Switching or Simplifying Antiretroviral Therapy

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 (viral loads). 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. The reasons for switching an antiretroviral regimen are distinct from the setting of virologic failure with documented antiretroviral resistance, which necessitates transition to a salvage regimen as guided by genotypic drug resistance testing. Currently, switching antiretroviral therapy for the purpose of improving convenience or tolerability arises more frequently in clinical practice than the need to switch due to drug resistance.[4]

Updating Antiretroviral Therapy to a Modern Regimen

A 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 antiretroviral therapy. In this situation, a regimen modification may benefit the person with HIV by reducing pill burden and decreasing the risk for long-term adverse effects. For example, an individual may have years of consistently suppressed HIV RNA levels while taking a regimen that includes zidovudine, an old nucleoside reverse transcriptase inhibitor (NRTI); in this setting, assuming there are no reasons based on past resistance results to continue the older agent and provided the new regimen has a high likelihood of success, switching to a carefully chosen modern regimen may reduce pill burden and long-term drug-related adverse effects. Similarly, changing older boosted protease inhibitors or older NNRTIs to current first-line INSTI options, such as dolutegravir or bictegravir, may lead to a reduction in pill burden and side effects.

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 done with a high likelihood of maintaining virologic suppression, there may be long-term benefits associated with simplifying their regimen. Multiple studies have demonstrated that taking fewer pills translates to better adherence and higher rates of long-term virologic control.[5,6,7,8,9] 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.[3,10,11] Simplifying
antiretroviral therapy may also have significant economic impact, including lower copayments for the patient, particularly if the switch involves a reduction in the number of medications in the regimen. [12, 13] 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 to take into account 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 of 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 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 4 to 8 weeks after the regimen change. [1]
Switching to an Integrase Strand Transfer Inhibitor

The 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 addition, the INSTI elvitegravir is a component of two convenient fixed-dose single-tablet regimens that have been utilized in several switch studies, though use of elvitegravir-containing single-tablet regimens has decreased due to relatively poorer tolerability, cobicistat-related drug interactions, and the relatively low barrier to resistance of elvitegravir. In recent years, a switch of antiretroviral therapy 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. 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 shows the virologic efficacy and potential benefits of such a switch.

Switch to Bictegravir

- **GS-380-1878** (Boosted PI to Bictegravir-Tenofovir alafenamide-Emtricitabine): In this trial, investigators evaluated the virologic impact of a change from a ritonavir-boosted PI to the single-tablet regimen of bictegravir-tenofovir alafenamide-Emtricitabine. 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. A total 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).

- **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. All participants had sustained suppressed HIV RNA for at least 3 months and none had a history of virologic failure. 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).

- **GS-380-1961** (Suppressive Antiretroviral Therapy to Bictegravir-Tenofovir alafenamide-Emtricitabine): In this trial, 470 adult nonpregnant women with HIV and virologic suppression were randomized in 1:1 ratio to switch to either bictegravir-tenofovir alafenamide-Emtricitabine or elvitegravir-cobicistat-tenofovir DF-Emtricitabine, or ritonavir-boosted atazanavir plus tenofovir DF-Emtricitabine. All participants had sustained suppressed HIV RNA for at least 3 months and none had a history of virologic failure. 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.

- **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 1:1 ratio to switch to either bictegravir-tenofovir alafenamide-Emtricitabine or dolutegravir plus tenofovir alafenamide-Emtricitabine. After 48 weeks of treatment, the bictegravir combination was non-inferior to the dolutegravir combination, with 93.3% and 91.1%, respectively, maintaining an HIV RNA level below 50 copies/mL. 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), regardless of prior virologic failure or NRTI resistance. Virologic failure in both arms was low and three individuals in the study met criteria for resistance testing (all in the dolutegravir arm), but no emergent drug resistance occurred.\[17\] Weight gain was greater for individuals who switched from tenofovir DF to tenofovir alafenamide and did not differ significantly between bictegravir and dolutegravir.\[17\]

- **BRAAVE-2020** (Suppressive 3-Drug ART to Bictegravir-Tenofovir alafenamide-Emtricitabine for Black Americans): 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 enrolled and were randomized to continue their baseline regimen or switch to bictegravir-tenofovir alafenamide-emplivirine.\[18\] Of 495 participants who were randomized and treated, 10% had an M184V/I mutation at entry.\[18\] After 24 weeks of follow up, the bictegravir combination was found to be non-inferior to 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.\[18\] 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**

- **NEAT022** (Boosted PI to Dolutegravir): In this trial, investigators enrolled older individuals with HIV and elevated cardiovascular disease risk, with the goal of analyzing efficacy and impact of a change from a ritonavir-boosted PI to dolutegravir.\[19\] All participants had routinely suppressed HIV RNA while taking a boosted PI and two NRTIs and none had documented NRTI resistance mutations. All were over the age of 50 and had Framingham estimated 10-year risk of cardiovascular event over 10%.\[19\] A total of 415 individuals were randomized to continue two NRTIs plus a boosted PI, or switch to the same two NRTIs plus dolutegravir.\[19\] 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.\[19\]

