Optimizing Antiretroviral Therapy in the Setting of Viral Suppression (Last updated December 18, 2019; last reviewed December 18, 2019)

With currently available antiretroviral therapy (ART), most persons with HIV can achieve and maintain HIV viral suppression. Furthermore, advances in antiretroviral (ARV) treatment and a better understanding of drug resistance make it possible to consider switching a person with HIV from one effective regimen to another in some situations (see below). When considering such a switch, clinicians must keep several key principles in mind to maintain viral suppression while addressing the concerns with the current regimen.

Reasons to Consider Regimen Optimization in the Setting of Viral Suppression

- To simplify a regimen by reducing pill burden and/or dosing frequency
- To enhance tolerability and/or decrease short- or long-term toxicity (see Adverse Effects of Antiretroviral Agents and Table 18 for a more in-depth discussion of possible toxicities)
- To prevent or mitigate drug-drug interactions (see Drug-Drug Interactions)
- To eliminate food or fluid requirements
- To allow for optimal use of ART during pregnancy or in cases where pregnancy may occur (see the Perinatal Guidelines)
- To reduce costs (see Cost Considerations and Antiretroviral Therapy)

General Principles of Regimen Optimization

Maintain Viral Suppression

The fundamental principle of regimen optimization is to maintain viral suppression without jeopardizing future treatment options. If a regimen switch results in virologic failure with the emergence of new resistance...
Careful Review of Antiretroviral Treatment and Drug Resistance History Before Optimization

The review of a patient’s full ARV history—including virologic responses and past ARV-associated intolerances, toxicities, and adverse reactions—is critical before any treatment switch (AI).

If a patient with pre-ART wild-type HIV achieves and maintains viral suppression after ART initiation, one can safely assume that no new drug resistance mutation emerged while the patient was on the suppressive regimen. In patients with a history of virologic failure or pre-treatment drug resistance, review of cumulative resistance test results and clinical response to prior regimens is essential when designing a new regimen.

Cumulative resistance test results refer to all previous and currently available results from standard genotype, proviral DNA genotype, phenotype, and tropism assays that can be used to guide the selection of a new regimen. Once selected, a drug-resistance mutation—even when it is not detected in the patient’s most recent drug resistance test—can be archived in the HIV reservoir and is likely to re-emerge under the appropriate selective drug pressure. When resistance data are not available, resistance can often be inferred from a patient’s ARV history. For patients with documented failure on a regimen that includes drugs with relatively low barriers to resistance, such as a non-nucleoside reverse transcriptase inhibitor (NNRTI), elvitegravir (EVG), raltegravir (RAL), lamivudine (3TC), or emtricitabine (FTC), one should assume that there is resistance to these drugs. If there is uncertainty about prior resistance, it is generally not advisable to switch a suppressive ARV regimen unless the new regimen is likely to be at least as active against potential resistant virus as the current suppressive regimen. This principle is particularly applicable when switching ARV-experienced individuals from a regimen with a relatively high barrier to resistance, such as those that include pharmacologically boosted protease inhibitors (PIs), dolutegravir (DTG), or bictegravir (BIC), to one with a lower barrier to resistance. The Panel on Antiretroviral Guidelines for Adults and Adolescents recommends that clinicians consult an HIV specialist when contemplating a regimen switch for a patient with a history of resistance to one or more drug classes (AIII).

If regimen switching is considered in patients with suppressed viral loads who do not have prior drug resistance data, proviral DNA genotypic resistance testing can be considered. For patients who have no prior virologic failures and who are on their first or second regimen, or for those who have genotypic test results from prior virologic failures, the use of the proviral DNA genotypic test is unlikely to provide valuable information. In individuals with a history of multiple prior failures or multiple prior ARV regimens, the use of proviral DNA genotypic testing may be useful. However, whenever proviral DNA genotypic testing is used, the results must be interpreted with caution because these assays may not detect all of a patient’s drug resistance mutations, especially those that were selected by a previous ART regimen. In addition, these assays may identify mutations that appear to be inconsistent with a patient’s response to treatment, making the clinical relevance of the assay results questionable. Overall, the clinical utility of these assays remains an area of active investigation (see Drug-Resistance Testing).

