Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents

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Regimen Switching in the Setting of Virologic Suppression  (Last updated Jan. 17, 2016; last reviewed July 14, 2016)

Panel’s Recommendations

- Advances in antiretroviral (ARV) treatment and a better understanding of HIV drug resistance make it possible to consider switching an effective regimen to an alternative regimen in some situations.
- The fundamental principle of regimen switching is to maintain viral suppression without jeopardizing future treatment options (AI).
- It is critical to review a patient’s full ARV history, including virologic responses, past ARV-associated toxicities, and cumulative resistance test results, if available, before selecting a new ART regimen (AI).
- Adverse events, the availability of ARVs with an improved safety profile, or the desire to simplify a regimen may prompt a regimen switch. Within-class and between-class switches can usually maintain viral suppression provided that there is no viral resistance to the ARV agents in the new regimen (AI).
- Consultation with an HIV specialist should be considered when considering a regimen switch for a patient with a history of resistance to one or more drug classes (BIII).
- More intensive monitoring to assess tolerability, viral suppression, adherence, and laboratory changes is recommended during the first 3 months after a regimen switch (AIII).

Rating of Recommendations:  A = Strong;  B = Moderate;  C = Optional
Rating of Evidence:  I = Data from randomized controlled trials;  II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes;  III = Expert opinion

With currently available antiretroviral therapy (ART), most HIV-infected patients are able to 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 an alternative regimen in some situations (see below). When considering such a switch, clinicians must consider several key principles to maintain viral suppression while addressing concerns with the current regimen.

Reasons to Consider Regimen Switching in the Setting of Viral Suppression

- To simplify the regimen by reducing pill burden and dosing frequency
- To enhance tolerability and decrease short- or long-term toxicity (see Adverse Events 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 should pregnancy occur (see Perinatal Guidelines)¹
- To reduce costs (see Cost Considerations and Antiretroviral Therapy)
- To switch from frequent parenteral administration of enfuvirtide to an oral agent that is better tolerated

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 (AI).
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.

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)

Strategies with Good Supporting Evidence

**Within-class switches** prompted by adverse events or the availability of in-class ARVs 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), from tenofovir disoproxil fumarate (TDF) to tenofovir alafenamide (TAF), from raltegravir (RAL) to elvitegravir/cobicistat (EVG/c) 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).

**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 rilpivirine (RPV), or replacing an NNRTI or a boosted PI with an integrase strand transfer inhibitor (INSTI). However, such switches should be avoided if there is any doubt about the activity of the other agents in the regimen.

**RTV-Boosted PI plus 3TC/FTC**

There is growing evidence that a boosted PI-based regimen plus 3TC can maintain virologic suppression in ART-naïve individuals without baseline resistance mutations and in patients with sustained viral suppression. Examples of such regimens include lopinavir/ritonavir (LPV/r) plus 3TC and atazanavir/ritonavir (ATV/r) plus 3TC. A study evaluating darunavir/ritonavir (DRV/r) plus 3TC is currently underway. A ritonavir-boosted PI plus 3TC may be a reasonable option when the use of TDF, TAF, or ABC is contraindicated or not desirable.

Strategies under Evaluation

Several strategies for switching regimens (described below) in patients with viral suppression are under investigation. These strategies cannot yet be recommended under most circumstances or at all until further investigation has been conducted.
Evidence is available. If used, patients should be closely monitored to assure viral suppression is maintained.

**RTV-Boosted PI plus INSTI**

The combination of a boosted PI with an INSTI (DRV/r plus RAL) has been studied in ART-naive patients. At week 96, DRV/r plus RAL was noninferior to DRV/r plus TDF/FTC based on the proportion of patients achieving viral suppression. However, in patients with low pretreatment CD4 T lymphocyte counts (<200 cells/mm³) and high viral loads (>100,000 copies/mL), DRV/r plus RAL was inferior to DRV/r plus TDF/FTC. 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. In another study, virologically suppressed patients switched to a regimen consisting of ATV/r plus RAL or ATV/r plus TDF/FTC. This regimen switch was associated with higher rates of virologic failure and treatment discontinuations than switching to ATV/r plus TDF/FTC. A regimen consisting of ATV/r plus RAL cannot currently be recommended.

**EVG/c/TAF/FTC plus DRV**

The single-tablet regimen EVG/c/TAF/FTC plus DRV has shown promising results as a simplification strategy in patients with complicated rescue regimens. A recent study enrolled 135 virologically suppressed patients who were receiving DRV-containing ART and had resistance to ≥2 ARV drug classes, but no INSTI resistance. The patients were then switched to a regimen of EVG/c/TAF/FTC plus DRV. At week 24, 97% of the patients maintained virologic suppression. The pill burden was reduced from an average of five tablets to two tablets. Currently, however, there is insufficient evidence to support this regimen switch other than in a well-controlled clinical trial or in special circumstances.

**Dolutegravir plus 3TC or FTC**

In a small (20-patient), single-arm study of DTG plus 3TC for ART-naive patients, all patients achieved and maintained viral suppression at 24 weeks. A clinical trial is underway to evaluate the role of this regimen as maintenance therapy in virologically suppressed patients who have no evidence of NRTI, INSTI, or PI resistance. Currently, however, there is insufficient evidence to support use of this regimen other than in a well-controlled clinical trial.

**Strategies Not Recommended**

**RTV-Boosted PI 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 slightly lower rates than standard therapy that includes 2 NRTIs. 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.

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

**Switching to Maraviroc**

Co-receptor usage in virologically suppressed patients can be determined from proviral DNA obtained from peripheral blood mononuclear cells. If this testing identifies R5-tropic virus, a component of the patient’s regimen may potentially be switched to maraviroc (MVC). However, although the use of MVC after DNA tropism testing has potential, this strategy cannot be recommended until more data from larger clinical studies are available (see Co-receptor Tropism Assays).
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 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 it 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 of HIV-Infected Patients on Antiretroviral Therapy).

References


