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

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Management of the Treatment-Experienced Patient

Virologic Failure and Suboptimal Immunologic Response  *(Last updated May 1, 2014; last reviewed May 1, 2014)*

<table>
<thead>
<tr>
<th>Panel's Recommendations</th>
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<tbody>
<tr>
<td>• Assessing and managing an antiretroviral (ARV)-experienced patient experiencing antiretroviral therapy (ART) failure is complex. Expert advice is critical and should be sought.</td>
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<tr>
<td>• Evaluation of virologic failure should include an assessment of adherence, drug-drug or drug-food interactions, drug tolerability, HIV RNA and CD4 T lymphocyte (CD4) cell count trends over time, treatment history, and prior and current drug-resistance testing results.</td>
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<tr>
<td>◦ Drug-resistance testing should be performed while the patient is taking the failing ARV regimen <em>(AI)</em> or within 4 weeks of treatment discontinuation <em>(AII)</em>. Even if more than 4 weeks have elapsed since the ARVs were discontinued, resistance testing can still provide useful information to guide therapy, though it may not detect previously selected resistance mutations <em>(CIII)</em>.</td>
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<tr>
<td>• The goal of treatment for ARV-experienced patients with drug resistance who are experiencing virologic failure is to establish virologic suppression (i.e., HIV RNA below the lower limits of detection of currently used assays) <em>(AI)</em>.</td>
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<td>• A new regimen should include at least two, preferably three, fully active agents <em>(AI)</em>. A fully active agent is one that is expected to have ARV activity on the basis of the patient’s treatment history and drug-resistance testing results and/or the drug’s novel mechanism of action.</td>
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<td>• In general, adding a single fully active ARV agent to a virologically failing regimen is not recommended because of the risk of development of resistance to all drugs in the regimen <em>(BII)</em>.</td>
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<td>• For some highly ARV-experienced patients, maximal virologic suppression is not possible. In this case, ART should be continued <em>(AI)</em> with regimens designed to minimize toxicity, preserve CD4 cell counts, and at least delay clinical progression.</td>
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<tr>
<td>• When no viable suppressive regimen can be constructed for a patient with multi-drug resistant HIV, the clinician should consider enrolling the patient in a clinical trial of investigational agents or contacting pharmaceutical sponsors that may have investigational agents available.</td>
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<tr>
<td>• Discontinuing or briefly interrupting therapy may lead to a rapid increase in HIV RNA and a decrease in CD4 cell count and increases the risk of clinical progression. Therefore, this strategy is not recommended <em>(AI)</em>.</td>
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**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 use of antiretroviral therapy (ART) regimens currently recommended for initial therapy, HIV-infected patients have a high likelihood of achieving and maintaining plasma HIV RNA levels below the lower limits of detection (LLOD) of currently used assays (see What to Start). Patients on ART who do not achieve this treatment goal or who experience virologic rebound often develop resistance mutations to one or more components of their regimens, depending upon the regimen initiated. It is estimated that nearly 25% of those receiving ART are not virologically suppressed.¹² Many patients with detectable viral loads are non-adherent to treatment. Depending on their treatment histories, some of these patients may have minimal or no drug resistance; others may have extensive resistance. Managing patients with extensive resistance is complex and usually requires consultation with an HIV expert. This section of the guidelines defines virologic failure in patients on ART and discusses strategies to manage these individuals.

**Virologic Definitions**

**Virologic Suppression:** A confirmed HIV RNA level below the LLOD of available assay.
**Virologic Failure:** The inability to achieve or maintain suppression of viral replication to an HIV RNA level <200 copies/mL.

**Incomplete Virologic Response:** Two consecutive plasma HIV RNA levels ≥200 copies/mL after 24 weeks on an ARV regimen. Baseline HIV RNA may affect the time course of response; some regimens will take longer than others to suppress HIV RNA levels.

**Virologic Rebound:** Confirmed HIV RNA ≥200 copies/mL after virologic suppression.

**Virologic Blip:** After virologic suppression, an isolated detectable HIV RNA level that is followed by a return to virologic suppression.

