Switching or Simplifying Antiretroviral Therapy

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Section 3: Antiretroviral Therapy
Topic 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 of 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] For example, an individual with HIV may need to switch antiretroviral therapy to avoid drug interactions with hepatitis C therapy. Additional considerations may include pregnancy, cost, changes to insurance coverage, desire to match a partner's regimen, or need for a regimen with a higher barrier to resistance if the individual is struggling with adherence. These reasons 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, clinicians more often switch antiretroviral therapy for the purpose of improved convenience or tolerability than for drug resistance. In a retrospective analysis of 246 patients who switched antiretroviral therapy, the most common reason for switching was simplification (33%), followed by toxicity (31%); only 6% switched due to virologic failure.[4] In this study, other reported reasons for switching included drug interactions, poor adherence, pregnancy, and clinical trial inclusion.

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 on an older regimen that contains zidovudine; 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 based on the patient's history, switching to a carefully chosen modern regimen may reduce pill burden and long-term drug-related adverse effects.

Switching Regimen to Reduce Pill Burden

Persons with HIV often request a change of antiretroviral therapy to reduce pill burden for the sake of convenience; if this can be done safely with a high likelihood of maintaining virologic suppression, there may be long-term benefits. 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 change.

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 the past history: prior antiretroviral therapy regimens, adherence, virologic failures, documented drug resistance, and medication intolerances. A past history of virologic failure is particularly important when considering a switch from a regimen of 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. 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, side effects, and cost or availability of the new regimen.

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 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.

Within-Class Switches Versus Between-Class Switches

The Adult and Adolescent ARV Guidelines emphasize considerations for within-class switches versus between-class switches in the setting of virologic suppression. For example, many within-class switches involve a change between agents of similar barrier to resistance (e.g. switching from efavirenz to rilpivirine or switching from tenofovir DF to tenofovir alafenamide). One exception to this is a switch in the integrase strand transfer inhibitor (INSTI) class from either dolutegravir or bictegravir to either raltegravir or elvitegravir; in this scenario, the switch involves changing a medication with a high barrier to HIV drug resistance (bictegravir or dolutegravir) to a medication with significantly lower barrier to drug resistance (elvitegravir or raltegravir). This change within the INSTI class is likely to maintain virologic suppression if there is no history of significant nucleoside reverse transcriptase inhibitor (NRTI) resistance, but preexisting NRTI resistance could compromise the new regimen and, in this situation, a direct switch within the INSTI class would not be advised. For between-class switches, a switch from a ritonavir- or cobicistat-boosted protease inhibitor to either dolutegravir or bictegravir is generally acceptable because of relatively similar barrier to resistance; however, a switch from a boosted PI to a non-nucleoside reverse transcriptase inhibitor (NNRTI) or to elvitegravir or raltegravir also involves a decrease in relative barrier to resistance and is generally only acceptable if no significant NRTI resistance or concern for NRTI resistance has occurred at any time in the patient's treatment history. Similarly, a switch from the INSTI dolutegravir or bictegravir to an antiretroviral

from a different class that has relatively lower barrier to resistance (such as an NNRTI) would be advisable only after careful review of past antiretroviral history, virologic failures, and resistance, and would not be recommended in the setting of past failures or resistance.

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. The following summaries outline key studies involving switches to an INSTI.

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.[14] 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.[14] 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).[14]

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.[15] 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%.[15] A total of 415 individuals were randomized to continue two NRTIs plus a boosted PI, or switch to the same two NRTIs plus dolutegravir.[15] 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.[15]
- 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.[16] 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.[16] The 48-week data showed 83% and 92% of participants from the early switch and late switch groups, respectively, maintained virologic suppression.[16] 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.[16]

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.[17] 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.[17] 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.[17] 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 tenofovirDF-emtricitabine with a boosted PI or switch to an elvitegravir-based regimen consisting of the fixed-dose combination elvitegravir-cobicistat-tenofovir DF-emtricitabine.[18] 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).[18] 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.[18]

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.[19] 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). Post-hoc analysis of SPIRAL did not identify prior virologic failure or NRTI resistance mutations as risk factors for virologic failure.[20] The exact reason for the difference in virologic failure outcomes between SPIRAL and SWITCHMRK is not known, though multiple factors may have played a role, including differences in study design, duration of virologic suppression at time of enrollment, specific PI drugs included, and definitions of virologic failure. In regard to long-term side effects in SPIRAL, patients who 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.[19,21,22]
- 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.[23] Investigators randomized participants to continue their current antiretroviral regimen or switch the lopinavir-ritonavir component of the regimen to raltegravir.[23] 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.[23] 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.[23] A post-hoc analysis examined the subset of participants with no prior history of virologic failure and found comparable virologic efficacy in the two different study arms in this subset, leading to the conjecture that some individuals with prior virologic failure had NRTI resistance that became exposed after a

switch from a medication with a higher genetic barrier to resistance (lopinavir-ritonavir) to one with a relatively lower genetic barrier to resistance (raltegravir).[23] On a positive note, the patients 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 in 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.

