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

**Reasons to Consider Regimen Switching in the Setting of Viral Suppression**

- To simplify a regimen by reducing pill burden and dosing frequency
- To enhance tolerability and decrease short- or long-term toxicity (see [Adverse Effects of Antiretroviral Agents](#) and [Table 15](#) for more in-depth discussion)
- To prevent or mitigate drug-drug interactions (see [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 [Perinatal Guidelines](#))
- To reduce costs (see [Cost Considerations and Antiretroviral Therapy](#))

**General Principles of Regimen Switching**

The fundamental principle of regimen switching is to maintain viral suppression without jeopardizing future treatment options (AI). If a regimen switch results in virologic failure with the emergence of new resistance...
mutations, the patient may require more complex or expensive regimens.

The review of a patient’s full antiretroviral (ARV) history—including virologic responses, past ARV-associated toxicities, and cumulative resistance test results (if available)—is warranted before any treatment switch (A1). If a patient with pre-ART wild-type HIV achieves and maintains viral suppression after ART initiation, one can assume that no new resistance mutation emerged while the patient was on the suppressive regimen.

Once selected, a resistance mutation is generally archived in the HIV reservoir and is likely to re-emerge under the appropriate selective drug pressure, even if not detected in the patient’s most recent resistance test. If resistance data are not available, resistance may often be inferred from a patient’s treatment history. For example, a patient who experienced virologic failure on a lamivudine (3TC)- or emtricitabine (FTC)-containing regimen in the past is likely to have the M184V substitution, even if it is not documented. For patients with documented failure on a non-nucleoside reverse transcriptase inhibitor (NNRTI) or an elvitegravir (EVG)- or raltegravir (RAL)-containing regimen, resistance to these drugs can also be assumed because these drugs generally have a lower barrier to resistance. 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 as active against potential resistant virus as the suppressive regimen. Consulting an HIV specialist is recommended when contemplating a regimen switch for a patient with a history of resistance to one or more drug classes.

When switching an ARV regimen in a patient with hepatitis B virus (HBV)/HIV coinfection, ARV drugs active against HBV infection should be continued as part of the new regimen. Discontinuation of these drugs may cause serious hepatocellular damage resulting from reactivation of HBV.

A commercially available test amplifies viral DNA in whole blood samples to detect the presence of archived resistance mutations in patients with suppressed HIV RNA. Its value in clinical practice is still being evaluated (see Drug-Resistance Testing).

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

**Specific Regimen Switching Considerations (also see Adverse Effects of Antiretroviral Agents)**

As with ART-naive patients, the use of a three-drug combination regimen is generally recommended when switching patients with suppressed viral loads to a new regimen. However, there is growing evidence that certain two-drug regimens can maintain virologic suppression, as discussed below. Monotherapy with either a boosted protease inhibitor (PI) or an integrase strand transfer inhibitor (INSTI) has been explored in several trials or cohort studies, and has been associated with an unacceptable rate of virologic failure and the development of resistance; therefore, monotherapy as a switching strategy is not recommended (AII).

**Strategies with Good Supporting Evidence**

**Within-class switches** prompted by adverse events or the availability of ARVs within the same class that offer a better safety profile, reduced dosing frequency, or lower pill burden usually maintain viral suppression, provided there is no drug resistance to the new ARV. Some examples of within-class switch strategies are switching from efavirenz (EFV) to rilpivirine (RPV),1 from tenofovir disoproxil fumarate (TDF) to tenofovir alafenamide (TAF),2 from RAL to elvitegravir/cobicistat (EVG/c)3 or dolutegravir (DTG), from ritonavir-boosted protease inhibitors (PIs/r) to PIs coformulated with cobicistat (PIs/c), or from boosted atazanavir (ATV/c or ATV/r) to unboosted ATV (when used with abacavir [ABC]/3TC).4-6

**Between-class switches** generally maintain viral suppression, provided there is no resistance to the other components of the regimen. Some examples of between-class switch strategies are replacing a boosted PI with RPV,7 or replacing an NNRTI or a boosted PI with an INSTI8-9 or maraviroc (MVC). However, such switches
should be avoided if there is any doubt about the activity of the other agents in the regimen. When switching to MVC, co-receptor usage in virologically suppressed patients can be determined from proviral DNA (see Co-receptor Tropism Assays) obtained from peripheral blood mononuclear cells. This strategy was used successfully in a randomized trial that switched virologically suppressed individuals from a regimen of two nucleoside reverse transcriptase inhibitors (NRTIs) plus a boosted PI to two NRTIs plus MVC.

Two-Drug Regimens

Boosted Protease Inhibitor plus Emtricitabine or Lamivudine

There is growing evidence that a boosted PI-based regimen plus 3TC (i.e., ATV/r plus 3TC, DRV/r plus 3TC, or LPV/r plus 3TC) can maintain virologic suppression in ART-naive individuals without baseline resistance mutations and in patients with sustained viral suppression. A ritonavir-boosted PI plus 3TC may be a reasonable option when the use of TDF, TAF, or ABC is contraindicated or not desirable (BI).