Optimization in a Person with Hepatitis B Virus Coinfection

When switching an ARV regimen in a patient with hepatitis B virus (HBV)/HIV coinfection, tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF) should be continued as part of the new regimen, unless these drugs are contraindicated. Both TDF and TAF are active against HBV. Discontinuation of these drugs may lead to reactivation of HBV, which may result in serious hepatocellular damage. In persons with HIV/HBV coinfection, using 3TC or FTC as the only drug in a regimen with HBV activity is not recommended (AII), as HBV resistance to these drugs can emerge. If TDF or TAF cannot be used as part of the ARV regimen, refer to Hepatitis B Virus/HIV Coinfection for recommendations.

Assess for Potential Drug Interactions

Before switching a regimen, it is important to review the ARV drugs in the new regimen and concomitant

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medications to assess whether there are any potential drug-drug interactions. For example, rilpivirine (RPV) may interact with acid-lowering agents, and TAF and BIC may interact with rifamycins (see Drug-Drug Interactions). In addition to new drug interactions, the discontinuation of some ARV drugs may also necessitate adjusting the dosage of concomitant medications. For example, discontinuation of pharmacokinetic (PK) boosters (ritonavir or cobicistat) may reduce the concentrations of some concomitant medications. Concomitant medications which may have previously been managed with dose adjustments will need to be re-evaluated in the context of the new ART regimen.

Assess for Potential for Pregnancy and Use of INSTI in Persons of Childbearing Potential

Persons of childbearing potential should have a pregnancy test before switching ART. If a person with HIV is found to be pregnant, clinicians should refer to the Perinatal Guidelines for recommendations on the safety and efficacy of ARV use in pregnancy.

Before initiating an INSTI-based regimen in a person of childbearing potential, clinicians should review Table 6b for information to consider when choosing an ART regimen. Preliminary data from a study conducted in Botswana suggested that there is an increased risk of neural tube defects (NTDs) (0.9%) in infants born to women who were receiving DTG at the time of conception. Follow-up data, however, showed that the prevalence of infant NTDs in association with maternal DTG exposure at conception is lower (0.3%), but still higher than in infants exposed to non-DTG containing ARV regimens (0.1%).

There are insufficient safety data on the use of BIC around the time of conception and during pregnancy to determine whether it is safe. An approach similar to that outlined for DTG should be considered for BIC-containing ART (AIII).

Monitoring after Switch

Close monitoring to assess tolerability, viral suppression, adherence, and safety is recommended during the first 3 months after a regimen switch (see below).

Specific Regimen Optimization Considerations

As with ART-naive patients, the use of a two-drug (as discussed below) or three-drug combination regimen is generally recommended when switching patients with suppressed viral loads (AI). Patients who have no resistance mutations or history of virologic failure can likely switch to any regimen that has been shown to be highly effective in ART-naive patients. Patients with prior drug resistance can be switched to a new regimen based on their ARV history and resistance testing results. Monotherapy with either a boosted PI or an INSTI has been explored in several trials or cohort studies. Monotherapy has been associated with a higher rate of virologic failure than combination regimens and has been associated with the development of resistance, especially INSTI monotherapy; therefore, monotherapy as an optimization strategy is not recommended (AI).

Optimization Strategies with Good Supporting Evidence for Persons with No History of Drug Resistance

Many clinical trials have enrolled participants with stably suppressed viral loads without underlying drug resistance and switched them to another regimen, typically including at least two fully active drugs. Most of these studies demonstrated maintenance of viral suppression; some of these studies are referenced below. The SWITCHMRK 1 and 2 studies illustrated the importance of considering the possibility of underlying drug resistance before switching therapy in those with virologic suppression. This is particularly important when the new regimen may not include three fully active agents. In the two SWITCHMRK studies, those with viral suppression on two NRTIs plus lopinavir/ritonavir (LPV/r) were switched to two NRTIs plus RAL. The studies showed that individuals with a history of previous virologic failure had an increased risk of virologic failure when switching to the RAL-based regimen. A possible explanation for this finding is that,
when only one of the accompanying NRTIs is fully active, viral suppression can be maintained by drugs with relatively high barriers to resistance, such as boosted PIs, DTG, and BIC, but not by those with lower barriers to resistance such as EVG, RAL, and NNRTIs. The strategies listed below support these observations and principles of optimizing therapy.