- **STRIIVING** (Switch to Dolutegravir-Abacavir-Lamivudine): In the open-label STRIIVING study, investigators enrolled adults with HIV who had suppressed HIV RNA levels and examined the consequences of switching to a fixed-dose combination of dolutegravir-abacavir-lamivudine versus continuing current therapy.\[20\] Enrollees (277 in the continue current therapy group and 274 in the early switch group) were required to have suppressed HIV RNA levels on 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. Twenty-four week data showed switching to dolutegravir-abacavir-lamivudine resulted in non-inferior rates of virologic suppression as compared to continuing current therapy (85% in the switch group versus 88% in the maintenance group). After 24 weeks, all participants switched to dolutegravir-abacavir-lamivudine.\[20\] The 48-week data showed 83% and 92% of participants from the early switch and late switch groups, respectively, maintained virologic suppression.\[20\] 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 reported as higher in this arm.\[20\]

**Switch to Elvitegravir**

- **Study 121 (STRATEGY-NNRTI)** (NNRTI to Boosted Elvitegravir): The STRATEGY-NNRTI study randomized adults with HIV on antiretroviral therapy to continue their current regimen of tenofovir DF-emtricitabine plus an NNRTI or switch to the elvitegravir-based regimen of elvitegravir-cobicistat-tenofovir DF-emtricitabine.\[21\] Entry criteria included suppressed HIV RNA on the current regimen for at least 6 months, no history of virologic failure, taking a first or second antiretroviral therapy regimen
only, and no documented resistance to tenofovir or emtricitabine. After 48 weeks, 93% of patients in the switch group and 88% in the no-switch group had an HIV RNA level less than 50 copies/mL. In addition, switching from an efavirenz-based regimen led to improvements in neuropsychiatric side effects.

**Study 115 (STRATEGY-PI)** (Boosted PI to Boosted Elvitegravir): The STRATEGY-PI study randomized 433 adults with HIV to continue their current regimen of tenofovir DF-emtricitabine with a boosted PI or switch to an elvitegravir-based regimen consisting of the fixed-dose combination elvitegravir-cobicistat-tenofovir DF-emtricitabine. At enrollment, 42% of participants were taking ritonavir-boosted atazanavir, 39% ritonavir-boosted darunavir, and 17% lopinavir-ritonavir. After 48 weeks, 94% (272 of 290) patients who switched to elvitegravir-cobicistat-tenofovir DF-emtricitabine had an HIV RNA level less than 50 copies/mL compared with 87% (121 of 139) in the tenofovir DF-emtricitabine plus boosted PI group, a statistically significant difference. The statistical superiority of the switch arm was driven by non-virologic factors (more treatment discontinuations for tolerability issues in the boosted PI group). Virologic failure was rare in both study arms (approximately 1% in each). Analysis of patients in the lopinavir-ritonavir subgroup showed that switching regimens was associated with small improvements in serum total cholesterol, LDL cholesterol, and triglyceride levels.

**Switch to Raltegravir**

**SPIRAL** (Boosted PI to Raltegravir): The SPIRAL study was an open-label study that randomized 273 adults with HIV who had suppressed HIV RNA for at least 6 months on a stable boosted PI-based antiretroviral therapy regimen to continue the ritonavir-boosted PI or switch to raltegravir. Approximately 44% of the enrollees were taking lopinavir-ritonavir, whereas 35% were taking ritonavir-boosted atazanavir; the remainder were taking other boosted PIs and, notably, very few were taking boosted darunavir. After 48 weeks, 89% (124 of 149) participants in the raltegravir arm had an HIV RNA level less than 50 copies/mL compared with 87% (116 of 134) in the ritonavir-boosted PI group (meeting criteria for non-inferiority in the switch arm). A post-hoc analysis of SPIRAL did not identify prior virologic failure or NRTI resistance mutations as risk factors for virologic failure. Participants switched to raltegravir (when compared to those who continued a boosted PI) had improvements in lipid parameters, cardiovascular biomarkers, and bone mineral density, as well as less increase in visceral adipose tissue and total adipose tissue.

**SWITCHMRK 1 and 2** (Boosted PI to Raltegravir): The SWITCHMRK 1 and 2 studies were double-blind, double-dummy, phase 3 trials that together enrolled 707 adults with HIV who had suppressed HIV RNA levels for at least 3 months on an antiretroviral regimen of two or more NRTIs plus lopinavir-ritonavir. Investigators randomized participants to continue their current antiretroviral regimen or switch the lopinavir-ritonavir component of the regimen to raltegravir. The studies were stopped at week 24 because of a significant difference in virologic efficacy between the two arms: 84% (293 of 347) of the participants in the raltegravir group had HIV RNA levels below 50 copies/mL compared with 91% (319 of 352) in the lopinavir-ritonavir group. In addition, 32 patients in the raltegravir group met criteria for virologic failure versus 17 in the lopinavir-ritonavir group, and there were high rates of integrase resistance in those who failed raltegravir. Participants who switched to raltegravir had improvement in diarrhea and serum lipid concentrations.

**Summary of Key Findings with INSTI Switch Studies**

Several key findings have emerged from the INSTI switch studies.