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 option, such as rilpivirine-based therapy, to examine the impact on central nervous system side effects and lipid parameters.[24,25,26,27,28] Although rilpivirine, doravirine, and etravirine are not part of first-line recommended antiretroviral regimens for treatment-naïve individuals,[29] these agents may serve as alternative NNRTI medications for some, either as a switch strategy or when constructing a salvage regimen.[26,27,30,31,32] The following summarizes key NNRTI switch studies.

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.[33] 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).[33] 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.[33] For those participants taking a boosted PI regimen at baseline, lipid parameters improved after the switch to doravirine.

Switch to Etravirine

- ETRA-SWITCH (Boosted PI to Etravirine): Investigators enrolled patients with suppressed HIV RNA level while taking a boosted PI-based regimen and no history of virologic failure and randomized them to switch to 2 NRTIs plus etravirine 400 mg daily (21 participants) or continue current antiretroviral therapy (22 participants).[30] After 48 weeks, there was a non-significant difference in viral load suppression rate (95% in the continue boosted PI group versus 91% in the switch to etravirine group, p=0.58). The etravirine switch group reported higher treatment satisfaction and had improvements in serum lipid parameters.[30]
- SSAT-029 (Efavirenz to Etravirine): In this trial, 38 men with suppressed HIV RNA levels while taking efavirenz-based therapy (including a proportion who were suffering from central nervous system side effects), were enrolled and randomized to immediately switch efavirenz to etravirine or switch after a delay.[34] After 12 weeks, patients had a significant improvement in neuropsychiatric side effects. In addition, all 38 participants maintained a suppressed HIV RNA level at 12 weeks.[34]
- SWITCH-EE (Efavirenz to Etravirine): In this randomized crossover trial performed in Switzerland, investigators enrolled 58 patients who had suppressed HIV RNA level while taking an efavirenz-based regimen for at least 3 months.[25] Participants in this trial reported no neuropsychiatric side effects from efavirenz. Participants were randomized to either switch to etravirine 400 mg daily plus an efavirenz placebo or to continue efavirenz and add an etravirine placebo, and after 6 weeks all participants crossed over to the alternate therapy option. A total of 55 patients completed the study and after the 12 weeks there was no significant difference in virologic efficacy or patient-reported preference for efavirenz versus etravirine; lipids did improve with the switch from efavirenz to etravirine.[25]

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 all patients to rilpivirine-tenofovir DF-emtricitabine.[26] Although rilpivirine plasma trough concentrations decreased initially after the switch (consistent with a lingering induction effect from efavirenz), rilpivirine concentrations returned to effective levels by 2 weeks. After the switch, 100% of participants maintained a suppressed viral load at 12 and 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. Serum creatinine increased a small amount after the switch, consistent with the known benign effects of rilpivirine on tubular secretion of creatinine.

- 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-emtrictabine.[35] 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.[35] 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.[35]
- 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.[36] 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.[36] The switch was well-tolerated and led to small reductions in total cholesterol and HDL cholesterol levels; there were no significant safety concerns.[36]
- 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.[32] 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.[32] 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.[32]

Summary of Key Findings with NNRTI Switch Studies

Although switch to doravirine data are somewhat limited, the DRIVE SWITCH study showed excellent virologic results, with improved lipid parameters for some individuals.[33] Several studies have shown that patients can safely switch from efavirenz to rilpivirine, with equivalent virologic suppression and improved central nervous system side effects.[26,37] As shown in the SPIRIT study, 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 that compromise the NRTI-backbone of the new regimen.[32] In addition, an observational cohort study reported a high risk of virologic failure with a switch to rilpivirine-tenofovir DF-emtricitabine in the presence of a pre-switch M184V/I mutation or when the baseline regimen included a third drug that was not an NNRTI.[31] Taken together, these studies demonstrate that patients who have taken prior regimens or who are taking a regimen with higher barrier to resistance are at greater risk of failing a switch to a regimen of lower barrier to resistance, such as rilpivirine-based therapy. On the other hand, patients who are virologically suppressed on a regimen with similar low barrier to

resistance (such as efavirenz) are more likely to succeed after a switch to rilpivirine and may experience an improvement in lipid parameters after the regimen change.