**Goal of ART Treatment and Virologic Responses**

The goal of ART is to suppress HIV replication to a level below which drug-resistance mutations do not emerge. Although the evidence is not conclusive, it is generally believed that selection of drug resistance mutations does not occur in patients with HIV RNA levels persistently suppressed to below the LLOD of current assays.3

There is controversy regarding the clinical implications of HIV RNA levels between the LLOD and <200 copies/mL in patients on ART. In addition, viremia at this threshold appears to occur more frequently because newer real-time PCR assays are more sensitive than PCR-based viral load platforms used in the past.4-6 Findings from a large retrospective analysis showed that an HIV RNA threshold for virologic failure of <200 copies/mL had the same predictive value for virologic rebound to >200 copies/mL as a threshold of <50 copies/mL.7 However, some studies have suggested that viremia at this low level (i.e., <200 copies/mL) can be predictive of progressive viral rebound9 and can be associated with the evolution of drug resistance.10 In contrast to in individuals with higher levels of HIV RNA, a substantial amount of circulating virus in those with low level of HIV RNA (<50 copies/mL) is believed to result from the release of HIV from long-lived latently infected cells and does not signify ongoing viral replication with the potential emergence of drug-resistant virus.11 Persistent HIV RNA levels ≥200 copies/mL are often associated with evidence of viral evolution and accumulation of drug-resistance mutation.12 This association is particularly common when HIV RNA levels are >500 copies/mL.13 Therefore, persistent plasma HIV RNA levels ≥200 copies/mL should be considered virologic failure.

Viremia blips (e.g., viral suppression followed by a detectable HIV RNA level and subsequent return to undetectable levels) are not usually associated with subsequent virologic failure.14

**Causes of Virologic Failure**

Virologic failure can occur in a patient for many reasons. Data from patient cohorts in the earlier era of combination ART suggested that suboptimal adherence and drug intolerance/toxicity accounted for 28% to 40% of virologic failure and regimen discontinuations.15,16 More recent data suggest that most virologic failure on first-line regimens occurs because of either pre-existing (transmitted) drug resistance or suboptimal adherence.17 Virologic failure is associated with both patient- and regimen-related factors.

**Patient-Related Factors:**

- Higher pretreatment or baseline HIV RNA level (depending on the specific regimen used)
- Lower pretreatment or nadir CD4 T-cell count (depending on the specific regimen used)
- Comorbidities (e.g., active substance abuse, psychiatric disease, neurocognitive deficits)
- Presence of drug-resistant virus, either transmitted or acquired
- Prior treatment failure
- Incomplete medication adherence and missed clinic appointments
• Interruption of or intermittent access to ART

**ARV Regimen-Related Factors:**

• Drug adverse effects and toxicities
• Suboptimal pharmacokinetics (variable absorption, metabolism, or, theoretically, penetration into reservoirs)
• Suboptimal virologic potency
• Prior exposure to suboptimal regimens (e.g., functional monotherapy)
• Food requirements
• High pill burden and/or dosing frequency
• Adverse drug-drug interactions with concomitant medications
• Prescription errors

**Management of Patients with Virologic Failure**

**Assessment of Virologic Failure**

If virologic failure is suspected or confirmed, a thorough work-up that includes consideration of the factors listed in the Causes of Virologic Failure section above is indicated. In many cases, the cause(s) of virologic failure can be identified. In some cases, however, no obvious cause(s) may be found. It is important to distinguish among the causes for virologic failure because the approaches to subsequent therapy differ. The following potential causes of virologic failure should be explored in depth.

• **Incomplete Adherence.** Assess the patient’s adherence to the regimen. Identify and address the underlying cause(s) for incomplete adherence (e.g., drug intolerance, difficulty accessing medications, depression, active substance abuse) and, if possible, simplify the regimen (e.g., decrease pill count or dosing frequency) (see Adherence).

• **Medication Intolerance.** Assess the patient’s tolerance of the current regimen and the severity and duration of side effects, keeping in mind that even minor side effects can affect adherence. Management strategies to address intolerance in the absence of drug resistance may include:
  - Using symptomatic treatment (e.g., antiemetics, antidiarrheals)
  - Changing one ARV in a regimen to another agent in the same drug class (see Adverse Effects section)
  - Changing from one drug class to another class (e.g., from a Non-Nucleoside Reverse Transcriptor Inhibitor [NNRTI] to a protease inhibitor [PI] or an integrase strand transfer inhibitor [INSTI]) if necessary (see Adverse Effects section).