- The SWITCHMRK and SPIRAL trials, when viewed together, clearly reinforce the concept that when considering a switch of antiretroviral therapy, especially a switch from a regimen with higher barrier to resistance (such as a boosted PI) to a regimen with lower barrier to resistance (such as raltegravir), it is vital to consider a patient's antiretroviral therapy history, including past virologic failures, prior drug resistance, length of time on antiretroviral therapy, and duration of viral suppression. When switching antiretroviral therapy, the activity of the NRTI backbone in the regimen is critical, especially when the
switch will reduce the relative resistance barrier of the anchor drug.[3]

- For antiretroviral therapy switch studies that followed the SWITCHMRK and SPIRAL trials (STRATEGY PI, STRATEGY NNRTI, STRIIVING, and others), inclusion criteria generally became stricter, requiring a longer duration of virologic suppression on antiretroviral therapy before enrollment and no history of virologic failure or drug resistance. For example, the STRATEGY studies, which had conservative enrollment criteria, showed that carefully selected patients are likely to experience success with a switch of therapy to the single-tablet regimen elvitegravir-cobicistat-tenofovir DF-emtricitabine and some patients, including those taking lopinavir-ritonavir or efavirenz, may experience improvements in side effects.

- 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 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 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 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. 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-naive individuals, these agents may serve as alternative NNRTI medications and may be utilized in switch regimens following intolerability or complications of PI- or INSTI-based antiretroviral regimen.[33,34,35,36] In particular, a switch to doravirine- or rilpivirine-based antiretroviral regimen 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 always be considered. The following summarizes key studies that involve a switch to doravirine or rilpivirine. Since clinicians now 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 2 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 to 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-264-0111** (Efavirenz to Rilpivirine): This phase 2b, single-arm, open-label trial enrolled 49 individuals taking a first regimen of efavirenz-tenofovir DF-emtricitabine (for at least 3 months, with suppressed HIV RNA levels, and no evidence of resistance to any of the study drugs) and examined the impact of switching to rilpivirine-tenofovir DF-emtricitabine.[30] Although rilpivirine plasma trough concentrations decreased initially after the switch (consistent with a lingering induction effect from efavirenz), concentrations returned to effective levels by 2 weeks. After the switch, 100% of participants maintained a suppressed viral load at 24 weeks and 94% at 48 weeks; virologic failure without resistance occurred in 2 participants. The investigators concluded that although efavirenz has an induction effect on rilpivirine after a switch, this effect is transient and does not require dose modification. Improvements in lipid parameters occurred by week 12 after the switch from efavirenz to rilpivirine and persisted to week 48.

- **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]
• **NEAR Rwanda** (Nevirapine to Rilpivirine): In the open-label NEAR-Rwanda study, investigators randomized 150 adults in Rwanda, all of whom had suppressed HIV RNA level while taking nevirapine plus 2 NRTIs, to either switch to rilpivirine-tenofovir DF-emtricitabine or continue nevirapine-based therapy.[40] After 24 weeks, virologic suppression (HIV RNA less than 50 copies/mL) was 90% (89 of 99) in the switch arm and 84% (43 of 51) in the continue therapy arm.[40] The switch was well-tolerated and led to small reductions in total cholesterol and HDL cholesterol levels; there were no significant safety concerns.[40]

• **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 regimen.[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 in those 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, etravirine, or rilpivirine is associated with improved lipid parameters.[34, 36, 37] A switch or simplification of boosted PI-based regimens to rilpivirine-based therapy may be an option for select patients, but this type of regimen change has 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, 41]

- **Switch to Rilpivirine if Baseline HIV RNA Greater than 100,000 copies/mL**: In antiretroviral treatment-naïve persons, rilpivirine-based therapy carries a higher risk of virologic failure in when the pretreatment HIV RNA level is 100,000 copies/mL or higher.[42] A common clinical question is whether a baseline HIV RNA level greater than 100,000 copies/mL is a contraindication to switching to rilpivirine if the patient has a suppressed HIV RNA level on antiretroviral therapy at the time the switch is being considered. 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.[43] 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 the time, the short- and long-term effects of such a switch on weight and on cardiometabolic parameters has not been confirmed. Investigations into the effects of such a switch are currently being studied in randomized clinical trials.
Within-Class 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 older studies focused on switching to tenofovir DF or abacavir and newer studies focused on switching to tenofovir alafenamide. 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.\(^{[44]}\) A switch off the older NRTIs, such as tenofovir DF, abacavir, or zidovudine may lead to an increase in body weight or BMI, though the mechanism has not been confirmed and long-term outcomes are still under investigation. In addition, since tenofovir DF combinations have become generic in the United States, some individuals may need to switch from tenofovir alafenamide to tenofovir DF due to cost or insurance coverage issues. The following prospective trials have examined within-class NRTI switches.

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.\(^{[45]}\) 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 estimated glomerular filtration rate (eGFR) above 50 mL/min.\(^{[45]}\) 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.\(^{[45]}\) Overall, participants switched to elvitegravir-cobicistat-tenofovir alafenamide-emtricitabine had non-inferior virologic responses compared with those in the no-switch group.\(^{[45]}\) Participants taking boosted atazanavir or efavirenz at baseline had superior responses if they switched to a tenofovir alafenamide-containing regimen, primarily because of differences in tolerability, not virologic failures. Notably, 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.