Three-Drug Regimens

Within-Class Switches
Within-class switches may be prompted by adverse events or the availability of ARVs in the same class that offer a better safety profile, reduced dosing frequency, higher barrier to resistance, lower pill burden, or do not require PK boosting. Within-class switches usually maintain viral suppression, provided there is no drug resistance to the new ARV. Some examples of within-class switch strategies that have been studied in individuals without underlying drug resistance include switching from:

- TDF\(^7,8\) or abacavir (ABC)\(^9\) to TAF
- RAL to DTG
- DTG,\(^10,11\) EVG/c,\(^12\) or RAL to BIC
- Efavirenz (EFV) to RPV,\(^8,13\) or to doravirine (DOR)\(^14\)
- Boosted atazanavir (ATV/c or ATV/r) to unboosted ATV (when used with ABC/3TC)\(^15-17\)

Between-Class Switches
Between-class switches generally maintain viral suppression, provided there is no resistance to the other components of the regimen. In general, such switches should be avoided if there is any doubt about the activity of the other agents in the regimen. As noted earlier, prior resistance test results will be very informative in guiding this switch. The following are between-class switches that have been studied:

- Replacing a boosted PI with an INSTI (e.g., DTG,\(^18\) BIC,\(^19\) or EVG\(^20,21\))
- Replacing a boosted PI with RPV\(^22\) or DOR\(^14\)
- Replacing an NNRTI with an INSTI\(^23,24\)
- Replacing a boosted PI with maraviroc (MVC).\(^25\) When switching to MVC, co-receptor usage in patients with virologic suppression can be determined from proviral DNA (see Co-receptor Tropism Assays).\(^25-27\)

Two-Drug Regimens
There is growing evidence that some two-drug regimens are effective in maintaining virologic control in patients who initiated therapy and achieved virologic suppression with three-drug regimens, provided their HIV is susceptible to both ARV drugs in the new regimen. However, since none of the two-drug regimens discussed below has adequate anti-HBV activity, these regimens are not recommended for individuals with HBV coinfection (AIII). Below are examples of successful strategies for switching from three- to two-drug regimens in persons with suppressed HIV.

Dolutegravir plus Rilpivirine
Two Phase 3 trials enrolled 1,024 participants with viral suppression for \(\geq 1\) year (defined by no HIV RNA \(>50\) copies/mL in the past 6 months, and no more than one instance of HIV RNA 50–200 copies/mL in the 6–12 months before enrollment) who were on their first or second regimen and had no history of virologic failure and no documented evidence of any major drug-resistance mutations.\(^28\) Participants were randomized to remain on their combination ART regimen or to switch to a regimen of once-daily DTG plus RPV (early-switch arm). Viral suppression was maintained in 95% to 96% of the participants in both arms at 48 weeks. At 52 weeks, those who were randomized to remain on their current regimens were allowed to switch to DTG plus RPV (late-switch arm). At 100 weeks, 89% of participants in the early-switch arm and 93% of those in the late-switch arm maintained HIV RNA <50 copies/mL.\(^29\) DTG plus RPV is available as a
coformulated single-tablet regimen. It is a reasonable option when the use of nucleoside reverse transcriptase inhibitors (NRTIs) is not desirable. DTG plus RPV should only be given to patients who do not have chronic HBV infection, have no evidence of resistance to either DTG or RPV, and have no significant drug-drug interaction that might reduce the concentration of either drug (AI).

**Dolutegravir plus Lamivudine**

A switch from three-drug regimens to DTG plus 3TC as maintenance strategy in patients with virologic suppression has been examined in a large randomized clinical trial (TANGO), in two small clinical trials, and in observational studies with good success. The result of the TANGO trial is discussed below.

The Phase 3 TANGO study enrolled participants who were on their first ARV regimen with HIV RNA <50 copies/mL for ≥6 months. Participants were randomized to switch to open label DTG plus 3TC (n = 369) or to continue their TAF-based triple therapy (n = 372). The participants had no history of virologic failure or evidence of resistance to DTG or 3TC and did not have HBV coinfection. At week 48, switching to DTG plus 3TC was non-inferior to continuing on the current regimen, with 93% of participants in both arms maintaining HIV RNA <50 copies/mL. No unexpected adverse events were identified as related to DTG or 3TC. Switching to a DTG plus 3TC regimen can be a good option for individuals who have no evidence of resistance to either drug and do not have HBV coinfection (AI).