In antiretroviral treatment-naïve patients, rilpivirine-based therapy carries a higher risk of virologic failure in patients who have a pre-treatment HIV RNA level of 100,000 copies/mL or higher.[38] 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. In trials such as SPIRIT, in which carefully selected patients with routinely suppressed HIV RNA levels on antiretroviral therapy switched to rilpivirine, a baseline (when treatment-naïve) HIV RNA above 100,000 copies/mL did not affect virologic efficacy. 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 patient currently has a suppressed viral load and if other pre-switch criteria are met. From a practical standpoint, most clinical switches to rilpivirine will involve a switch to the single-tablet regimen rilpivirine-tenofovir DF-emtricitabine or rilpivirine-tenofovir alafenamide-emtricitabine, both of which have an FDA indication for use to replace a stable antiretroviral regimen if the following patient criteria are met: (1) no history of virologic failure, (2) HIV RNA levels suppressed below 50 copies/mL for at least 6 months, and (3) no resistance to emtricitabine, rilpivirine, or tenofovir.

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 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.[26] Similarly, when switching efavirenz to etravirine, a dose adjustment of etravirine does not seem to be necessary. Most of the trials involving a switch to rilpivirine documented an expected mild decrease in estimated glomerular filtration rate after the switch, consistent with known blockage of tubular creatinine secretion by rilpivirine (which does not correlate with a worsening of actual or true creatinine clearance).

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 regime, 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 might be considered if a patient starts abacavir and experiences side effects or develops evidence of 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. Tenofovir alafenamide is a tenofovir prodrug available as part of multiple combination tablets: tenofovir alafenamide-emtricitabine, elvitegravir-cobicistat-tenofovir alafenamide-emtricitabine, rilpivirine-tenofovir alafenamide-emtricitabine, and bictegravir-tenofovir alafenamide-emtricitabine. Because tenofovir alafenamide is a prodrug that does not become converted to the active metabolite until it reaches target cells, plasma tenofovir levels are estimated to be 90% lower than with tenofovir DF, leading to lower rates of renal proximal tubule wasting and bone mineral density loss.[39] In current clinical practice, the most common switches within the NRTI class involve switches to tenofovir alafenamide. The following 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.[40] 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.[40] 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.[40] Overall, participants switched to elvitegravir-cobicistat-tenofovir alafenamide-emtricitabine had non-inferior virologic responses compared with those in the no-switch group.[40] 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.[41] 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.[41] 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.[41] 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).[42] 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 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%).[42]

- 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.[43] Inclusion criteria were CD4 count above 200 cells/mm^3, suppressed HIV RNA level for at least 6 months, stable antiretroviral therapy regimen for at least 4 months, HBV DNA level below 9 $\log_{10}$ 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.[43] 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 to elvitegravir-cobicistat-tenofovir alafenamide-emtricitabine, 92% of participants had an HIV RNA less than 50 copies/mL and 92% had an HBV DNA less than 29 copies/mL (compared to 86% at study baseline). Notably, markers of renal proximal tubular wasting and bone turnover improved, similar to other studies that switched tenofovir DF to tenofovir alafenamide.
- 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).[44] 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).[44] 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).[44] 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.[44]
- GS-366-1216: In this randomized controlled trial, investigators enrolled individuals with suppressed HIV RNA level for at least 6 months on a rilpivirine-tenofovir DF-emtricitabine, creatinine clearance above 50 mL/min, and no genotypic resistance to study drugs.[45] 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).[46] 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.[46]
- 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).[47] 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.[47]

- ROCKET I (Abacavir-Lamivudine to Tenofovir DF-Emtricitabine): In this randomized, open-label trial, 157 adults with hypercholesterolemia and HIV RNA levels less than 50 copies/mL while taking a regimen of efavirenz plus abacavir-lamivudine switched to efavirenz-tenofovir DF-emtricitabine or continued their current regimen.[48] Analysis at week 12 showed that participants in the switch arm tolerated the new regimen well and had significant improvement in lipid parameters. No participant in either study arm experienced virologic rebound.[48]
- ROCKET II (Abacavir-Lamivudine to Tenofovir DF-Emtricitabine): In this randomized, open-label trial, investigators examined the impact on lipid levels of switching the NRTI backbone in 85 adults with HIV RNA levels less than 50 copies/mL on a regimen of abacavir-lamivudine plus lopinavir-ritonavir.[49] Participants were randomized to continue their current antiretroviral therapy or switch the abacavir-lamivudine to tenofovir DF-emtricitabine. Analysis at week 12 showed that 90% (34 of 38) patients in the tenofovir DF-emtricitabine arm and 95% (37 of 39) in the abacavir-lamivudine arm maintained an HIV RNA level less than 50 copies/mL. When compared with participants who continued on abacavir-lamivudine, those who switched to tenofovir DF-emtricitabine had a statistically significant decrease in total cholesterol (difference 0.82 mmol/L) and LDL levels (difference 0.27 mmol/L).[49]
- 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.[50] 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.[51,52]

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.[53]
- 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.[54] 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.[54]

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).