- **Study 112** (Other NRTIs to Tenofovir alafenamide): This single-arm, open-label study evaluated switching adults with mild-to-moderate renal insufficiency to a tenofovir alafenamide-containing combination regimen.\(^{[46]}\) Investigators enrolled individuals on antiretroviral therapy with consistently suppressed HIV RNA levels (for at least 6 months) and creatinine clearance 30 to 60 mL/min, with no history of resistance to tenofovir DF, emtricitabine, or elvitegravir. Prior to the switch, 65% of participants were taking tenofovir DF and 42% had “significant proteinuria”. All 242 participants switched to the combination pill elvitegravir-cobicistat-tenofovir alafenamide-emtricitabine.\(^{[46]}\) The change of therapy did not lead to significant changes to estimated creatinine clearance (though improvement in estimated creatinine clearance with the elvitegravir-cobicistat-tenofovir alafenamide-emtricitabine regimen may have been obscured by increases in estimated serum creatinine from cobicistat), but it did lead to significant improvements in markers of proximal tubule dysfunction and bone mineral density.\(^{[46]}\) Of note, participants in this trial had chronic renal insufficiency secondary to a variety of causes and it is unclear how many had true tenofovir DF-induced proximal tubulopathy prior to the change of therapy.

- **Study 119**: In this open-label trial, investigators randomized 136 adults on salvage antiretroviral therapy with multi-drug resistant HIV to continue the same regimen or switch to a simplified salvage regimen of elvitegravir-cobicistat-tenofovir alafenamide-emtricitabine plus once-daily darunavir (800 mg).\(^{[47]}\) Inclusion criteria for this trial consisted of HIV RNA less than 50 copies/mL for at least 4 months on a darunavir-containing salvage regimen, at least 2 prior episodes of virologic failure and multi-class drug resistance, but no darunavir resistance-associated mutations, no INSTI resistance,
less than or equal to 3 thymidine analog mutations (TAM’s), and no Q151 mutation complex or T69
insertion complex resistance patterns. Participants were also required to have an estimated creatinine
clearance above 50 mL/min. The antiretroviral regimen switch was well tolerated and led to
significantly higher rates of suppressed HIV RNA levels (less than 20 copies/mL) at 48 weeks, as
opposed to continuing baseline therapy (90% versus 72%).[47]

- **Study 1249** (Tenofovir DF to Tenofovir alafenamide): In this single-arm study, investigators enrolled 72
  individuals with chronic HIV and hepatitis B virus (HBV) coinfection and switched their antiretroviral
  therapy to the single-tablet regimen elvitegravir-cobicistat-tenofovir alafenamide-emtricitabine.[48]
  Inclusion criteria were CD4 count above 200 cells/mm³, suppressed HIV RNA level for at least 6
  months, stable antiretroviral therapy regimen for at least 4 months, HBV DNA level below 9 log₁₀
  IU/mL, absence of hepatic decompensation, no evidence of hepatitis C or D virus coinfection, and
  estimated creatinine clearance of at least 50 L/min.[48] At study entry, 96% of participants were
taking tenofovir DF-containing antiretroviral therapy, 99% had positive hepatitis B surface antigen,
42% positive HBe antigen, and 86% HBV DNA level below 29 IU/mL. At 48 weeks following the switch,
92% of participants had an HIV RNA less than 50 copies/mL, 92% had an HBV DNA less than 29
copies/mL (compared to 86% at study baseline), and markers of renal proximal tubular wasting and
bone turnover improved.[48]

- **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).[49] 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, a non-
statistically significant difference).[49] The group that switched to tenofovir alafenamide-emtricitabine
experienced greater improvements in median eGFR as compared to the tenofovir DF-emtricitabine
arm (+8.4 mL/min versus +2.8 mL/min, a statistically significant difference).[49] 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.[49]

- **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 study drugs.[50] Participants (total of 630) were
randomized equally to continue the baseline regimen or switch to rilpivirine-tenofovir alafenamide-
emtricitabine (each with matching placebo). 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 non-inferior virologic efficacy of the regimen switch.

**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).[51] At 48 weeks, participants in the two arms had similar rates of HIV RNA
level 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.[51]

- **TOTEM** (Other NRTIs to Tenofovir DF-Emtricitabine): In the TOTEM trial, French investigators
  randomized 91 adults with dyslipidemia (abnormal fasting triglycerides or LDL cholesterol) and HIV
  RNA levels less than 400 copies/mL to change the NRTI backbone to tenofovir DF-emtricitabine or
  maintain the same regimen (prior to the switch, most were taking zidovudine-lamivudine and a
  smaller proportion were taking abacavir-lamivudine or older NRTI combinations).[52] After 12 weeks,
patients who switched to tenofovir DF-emtricitabine had improvements in lipid levels when compared with those who did not switch; there were no differences in the virologic suppression rate at 12 weeks in the two groups.[52]

- **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.[53] 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 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 enrollees 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.[54,55]

### Switch to Abacavir

- **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.[56]

- **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.[57] 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.[57]

### Summary of Findings with NRTI Switch Studies

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).

Although a switch from older NRTIs to tenofovir alafenamide generally maintains virologic efficacy and may reduce risks of certain comorbidities, recently, concerns have been raised regarding an increase in weight and BMI for some individuals. Even though an increase in weight or BMI alone does not necessarily indicate an increase in health risks, in some instances, this may lead to a higher likelihood of glucose intolerance, hypertension, or other cardiometabolic comorbidities. Therefore, the pros and cons of such a switch should always be considered and discussed with the patient. Furthermore, tenofovir DF-lamivudine is now available as a generic formulation in the United States, so cost considerations and insurance restrictions may also need to be taken into account when comparing tenofovir DF versus tenofovir alafenamide combination tablets.