**Ritonavir-Boosted Protease Inhibitor plus Lamivudine**

A ritonavir-boosted protease inhibitor (PI/r) plus 3TC may be a reasonable option when the continued use of TDF, TAF, or ABC is contraindicated or not desirable. There is growing evidence that a PI/r-based regimen plus 3TC can maintain viral suppression in patients who initiated triple-drug therapy, who achieved sustained viral suppression for ≥1 year, and who have no evidence of, or risk for drug resistance to, either the PI/r or 3TC. Examples of boosted PI plus 3TC regimens that have been studied in clinical trials include the following:

- ATV/r plus 3TC (CI),
- Darunavir/ritonavir (DRV/r) plus 3TC (BI),
- LPV/r plus 3TC (CI).

**Boosted Darunavir plus Dolutegravir**

An open-label, Phase 3b, non-inferiority clinical trial randomized 263 participants who were on boosted DRV plus two NRTIs to continue on the same regimen or switch to boosted DRV plus DTG (study recruitment was stopped prematurely due to slow recruitment). At 48 weeks, the study demonstrated that switching to DTG plus boosted DRV was non-inferior to continuing triple therapy. In both arms, approximately 87% of participants maintained viral suppression at HIV RNA <50 copies/mL, and both groups had comparable rates of adverse events. Because of the small sample size of this study, the regimen of boosted DRV plus dolutegravir is only recommended if there are no other alternative options (CI). Similar results were observed in two small observational studies (13 participants and 56 participants).

**Optimization Strategies for Persons with Viral Suppression and a History of Limited Drug Resistance**

There are some data demonstrating the safety and efficacy of within-class switches for individuals with underlying drug resistance who are on a stable ARV regimen with suppressed HIV RNA. However, there are limited data regarding between-class switches in this population, and support for such a switch generally depends on findings extrapolated from other studies, as discussed below.

**Within-Class Switch from One High-Resistance Barrier Drug to Another (e.g., from DTG to BIC [BI])**

The GS 4030 study enrolled 565 individuals who were stably suppressed on DTG plus two NRTIs. The participants were randomized to either remain on their current regimen or switch to BIC/FTC/TAF. After 48
weeks, the groups had similar rates of sustained suppression.\textsuperscript{43} The rates of viral suppression were similar for those with a documented history of NRTI resistance (approximately 25\% of participants) and those without a history of NRTI resistance.\textsuperscript{43}

**Between-Class Switch from One High-Resistance Barrier Drug to Another (e.g., from a Boosted PI to a BIC- or DTG-Containing Regimen with At Least One Fully Active NRTI)**

The GS 4030 study provides theoretical support for replacing a boosted PI-regimen with a BIC- or DTG-containing regimen, if at least one of the NRTIs in the regimen is fully active.\textsuperscript{42,43} Although there are no switch studies testing this strategy, based on the GEMINI studies in treatment-naive patients, a DTG plus 3TC regimen (\textit{when both ARVs are fully active}) is highly effective. In addition, the TANGO study (described above), demonstrated that in the setting of no underlying drug resistance, DTG plus 3TC, as the active NRTI, was a very effective switch strategy. In the DAWNING study,\textsuperscript{44} in the setting of virologic failure with underlying NRTI resistance, DTG plus one fully active NRTI was more effective than LPV/r plus one fully active NRTI. Based upon standard optimization principles, if DTG plus two NRTIs, one of which is fully active, was effective in those with virologic failure, it should also be effective in those already virologically suppressed (BIII).

**Optimization Strategies for Persons with Viral Suppression and a History of Complex Underlying Resistance**

Before optimization of the ARV regimen of a person with viral suppression who has a history of treatment failure and drug resistance, a careful review of the individual’s ARV history and cumulative drug resistance profile should be undertaken. Consultation with a clinician with expertise in HIV drug resistance is recommended (AIII).