The outcome of the SWIFT study showed a lower rate of virologic failure in the group that switched to tenofovir DF, which is consistent with prior trials showing lower rates of virologic failure with tenofovir DF versus abacavir, particularly in the setting of a high baseline viral load.[55] It is difficult to predict whether these results would hold true if a similar trial were undertaken with modern antiretroviral anchor drugs that have a relatively high barrier to resistance, such as boosted darunavir or dolutegravir.

Safely switching tenofovir DF 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; if it is required that a patient with HIV-hepatitis B coinfection switches from tenofovir DF (or tenofovir alafenamide) to abacavir, generally one would augment the regimen with an additional anti-hepatitis B antiviral agent, such as entecavir. 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.

Simplifying Antiretroviral Therapy to A 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 reached 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 reducing cost.[3] The strategy of simplifying to antiretroviral monotherapy is not recommended due to multiple studies showing elevated risk of virologic failure and drug resistance.[1] In contrast, accumulating data support the efficacy of simplifying to certain dual therapy options for carefully selected individuals. For example, clinical trial data have demonstrated that dual therapy maintenance options using a potent agent, such as dolutegravir or boosted darunavir, plus a second antiretroviral agent, such as lamivudine or rilpivirine, are effective at maintaining viral suppression for select individuals. There are also 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).

The Adult and Adolescent ARV Guidelines highlight growing data for the following two-drug options: (1) a boosted PI (darunavir, atazanavir, or lopinavir) plus emtricitabine or lamivudine, (2) dolutegravir plus rilpivirine, and (3) dolutegravir plus lamivudine. These regimens are generally considered to be the most acceptable dual regimen maintenance options, but an individual patient's history of virologic failure and past resistance mutations must be carefully considered before transitioning to any of these two-drug regimens. The Adult and Adolescent ARV Guidelines state that a ritonavir-boosted PI plus lamivudine may be a reasonable option when the use of tenofovir DF, tenofovir alafenamide, or abacavir is contraindicated or not desirable, and that dolutegravir plus rilpivirine dual therapy is also a reasonable option in such circumstances as long as resistance to rilpivirine and dolutegravir is not expected.[1] The single-tablet combination dolutegravir-rilpivirine is approved by the Food and Drug Administration (FDA) for maintenance antiretroviral therapy for persons with suppressed HIV RNA level, on a stable regimen for at least 6 months, no history of virologic failure, and no history of resistance mutations to either of the antiretroviral components.

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 overall high likelihood of virologic suppression after a switch. Outside of a clinical trial setting, these simplification strategies should not be undertaken for patients with poor adherence, extensive resistance, salvage regimens, or otherwise difficult to control HIV infection. The following studies summarize existing data on simplification to dual therapy versus continuing standard three-drug antiretroviral therapy.

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.[56,57] 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.[57] 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.[58] 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.[59] 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).[59]
- 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).[60] 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%).[60]
- 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 NRTI's (n = 156), or continue their current regimen (n = 82).[61] 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 or switched to maraviroc plus two NRTIs (95%).[61]
- 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.[62] 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.[62]

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.[63] 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.[63] Subsequent analyses using ultra-sensitive HIV RNA assays showed there was no difference in residual viremia between the dual and triple antiretroviral arms.[63]
- LAMIDOL (Dolutegravir plus Lamivudine): In this noncomparative, single-arm study, individuals with well-controlled HIV on stable three-drug antiretroviral therapy were enrolled.[64] 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).[64] 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.[64] No resistance mutations occurred in those who did not have an HIV RNA below 50 copies/mL at 48 weeks.

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.[65] 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.[65]

Simplification to Cabotegravir Plus Rilpivirine

- LATTE (Cabotegravir plus Rilpivirine): In the 4-arm induction portion of this phase 2 trial, investigators randomized 243 adults to receive dual NRTIs plus either efavirenz or one of three oral doses of the investigational long-acting integrase inhibitor cabotegravir.[66] 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.[66] 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 drugs cabotegravir and rilpivirine as maintenance antiretroviral therapy.[67] 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. For the maintenance phase, subjects who tolerated the oral agents and had a suppressed HIV RNA 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).[67] 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. The intramuscular agents caused injection site reactions, but most participants still reported favoring the long-acting injections over oral therapy.