Safely switching tenofovir DF or tenofovir alafenamide to abacavir assumes the patient has documented HLA-B*5701 negativity and no significant NRTI resistance (especially no M184V/I mutation, which increases susceptibility to tenofovir DF but causes low-level resistance to abacavir). In addition, if switching from
tenofovir DF to abacavir, it is important to know the patient's hepatitis B status, as tenofovir DF is active against hepatitis B and abacavir is not. Furthermore, tenofovir DF and abacavir have differing safety profiles, with tenofovir DF having greater risk for nephrotoxicity and decreased bone mineral density, yet with some lipid-lowering benefits over abacavir. 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. In this situation, clinicians may consider a switch to a 2-drug regimen to eliminate tenofovir alafenamide, tenofovir DF, and abacavir from the regimen.
Simplifying Therapy to An Oral or Injectable Two-Drug Regimen

In recent years, a number of studies have examined switching to dual or mono antiretroviral therapy for maintenance, meaning for continued use after virologic suppression has been achieved on a standard three-drug regimen. The goals of this simplification strategy are to minimize pill burden and medication-related adverse effects, with the added benefit of preserving future antiretroviral therapy options and possibly reducing cost.[3] Furthermore, 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 viral load. This long-acting, parenteral two-drug option requires careful consideration of eligibility based on clinical, logistical, and cost/coverage factors.

- **FDA Approved Dual Simplification Regimens**: Accumulating data support the efficacy of simplifying to certain dual therapy options for carefully selected individuals and the United States Food and Drug Administration (FDA) has approved the following 2-drug combinations as maintenance regimens in persons with suppressed HIV RNA levels: oral dolutegravir-rilpivirine, oral dolutegravir-lamivudine, and long-acting injectable cabotegravir plus rilpivirine. Note that dolutegravir-lamivudine is also approved for use as initial therapy for individuals who meet certain specified parameters. The following summarizes the indications for these 2-drug combination 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.
  - Cabotegravir-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 with no history of treatment failure and with no known or suspected resistance to either cabotegravir or rilpivirine.

- **Antiretroviral Therapy Guideline Recommendations for Dual Maintenance Therapy**: There are significant data that support the use, in certain clinical situations, of the following two-drug oral antiretroviral therapy options: (1) dolutegravir plus rilpivirine, and (2) dolutegravir plus either lamivudine or emtricitabine, (3) a boosted PI (darunavir, atazanavir, or lopinavir) plus lamivudine, or (4) boosted darunavir plus dolutegravir.[1] There are a number of ongoing studies further examining these and other 2-drug maintenance regimens, with a caveat that most of these studies include at least one agent of high barrier to resistance (e.g. dolutegravir or boosted darunavir). In addition, long-acting, injectable cabotegravir plus rilpivirine combination, given every 1 or 2 months, is another 2-drug maintenance option for individuals who have good adherence and engagement in healthcare, are virologically suppressed for a minimum of 3 to 6 months on oral antiretroviral therapy, and who have no issue with coming to clinic regularly to receive their injections.[1]

- **Considerations Prior to Switching to a 2-Drug Maintenance Regimen**: Persons switching to a 2-drug maintenance regimen should meet the following criteria: (1) suppressed HIV-1 RNA levels (less than 50 copies/mL) on a stable antiretroviral regimen (with a switch to dolutegravir-rilpivirine the HIV RNA levels should be suppressed for at least 6 months), (2) no history of treatment failure, (3) no known substitutions associated with resistance to the individual components of the 2-drug regimen. It is also important to review a patient’s HBV status prior to switching to any of these two-drug maintenance regimens, since none of the commonly used 2-drug maintenance regimens provide effective treatment for HBV. Thus, for a person who has coinfection with HIV and HBV, a switch to any of the two-drug maintenance antiretroviral options is generally not done as they would need to receive an additional two oral medications that drugs that are active against HBV.

- **Special Considerations with Switch to Long-Acting Injectable 2-Drug Regimen**: For some individuals, the option of switching to long-acting injectable cabotegravir and rilpivirine may...
be attractive to eliminate pill burden and it may benefit persons who do not have a safe, private place
to store oral medications, particularly if they do not want to disclose their HIV status to persons they
are living with. There are, however, potential downsides, including a need for frequent clinic visits for
intramuscular injections (two gluteal injections at each visit), 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. The injectable combination may be given with or without a
lead-in of oral versions of cabotegravir and rilpivirine. 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.

Dual Therapy Maintenance Regimens: Randomized Trials

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, few (if any) virologic failures, and an overall high likelihood of virologic
suppression after a switch. Outside a clinical trial setting, these simplification strategies should not be
undertaken for patients with poor adherence, extensive resistance, salvage regimens, or otherwise difficulty
achieving suppression of HIV RNA levels. These recommendations also pertain to the long-acting injectable
regimen cabotegravir plus rilpivirine and this regimen should not be prescribed for individuals who have
detectable viral loads or are unable to make clinic visits for regular injections. The following summarizes
published data on simplification to dual antiretroviral therapy (oral or injectable) versus continuing standard
three-drug oral antiretroviral therapy.

