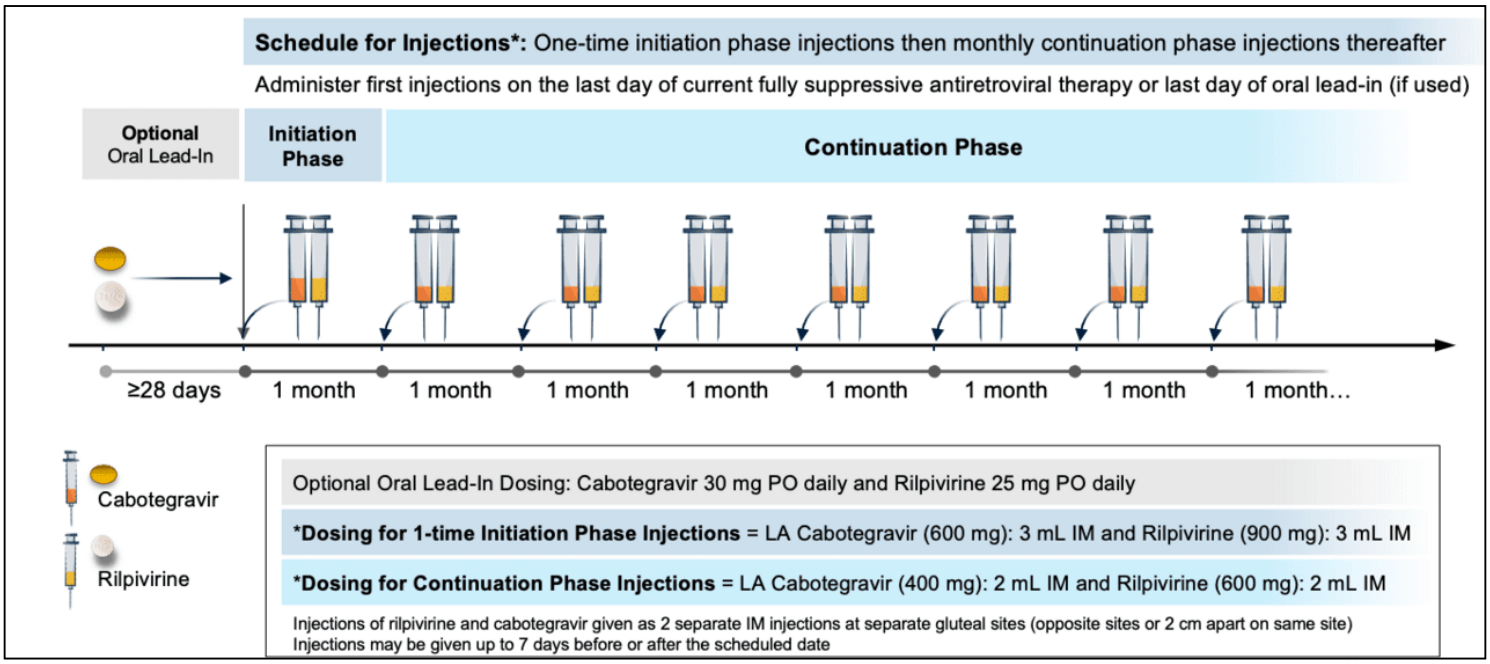

Figure 2 Every 2-Month Dosing Schedule of Injectable Cabotegravir and Rilpivirine, with Optional Oral Lead-In

Illustration: David H. Spach, MD