One randomized controlled trial conducted in this patient population is described below.

**Elvitegravir/Cobicistat/Tenofovir Alafenamide/Emtricitabine plus Darunavir**

Switching to the combination of EVG/c/TAF/FTC plus DRV has been shown to be a potential optimization strategy in patients on complicated salvage regimens.\textsuperscript{45} A randomized controlled trial enrolled 135 patients with virologic suppression who were receiving DRV-containing ART and had resistance to at least two ARV drug classes, but no INSTI resistance. Participants had up to three thymidine analog resistance mutations and/or the K65R mutation, but no history of either the Q151M mutation or T69 insertion. The participants were randomized 2:1 to either switch to a regimen of EVG/c/TAF/FTC plus DRV or remain on their current regimen. At 48 weeks, optimization to EVG/c/TAF/FTC plus DRV was superior to continuation on a current regimen with 94.4\% of participants in the switch arm and 76.1\% in the continuation arm maintaining viral suppression.\textsuperscript{46-52} With regimen simplification, the pill burden was reduced from an average of five tablets per day to two tablets per day. EVG/c/TAF/FTC plus DRV would be an appropriate option for individuals who have treatment and drug resistance histories similar to those of participants included in this study (AII).

**Optimization Strategies Not Recommended**

**Boosted Protease Inhibitor Monotherapy**

The strategy of switching patients with virologic suppression without PI resistance from one ART regimen to PI/r monotherapy has been evaluated in several studies. The rationale for this strategy is to avoid NRTI toxicities and decrease costs while taking advantage of the high barrier to resistance of PIs. PI/r monotherapy maintains virologic suppression in most patients, but at lower rates than regimens that include one or two NRTIs.\textsuperscript{46-48} Low-level viremia, generally without the emergence of PI resistance, appears to be more common with monotherapy than with regimens that include one or two NRTIs. In most studies, resuming NRTIs in patients who are experiencing low-level viral rebound has led to re-suppression.\textsuperscript{49-52} No clinical trials have evaluated the use of coformulated PI/c regimens as monotherapy or compared different PI/r monotherapy regimens. Based on the results from these studies, boosted-PI monotherapy is not recommended (AII).
**Dolutegravir Monotherapy**
The strategy of switching patients with virologic suppression to DTG monotherapy has been evaluated in cohort studies and in clinical practice\(^53,54\) and in a randomized controlled trial.\(^55\) This strategy has been associated with an unacceptable rate of virologic failure and subsequent development of INSTI resistance; therefore, a switch to DTG monotherapy is not recommended (AI).

**Boosted Atazanavir plus Raltegravir**
In a randomized study, patients with virologic suppression switched to a regimen consisting of ATV/r plus RAL or ATV/r plus TDF/FTC. The ATV/r plus RAL regimen switch was associated with higher rates of virologic failure and treatment discontinuation than the switch to ATV/r plus TDF/FTC.\(^56\) A regimen consisting of ATV/r plus RAL cannot currently be recommended (AI).

**Maraviroc plus Boosted Protease Inhibitor**
In a randomized controlled trial, patients with virologic suppression who were on a regimen of two NRTIs plus a boosted PI and who had only CCR5-tropic HIV (as detected by proviral DNA testing) were randomized to continue their current regimen or to switch to MVC plus two NRTIs or to MVC plus a boosted PI. The boosted PI plus MVC regimen switch was associated with higher rates of virologic failure and treatment discontinuation than the other two regimens. Based on these results, a regimen consisting of a boosted PI and MVC cannot be recommended (AI).\(^57\)

**Maraviroc plus Raltegravir**
In a nonrandomized pilot study, patients with virologic suppression were switched from their prescribed regimen to MVC plus RAL. This combination led to virologic relapse in five out of 44 patients.\(^58\) Based on these study results, use of MVC plus RAL is not recommended (AII).