Simplification to Dolutegravir plus 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.[58] Participants also had to have negative
hepatitis B surface antigen, no history of virologic failure, and were required to be taking 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.[58,59]

Simplification to Dolutegravir plus Lamivudine

- ASPIRE (Dolutegravir plus Lamivudine): In this open-label randomized trial, individuals with
suppressed HIV RNA levels for at least 48 weeks on standard 3-drug antiretroviral therapy, no history
of virologic failure, no known NRTI or integrase resistance, and creatinine clearance about 50 mL/min,
were enrolled and randomized to either continue current therapy or simplify to dolutegravir plus
lamivudine dual maintenance therapy.[60] A total 90 individuals were randomized (45 to each arm)
and by week 24, three individuals in each arm experienced treatment failure (a non-significant
difference). Only one of the treatment failures in the dolutegravir plus lamivudine dual therapy arm
was a case of virologic failure and this individual did not develop resistance to either agent in the
regimen.[60] Subsequent analyses using ultra-sensitive HIV RNA assays showed there was no
difference in residual viremia between the dual and triple antiretroviral arms.[60]
- LAMIDOL (Dolutegravir plus Lamivudine): In this noncomparative, single-arm study, individuals with
well-controlled HIV on stable three-drug antiretroviral therapy were enrolled.[61] Inclusion criteria
required a nadir CD4 count above 200 cells/mL and HIV RNA less than 50 copies/mL for at least 2
years while taking standard 3-drug antiretroviral therapy, no evidence of hepatitis B coinfection, no
history of virologic failure, and only one to two antiretroviral treatment modifications in the past (with
no modification within the past 6 months).[61] Individuals in this trial were all switched to dolutegravir plus two NRTIs for 8 weeks, then those who tolerated that switch and maintained an HIV RNA less than 50 copies/mL entered a second phase of the study in which they received a simplified dual therapy regimen consisting of dolutegravir plus lamivudine. At 48 weeks (40 weeks after the switch to dual therapy with dolutegravir plus lamivudine), 97% of participants maintained virologic suppression.[61] No resistance mutations occurred in those who did not have an HIV RNA below 50 copies/mL at 48 weeks.

- **TANGO**: (Dolutegravir-Lamivudine): In the open-label, phase 3 TANGO trial, investigators randomized adults who had suppressed HIV RNA levels on a 3- or 4-drug regimen to remain on the regimen or to switch to a 2-drug regimen of fixed-dose dolutegravir-lamivudine.[62] Participants who achieved viral suppression by week 24 of the induction phase were further randomized in a maintenance phase to either continue dual NRTIs plus efavirenz or, for those taking cabotegravir, to simplify to a two-drug regimen consisting of the existing dose of oral cabotegravir plus oral rilpivirine.[64] At 96 weeks, patients receiving the two-drug regimen of oral cabotegravir and oral rilpivirine had similar rates of virologic suppression as those taking two NRTIs plus efavirenz.

- **LATTE-2** (Cabotegravir plus Rilpivirine): In a phase 2b open-label study, investigators evaluated the efficacy of the long-acting injectable cabotegravir and rilpivirine as maintenance antiretroviral therapy.[65] A total of 309 adults were enrolled and during the induction phase of the study received abacavir-lamivudine plus oral cabotegravir for 20 weeks, with the addition of oral rilpivirine during weeks 16 to 20.[65] For the maintenance phase, participants who tolerated the oral agents and had suppressed HIV RNA levels were randomized 2:2:1 to one of three regimens: (1) intramuscular injectable cabotegravir plus intramuscular injectable rilpivirine dual therapy, every 4 weeks (n = 115), (2) intramuscular injectable cabotegravir plus intramuscular injectable rilpivirine dual therapy, every 8 weeks (n = 115), or (3) the oral three-drug regimen of cabotegravir plus abacavir-lamivudine (n = 56).[65] After 96 weeks, the virologic suppression was maintained in 84% (47 of 56) in the oral treatment group, 87% (100 of 115) in the 4-week group, and 94% (108 of 115) in the 8-week group.[65] The intramuscular agents caused injection site reactions, but most participants still reported favoring the long-acting injections over oral therapy.[65]

- **FLAIR-48 Week Data** (Monthly, Long-Acting Injectable Cabotegravir plus Rilpivirine): In this phase 3, randomized, open-label, noninferiority trial, antiretroviral-naive adults who had suppressed HIV RNA levels below 50 copies/mL were randomized to either continue oral therapy or switch to oral cabotegravir plus rilpivirine for 1 month followed by a transition to injectable intramuscular long-acting cabotegravir plus rilpivirine (n = 283 in the oral antiretroviral therapy arm and 283 in the long-acting antiretroviral therapy arm).[66] 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 long-acting injectable therapy and 2.5% with continued oral antiretroviral therapy), which met the criteria for non-inferiority of the long-acting combination.[66] Injection site reactions were common in the long-acting antiretroviral therapy group (86% experienced some reaction), though most were mild and short-lived.[66] 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.[67,68]

- **ATLAS** (Switch to Monthly Cabotegravir plus Rilpivirine): For this phase 3, open-label, noninferiority
Simplification to Boosted PI plus Another Agent

- **ATLAS** (Boosted Protease Inhibitor plus Lamivudine): This open-label, single-arm pilot study assessed a switch from triple antiretroviral therapy that included boosted atazanavir to a dual regimen of boosted atazanavir plus lamivudine in 40 adults.[73,74] After 144 weeks, 23% (9 of 40) of the individuals had treatment failure, though only 2 were virologic failures (and no resistance occurred); the other discontinuations were due to intolerability.[74] Patients in the switch arm had significant improvements in renal function and bone mineral density and no change to neurocognitive function.