• **Pharmacokinetic Issues.**
  - Review food requirement for each medication, and assess whether the patient adheres to the requirement.
  - Review recent history of gastrointestinal symptoms such as vomiting or diarrhea that may result in short-term malabsorption.
  - Review concomitant medications and dietary supplements for possible adverse drug-drug interactions (consult Drug Interactions section and tables for common interactions) and make appropriate substitutions for ARV agents and/or concomitant medications, if possible.
  - Consider therapeutic drug monitoring (TDM) if pharmacokinetic drug-drug interactions or impaired drug absorption leading to decreased ARV exposure is suspected (see also Exposure-Response Relationship and Therapeutic Drug Monitoring).
• **Suspected Drug Resistance.** Perform resistance testing while the patient is still taking the failing regimen or within 4 weeks after the regimen is discontinued if the patient’s plasma HIV RNA level is >1000 copies/mL (AI), and possibly even if between 500 to 1000 copies/mL (BII) (see Drug-Resistance Testing). In some patients, resistance testing should be considered even after treatment interruptions of more than 4 weeks—recognizing that the lack of evidence of resistance in this setting does not exclude the possibility that resistance mutations may be present at low levels (CIII). Evaluate the extent of drug resistance, taking into account the patient’s past treatment history and prior resistance test results. Drug resistance is cumulative; thus, all prior treatment history and resistance test results should be considered when evaluating resistance. Routine genotypic or phenotypic testing provides information relevant for selecting nucleoside reverse transcriptase inhibitors (NRTIs), NNRTIs, and PIs. Additional drug-resistance tests for patients experiencing failure on INSTIs and/or a fusion inhibitor (AII), and viral tropism tests for patients experiencing failure on a CCR5 antagonist (BIII) are also available. Typically, these tests must be ordered separately from tests for resistance to NRTIs, NNRTIs, and PIs. (See Drug-Resistance Testing.)

**Managing Virologic Failure**

Once virologic failure is confirmed, every effort should be made to assess if poor adherence and drug-drug or drug-food interactions may be contributing to the inadequate virologic response to ART. In general, if virologic failure persists after these issues have been adequately addressed, the regimen should be changed as soon as possible to avoid progressive accumulation of resistance mutations. In addition, several studies have shown that virologic responses to new regimens are greater in individuals with lower HIV RNA levels and/or higher CD4 cell counts at the time of regimen changes. Discontinuing or briefly interrupting therapy in a patient with viremia may lead to a rapid increase in HIV RNA and a decrease in CD4 cell count and increases the risk of clinical progression. Therefore, this strategy is not recommended (AI) (see Discontinuation or Interruption of Antiretroviral Therapy).

Ideally, a new ARV regimen should contain at least two, and preferably three, fully active drugs whose expected activity is based on the patient’s drug treatment history, resistance testing, or the mechanistic action of a new drug class (AI). Despite drug resistance, some ARV drugs (e.g., NRTIs) may contribute partial ARV activity to a regimen, but other agents (e.g., enfuvirtide [T-20], NNRTIs, raltegravir [RAL]) likely will not. Using a “new” drug that a patient has not previously taken does not ensure that the drug will be fully active; there is still the potential for drug-class cross-resistance that reduces drug activity. In addition, archived drug-resistance mutations may not be detected by standard drug-resistance tests, particularly if testing is performed when the patient is not taking the drug in question. This illustrates the importance of considering both treatment history and prior and current drug-resistance test results when designing a new regimen. Drug potency and viral susceptibility are more important factors to consider than the number of component drugs.

In general, patients who receive at least three active drugs selected on the basis of past and present drug resistance test results and treatment history, experience better and more sustained virologic responses than those receiving regimens with fewer active drugs. However, in select cases, adding a fully active ritonavir-boosted [RTV] PI (PI/r) to a single active drug may result in a regimen that is as effective as a regimen that includes more active agents. Active ARV drugs are those with activity against drug-resistant viral strains. These include newer members of existing drug classes that are active against HIV that are resistant to older drugs in the same classes (e.g., ETR, DRV and tipranavir [TPV], and dolutegravir [DTG]) and drugs with unique mechanisms of action (e.g., the fusion inhibitor T-20, the CCR5 antagonist maraviroc [MVC] in patients with no detectable CXCR4-using virus). In the presence of certain drug resistance mutations, the recommended doses of select ARVs, such as DRV/r and DTG need to be given twice daily instead of once daily to achieve higher drug concentrations. Drug-resistance tests for patients experiencing failure on a FI and/or INSTIs, and viral tropism tests for patients experiencing failure on a CCR5 antagonist are also available, although these assays must be performed independent of routine drug resistance testing (see Drug-Resistance Testing).
Clinical Scenarios of Virologic Failure

- **HIV RNA above the LLOD and <200 copies/mL.** Confirm that levels remain above the LLOD and assess adherence and drug-drug interactions (including those with over the counter products and supplements) and drug-food interactions. Patients with HIV RNA typically below the LLOD with transient increases in HIV RNA (i.e., blips) do not require a change in treatment (AII). Although there is no consensus on how to manage patients with persistent HIV RNA levels above the LLOD and <200 copies/mL, the risk of emerging resistance is believed to be relatively low. Therefore, these patients should be followed on their current regimens with HIV RNA levels monitored at least every 3 months to assess the need for changes in ART in the future (AIII).