Summary of Findings of Dual Therapy Simplification Studies

Potential Use of Dual Medication Maintenance Therapy

Taken together, the retrospective trial results emphasize that simplification to dual maintenance therapy may be a useful strategy for select treatment-experienced patients, such as those with a suppressed HIV RNA for a long period of time, a robust CD4 cell count, and a high genotypic susceptibility score (GSS) for the dual therapy regimen. Although many of these observational and retrospective trials have demonstrated success with this simplification strategy, the number of participants in most of these trials, except for the phase 3 SWORD-1 and SWORD-2 trials, were small and participants were very carefully selected to have sustained virologic suppression prior to the switch. If simplifying to dual therapy, the best available data are with dolutegravir plus rilpivirine or dolutegravir plus lamivudine; in addition, there are good data with ritonavir-

boosted darunavir plus a second agent. In late 2017, the U.S. Food and Drug Administration approved the fixed-dose regimen dolutegravir-rilpivirine, with the indication for dolutegravir-lamivudine to replace an existing antiretroviral regimen in persons with suppressed HIV RNA levels (on a stable antiretroviral regimen that they have been taking for at least 6 months). More data are needed prior to recommending other dual simplification maintenance options.

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).[68] 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.[69] 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.[69] 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 achieve repeat viral suppression when antiretroviral therapy was re-intensified with NRTIs.[70] 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.[71]
- 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.[72,73] At 96 weeks, virologic efficacy rates were comparable (88% in the monotherapy arm and 84% in the combination therapy arm).[73] 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.[74]
- 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).[75] 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.[75]
- 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.[76] 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.[76] 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.[77] 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.[78] 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 participatns 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.[79] 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.[80] 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.[81] 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).[82] Subjects enrolled were also required to have no evidence of active hepatitis B replication, no history of INSTI failure, and no known INSTI resistance.[82] 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).[82]
- 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).[83] 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. 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.[83] 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 the virologic failure and dolutegravir resistance, the trial was stopped early.[83] The study investigators concluded that the genetic barrier of dolutegravir monotherapy is not sufficient to support dolutegravir monotherapy.

Summary Points

- There are a number of reasons to consider an antiretroviral therapy regimen switch, even if a patient has stable virologic suppression: a switch or simplification of antiretroviral therapy may benefit the patient and promote adherence by increasing tolerability and 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; combined, these factors help gauge the likelihood of success after a regimen switch or simplification.
- 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; as demonstrated in the SWITCHMRK trials (in which a boosted PI was switched to raltegravir), the activity of the NRTI backbone is crucial for maintaining virologic suppression after this type of regimen change.
- Select patients (those without multiple past regimens, virologic failures, or resistance) may successfully switch from a boosted PI to the single-tablet regimen elvitegravir-cobicistat-tenofovir DF-emtricitabine, and those who switch from an older boosted PI, such as lopinavir-ritonavir, are likely to experience an improvement in lipid parameters; select patients may also switch their NNRTI-based regimen to elvitegravir-cobicistat-tenofovir DF-emtricitabine and those switching from efavirenz are likely to experience an improvement in neuropsychological side effects.
- 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.
- Several combination formulations that include tenofovir alafenamide offer new options for switching or simplifying therapy to reduce the risk of long-term renal or bone toxicity, with trials demonstrating the effectiveness of switching first-line antiretroviral therapy to elvitegravir-cobicistat-tenofovir alafenamide-emtricitabine, switching tenofovir DF-emtricitabine to tenofovir alafenamide-emtricitabine, switching salvage therapy to elvitegravir-cobicistat-tenofovir alafenamide-emtricitabine plus darunavir, and switching antiretroviral therapy to elvitegravir-cobicistat-tenofovir alafenamide-emtricitabine for individuals with HIV-hepatitis B coinfection.
- Simplification of standard antiretroviral therapy to dual therapy has been shown to be effective with dolutegravir plus rilpivirine and the fixed-dose combination of dolutegravir-rilpivirine is approved for use as a step-down two-drug maintenance regimen in persons with sustained suppressed HIV RNA levels (for at least 6 months) and no resistance to either dolutegravir or rilpivirine. Dual regimens that incorporate ritonavir-boosted darunavir appear promising, but more data are needed before recommending these regimens as maintenance regimens.
- 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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