- **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.[75] 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.

- **HARNESS** (Boosted Atazanavir plus Raltegravir): This trial enrolled 109 individuals with suppressed HIV RNA levels (for at least 3 months) on two NRTIs plus a third agent who were struggling with tolerability issues.[76] Participants were randomized to switch to a dual-therapy regimen of raltegravir plus ritonavir-boosted atazanavir or a standard triple-drug regimen of ritonavir-boosted atazanavir plus tenofovir DF-emtricitabine. Participants who switched to a dual therapy regimen had a higher rate of virologic rebound (10% versus 3%) at 24 weeks when compared to those who received a standard three-drug regimen (although most cases of virologic rebound were in the low-level viremia range and only one instance of new significant INSTI resistance occurred).[76]

- **QLE** (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).[77] 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 non-inferior virologic responses when compared with those who continued lopinavir-ritonavir plus two NRTIs (88% versus 87%).[77]

- **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).[78] 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%).[78]

- **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.[79] 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 non-inferior to the three-drug regimen.[79]

- **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 2-drug combination of boosted darunavir plus dolutegravir (n = 131).[80] 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 3-drug combination regimen, which meets criteria for non-inferiority.[80]

### Summary of Findings of Dual Therapy Simplification Studies

#### Potential Use of Dual Medication Maintenance Therapy

Taken together, available trial data suggest simplification to dual maintenance therapy may be a useful strategy for select treatment-experienced individuals, such as those with a suppressed HIV RNA for a long period of time and no prior history of resistance. If simplifying to dual oral therapy, the best available data are with dolutegravir plus rilpivirine and next with dolutegravir plus lamivudine; both as these combinations are available as a single tablet once daily option. There are also positive, but less robust, data with ritonavir-boosted protease inhibitors (atazanavir, darunavir, or lopinavir) plus lamivudine, and with dolutegravir plus boosted darunavir, but all of these requires taking multiple pills daily. Clinical trial data support switching to long-acting, intramuscular cabotegravir plus rilpivirine for carefully selected individuals, though they must be able to attend clinic every month for the injections and 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. The following summarizes key criteria that should be met when simplifying or switching to either dolutegravir-rilpivirine, or dolutegravir-lamivudine, or intramuscular cabotegravir plus rilpivirine as a simplified chronic maintenance regimen.

- **Dolutegravir-Rilpivirine**: The fixed-dose regimen dolutegravir-rilpivirine is indicated to replace an existing antiretroviral regimen in persons who have (1) suppressed HIV RNA levels less than 50 copies/mL (on a stable antiretroviral regimen for at least 6 months), (2) no evidence of prior antiretroviral treatment failure, (3) no known resistance mutations to either dolutegravir or rilpivirine, and (4) no evidence of HBV infection.[1]

- **Dolutegravir-Lamivudine**: The fixed-dose regimen dolutegravir-lamivudine is indicated to replace an existing antiretroviral regimen in persons who have (1) suppressed HIV RNA levels less than 50 copies/mL (on a stable antiretroviral regimen for at least 6 months), (2) no evidence of prior antiretroviral treatment failure, (3) no known resistance mutations to either dolutegravir or lamivudine, and (4) no evidence of HBV infection.
copies/mL on a stable antiretroviral regimen, (2) no evidence of prior antiretroviral treatment failure, (3) no known resistance mutations to either dolutegravir or lamivudine (e.g. the M184V mutation), and (4) no evidence of HBV infection.[1]

- **Long-acting, Intramuscular, Cabotegravir plus Rilpivirine**: This 2-drug, co-packaged product of long-acting cabotegravir and rilpivirine is indicated as a complete regimen to replace a current antiretroviral regimen in those who are virologically suppressed on a stable antiretroviral regimen with no history of treatment failure and with no known or suspected resistance to either cabotegravir or rilpivirine. Individuals should have a suppressed viral load, no resistance to cabotegravir or rilpivirine, and no hepatitis B infection. They should be willing to switch to oral formulations of cabotegravir and rilpivirine for 4 weeks to document tolerability before switching to monthly intramuscular doses of cabotegravir and rilpivirine in the clinic. The injections should be given as two separate gluteal injections at each visit (either on different sides of the gluteals or at least 2 cm apart on the same side).