**Monitoring after Treatment Changes**
After a treatment switch, patients should be evaluated closely for 3 months (e.g., a clinic visit or phone call 1 to 2 weeks after the change and a viral load test to check for rebound viremia 4 to 8 weeks after the switch) (AIII). The purpose of this close monitoring is to assess medication tolerance and to conduct targeted laboratory testing if the patient had pre-existing laboratory abnormalities or if there are potential concerns with the new regimen. For example, if lipid abnormality is a reason for the ARV change or is a concern with the new regimen, fasting cholesterol subsets and triglycerides should be assessed within 3 months after the change in therapy. In the absence of any new complaints, laboratory abnormalities, or evidence of viral rebound at this 3-month visit, clinical and laboratory monitoring of the patient may resume on a regularly scheduled basis (see Laboratory Testing for Initial Assessment and Monitoring).

**References**


42. Sax PE, Rockstroh J, Luetkemeyer A, et al. Switching to a single-tablet regimen bictegravir, emtricitabine, and tenofovir alafenamide (B/F/TAF) from dolutegravir (DTG) plus emtricitabine and either tenofovir alafenamide or tenofovir disoproxil fumarate (F/TAF or F/TDF). Presented at: International AIDS Society. 2019. Mexico City, Mexico.


Discontinuation or Interruption of Antiretroviral Therapy  (Last updated April 8, 2015; last reviewed April 8, 2015)

Discontinuation of antiretroviral therapy (ART) may result in viral rebound, immune decompensation, and clinical progression.1-5 Thus, planned interruptions of ART are not generally recommended. However, unplanned interruption of ART may occur under certain circumstances as discussed below.

**Short-Term Therapy Interruptions**

Reasons for short-term interruption (days to weeks) of ART vary and may include drug toxicity; intercurrent illnesses that preclude oral intake, such as gastroenteritis or pancreatitis; surgical procedures; or interrupted access to drugs. Stopping ART for a short time (i.e., less than 1 to 2 days) because of a medical/surgical procedure can usually be done by holding all drugs in the regimen. Recommendations for some other scenarios are listed below:

**Unanticipated Short-Term Therapy Interruption**

*When a Patient Experiences a Severe or Life-Threatening Toxicity or Unexpected Inability to Take Oral Medications:*

- All components of the drug regimen should be stopped simultaneously, regardless of drug half-life.

**Planned Short-Term Therapy Interruption (Up to 2 Weeks)**

*When All Regimen Components Have Similar Half-Lives and Do Not Require Food for Proper Absorption:*

- All drugs may be given with a sip of water, if allowed; otherwise, all drugs should be stopped simultaneously. All discontinued regimen components should be restarted simultaneously.

*When All Regimen Components Have Similar Half-Lives and Require Food for Adequate Absorption, and the Patient Cannot Take Anything by Mouth for a Short Time:*

- Temporary discontinuation of all drug components is indicated. The regimen should be restarted as soon as the patient can resume oral intake.

*When the Antiretroviral Regimen Contains Drugs with Different Half-Lives:*

- Stopping all drugs simultaneously may result in functional monotherapy with the drug with the longest half-life (typically a non-nucleoside reverse transcriptase inhibitor [NNRTI]), which may increase the risk of selection of NNRTI-resistant mutations. Some experts recommend stopping the NNRTI first and the other antiretroviral drugs 2 to 4 weeks later. Alternatively, the NNRTI may be replaced with a ritonavir- or cobicistat-boosted protease inhibitor (PI/r or PI/c) for 4 weeks. The optimal time sequence for staggered discontinuation of regimen components, or replacement of the NNRTI with a PI/r or PI/c, has not been determined.

**Planned Long-Term Therapy Interruptions**

Planned long-term therapy interruptions are **not recommended** outside of controlled clinical trials (AI). Several research studies are evaluating approaches to a functional (virological control in the absence of therapy) or sterilizing (virus eradication) cure of HIV infection. Currently, the only way to reliably test the effectiveness of these strategies may be to interrupt ART and closely monitor viral rebound over time in the setting of a clinical trial.

If therapy must be discontinued, patients should be aware of and understand the risks of viral rebound, acute retroviral syndrome, increased risk of HIV transmission, decline of CD4 count, HIV disease progression, development of minor HIV-associated manifestations such as oral thrush or serious non-AIDS complications (e.g., renal, cardiac, hepatic, or neurologic complications), development of drug resistance, and the need for

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chemoprophylaxis against opportunistic infections as a result of CD4 decline. Patients should be counseled about the need for close clinical and laboratory monitoring during therapy interruptions.

References