Dolutegravir plus Rilpivirine

Two Phase 3 trials enrolled 1,024 participants with viral suppression for at least 1 year and no history of virologic failure. Participants were randomized to stay on their combination ART regimen or to switch to a regimen of once-daily DTG plus RPV. Virologic suppression was maintained in 95 to 96% of the participants in both arms at 48 weeks. DTG plus RPV can be a reasonable option when the use of NRTIs is not desirable and when resistance to either DTG or RPV is not expected (AI).

Strategies for Virologically Suppressed Patients with a History of Treatment Failure

Elvitegravir/Cobicistat/Tenofovir Alafenamide/Emtricitabine plus Darunavir

The combination of EVG/c/TAF/FTC plus darunavir (DRV) has been shown to be a potential simplification strategy in patients with complicated salvage regimens. A randomized controlled trial enrolled 135 virologically suppressed patients who were receiving DRV-containing ART and had resistance to at least two ARV drug classes, but no INSTI resistance. Eligible participants could have up to three thymidine analog resistance mutations and/or K65R mutations, but no history of either Q151M or T69 insertion mutations. The patients were randomized 2:1 to either switch to a regimen of EVG/c/TAF/FTC plus DRV or remain on their original regimen. At 24 weeks, 97% of the patients in the EVG/c/TAF/FTC plus DRV arm maintained virologic suppression. The pill burden was reduced from an average of five tablets per day to two tablets per day.

Strategies with Some Supporting Evidence

Other switching strategies in patients with viral suppression have some evidence to support their use. These strategies cannot yet be recommended under most circumstances, or at all, until further evidence is available. If used, patients should be closely monitored to assure viral suppression is maintained. Some of these strategies are listed below.

Boosted Darunavir plus Raltegravir

The efficacy of this combination in patients with lower viral load levels was established in ART-naive patients. At 96 weeks, DRV/r plus RAL was noninferior to DRV/r plus TDF/FTC, but was inferior in patients with low pre-treatment CD4 T lymphocyte counts (<200 cells/mm³) and high viral loads (>100,000 copies/mL). The efficacy of switching to DRV/r plus RAL in virologically suppressed patients with no resistance to either DRV or RAL has not been explored.

Dolutegravir plus Lamivudine or Emtricitabine

The Lamidol trial evaluated a regimen of DTG and 3TC as a maintenance strategy in virologically suppressed patients who have no evidence of NRTI, INSTI, or PI resistance. At 24 weeks, 103 of the 104 participants remained virologically suppressed. In a small (20-patient), single-arm study of DTG plus 3TC for ART-naive patients, 90% of patients achieved and maintained viral suppression at 48 weeks. However, there is currently insufficient evidence to support use of this regimen, given that Lamidol was a single-arm trial and
has reported only short-term outcomes.

**Strategies Not Recommended**

**Boosted Protease Inhibitor Monotherapy**
The strategy of switching virologically suppressed patients 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.\(^{17,23,24}\) Low-level viremia, generally without the emergence of PI resistance, appears to be more common with monotherapy. In most studies, resumption of NRTIs in patients experiencing low-level viral rebound has led to re-suppression.\(^{25-28}\)

On the basis of the results from these studies, PI/r monotherapy should generally be avoided (BI). No clinical trials evaluating the use of coformulated cobicistat-boosted PIs as monotherapy or comparing available PI/r monotherapy regimens have been conducted.

**Dolutegravir Monotherapy**
The strategy of switching virologically suppressed patients to DTG monotherapy has been evaluated in uncontrolled trials\(^ {29}\) and in cohorts.\(^ {30}\) It is associated with an unacceptable risk of virological failure and subsequent development of resistance. This strategy cannot be recommended (AII).

**Boosted Atazanavir plus Raltegravir**
In a randomized study, virologically suppressed patients 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 discontinuations than switching to ATV/r plus TDF/FTC.\(^ {31}\) A regimen consisting of ATV/r plus RAL cannot currently be recommended (AII).

**Maraviroc plus Boosted Protease Inhibitor or Raltegravir**
In a randomized controlled trial, virologically suppressed patients who were on a combination of NRTI plus a boosted PI, and who had CCR5-tropic HIV detected by proviral DNA testing, were randomized to one of three arms:
1. Patients remained on the same regimen,
2. Patients were switched to a regimen consisting of two NRTIs plus MVC, or
3. Patients were switched to a regimen consisting of a boosted PI plus MVC.

The boosted PI plus MVC regimen switch was associated with higher rates of virologic failure and treatment discontinuations than the other two regimens. Based on these results, a regimen consisting of a boosted PI and MVC cannot be recommended (AII).\(^ {32}\)

**Maraviroc plus Raltegravir**
In a nonrandomized pilot study, virologically suppressed patients were switched from their prescribed regimen to MVC plus RAL. This combination led to virologic relapse in 5 out of 44 patients.\(^ {33}\) Based on these study results, a combination of MVC and RAL is not recommended (AII).

**Monitoring after Treatment Changes**
After a treatment switch, patients should be evaluated more closely for several months (i.e., 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). The purpose of more intensive monitoring is to assess medication tolerance and 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 abnormalities were present and/or were a reason for the ARV change, or if lipid abnormalities are 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


*Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV*

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