**Potential Cost Savings with Dual Antiretroviral Maintenance Therapy**

One potential advantage of dual antiretroviral maintenance therapy is the cost savings it could offer as compared to standard triple antiretroviral therapy. For example, a mathematical modeling analysis examined the cost-effectiveness of several antiretroviral therapy scenarios, including no antiretroviral therapy, standard three-drug antiretroviral therapy with dolutegravir-abacavir-lamivudine, initial dual therapy with lamivudine plus dolutegravir, or an induction-maintenance strategy that involved 48 weeks of dolutegravir-abacavir-lamivudine, followed by maintenance with dolutegravir-lamivudine (assuming virologic suppression was achieved on three-drug therapy).[81] The strategies were all equally effective in terms of virologic suppression in the mathematical analysis and both the induction-maintenance and initial dual antiretroviral therapy strategies were cost-effective; the incremental cost-effectiveness ratio (ICER) for the induction-maintenance strategy was $22,500 per quality adjusted life year (QUALY), which is well below accepted standards for cost-effectiveness. The authors estimated that with 50% uptake of the induction-maintenance strategy, $550 million healthcare dollars would be saved within 5 years. Thus far, however, efficacy data for the dual antiretroviral therapy combination of dolutegravir plus lamivudine is limited to small pilot studies, so further clinical trial data are needed before these strategies are implemented routinely in clinical practice. Cost-analysis studies have not been performed with the dual maintenance regimen dolutegravir-rilpivirine.
Simplifying Maintenance Therapy to Monotherapy

Monotherapy with Boosted PIs (Randomized Trials)

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 ARV 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.[82] 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.[82] Later analysis showed that patients without hepatitis C virus co-infection 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 achieve repeat viral suppression when antiretroviral therapy was re-intensified with NRTIs.[83] Similar to the MONOI trial, resistance analysis of those who failed in the MONET trial showed that development of resistance-associated mutations was rare, even in those who failed boosted darunavir monotherapy.[84]

- **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.[85, 86] At 96 weeks, virologic efficacy rates were comparable (88% in the monotherapy arm and 84% in the combination therapy arm).[86] 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.[87]

- **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).[88] 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 re-initiated NRTIs for combination therapy due to low-level viral rebound.[88]

- **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.[89] 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.[89] At the end of trial, only 58% of participants in the switch group were still taking monotherapy. A 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.[90] 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 level on a first-line triple antiretroviral therapy regimen and switched the regimen to either monotherapy with once-daily ritonavir-boosted darunavir monotherapy
or triple therapy with 2 NRTIs plus once-daily ritonavir-boosted darunavir. 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%).

**Monotherapy with Boosted PIs (Systematic Reviews and Meta-Analyses)**

A review of trials in which participants switched from standard triple therapy to boosted PI monotherapy found a reduction in rates of several long-term side effects, such as lipoatrophy, but the authors do not recommend routine use of this strategy because of the increased risk of virologic failure. The article also highlights that switching off tenofovir DF may lead to an increase in lipid levels, even if switching to boosted PI monotherapy. A meta-analysis of 13 randomized trials of boosted PI monotherapy showed lower rates of HIV RNA suppression overall with this strategy as compared to standard three-drug antiretroviral therapy, though re-intensification of therapy (as in the PIVOT and OKO4 trials) led to similar clinical outcomes and there was no difference in resistance mutation development or neurocognitive outcomes. Overall, data for simplifying to boosted PI monotherapy are mixed, but given the risk of losing virologic control this strategy is not recommended.

**Monotherapy with Dolutegravir**

There has also been interest in simplification to dolutegravir monotherapy. However, 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 risk of failure and development of integrase resistance. Unless further data become available from well-designed trials, this strategy should not be utilized. An analysis that assessed the effects of this simplification is:

- **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). Subjects enrolled were also required to have no evidence of active hepatitis B replication, no history of INSTI failure, and no known INSTI resistance. After 24 weeks, 94% (29 of 31) participants who switched to dolutegravir monotherapy maintained an HIV RNA level less than 50 copies/mL. Among the two failures, one discontinued dolutegravir and the other developed resistance to dolutegravir with new mutations (Q148H and G140S).

- **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). Entry criteria included nadir CD4 count greater than 200 cells/mm³, HIV RNA peak of less than 100,000 copies/mL, no baseline HIV drug resistance, and no previous virologic failure. 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 who were still enrolled on standard maintenance therapy crossed over to the dolutegravir monotherapy arm. 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. The study investigators concluded that the genetic barrier of dolutegravir monotherapy is not sufficient to support dolutegravir monotherapy.
Summary Points

- Even if a person with HIV has stable virologic suppression, there may be reasons to consider an antiretroviral therapy regimen, especially if the change is associated with increased medication tolerability and/or convenience.
- 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, and adherence.
- Assessing past treatment failures and resistance is especially important if the antiretroviral therapy regimen switch being considered involves transition 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 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 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 baseline (pre-antiretroviral therapy) HIV RNA level greater than 100,000 copies/mL is not a contraindication to switching to rilpivirine if the current HIV RNA is suppressed on antiretroviral therapy. A switch to doravirine or INSTI-based combinations can also be considered.
- 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 and may reduce the size of pills. However, recent data suggest this may also lead to weight gain for some individuals (clinical significance has not been determined).
- The FDA has approved the following 2-drug regimens as maintenance antiretroviral therapy: oral dolutegravir-rilpivirine, oral dolutegravir-lamivudine, and long-acting injectable cabotegravir plus rilpivirine. These 2-drug regimens should only be used in persons sustained suppressed HIV RNA levels (ideally for at least 6 months), no resistance to either of the medications in the regimen, and no evidence for chronic HBV infection.
- Dual regimens that incorporate boosted darunavir, including darunavir plus ritonavir and the fixed dose combination darunavir-cobicisat, appear promising as part of dual therapy when given with dolutegravir.
- 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.
Citations


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