- **HIV RNA ≥200 and <1000 copies/mL.** Confirm that levels remain in this range, assess adherence, drug-drug interactions (including those with over the counter products and supplements), and drug-food interactions. In contrast to patients with HIV RNA levels persistently <200 copies/mL, those with persistent HIV RNA levels ≥200 copies/mL often develop drug resistance, particularly when their HIV RNA levels are >500 copies/mL. Persistent plasma HIV RNA levels in the 200 to 1,000 copies/mL range should be considered as virologic failure and resistance testing should be attempted if the HIV RNA level is >500 copies/mL. For individuals with sufficient therapeutic options, consider treatment change (BIII).

- **HIV RNA >1000 copies/mL and NO drug resistance identified.** This scenario is almost always associated with non-adherence. Conduct a thorough assessment to determine the level of adherence and identify any drug-drug and drug-food interactions. Consider the timing of the drug-resistance test (e.g., Was the patient off ART for more than 4 weeks and/or nonadherent with the regimen at the time testing was performed?). Consider resuming the same regimen or starting a new regimen. Two to four weeks after treatment is resumed repeat viral load testing and—if viral load remains >500 copies/mL—perform genotypic testing to determine whether a resistant viral strain emerges (CIII).

- **HIV RNA >1000 copies/mL and drug resistance identified.** The goals in this situation are to suppress HIV RNA levels maximally (i.e., to below the LLOD) and to prevent further selection of resistance mutations. With the availability of several newer ARVs, including some with new mechanisms of action, it is now possible to achieve these goals in many patients, including in those with extensive treatment experience and drug resistance. In the case of virologic failure, consider changing the treatment regimen sooner, rather than later, to minimize continued selection of resistance mutations. In a patient with ongoing viremia and evidence of resistance, some drugs in a regimen (e.g., NNRTIs, T-20, or INSTIs) should be discontinued promptly to decrease the risk of selection of additional drug-resistance mutations and to preserve the activity of these drug classes in future regimens. A new regimen should include at least two, and preferably three, fully active agents (AII). If only two active drugs can be identified, whenever possible, an active ritonavir-boosted PI (PI/r) should be prescribed as part of the regimen because of its higher genetic barrier for resistance. In a new regimen, it is the number of active agents and not necessarily the drug class that is most important. This principle was demonstrated in the OPTIONS study; virologic outcomes in those taking at least 2 fully active drugs were equal, whether or not the regimen was supplemented with NRTIs.39

Patients who fail a first-line, NNRTI-based regimen often have resistance to the NNRTI, as well as the cytosine analog components of the regimen (e.g., lamivudine [3TC] and emtricitabine [FTC]). The optimal management strategy for these patients is not known, but a number of studies have now demonstrated the activity of a fully active ritonavir-boosted PI (PI/r) alone or with another fully active drug or even with an agent that has only partial activity. Three of these trials were head-to-head comparisons in this patient population.41-43 Despite evidence of NRTI resistance in many of these patients, two of the studies found that regimens consisting of a PI/r combined with NRTIs were as active as the PI/r combined with RAL,41,43 two other studies showed that the PI/r plus NRTIs combination was more active than the PI/r alone.32,43 Resistance testing should be used to
guide therapy; however, on the basis of these studies, even those with NRTI resistance can be treated with a PI/r plus 2 to 3 NRTIs or RAL (AI). Although data are limited, the second generation NNRTI ETR or the new INSTI DTG combined with a PI/r may also be an option in this situation.

• **Highly drug resistant HIV.** In recent years, use of currently available ARV drugs has resulted in a dramatic decline in the number of patients who have few treatment options because of multi-class drug resistance. Despite this decline, there remains a subset of patients who have experienced toxicity and/or developed resistance to all or most currently available drugs such that design of a regimen with two or three fully active drugs is not possible. These patients may have started therapy before newer, more potent ARVs were available; thus, they developed resistance but had no options for salvage therapy. Standard genotypic testing for RT and PR mutations may be inadequate to identify fully active drugs to add to a new regimen. Additional testing for INSTI resistance, as well as genotypic and phenotypic testing for PR and RT mutations, may be necessary. A tropism assay can also help to determine whether MVC can be added to the new regimen.

If maximal virologic suppression cannot be achieved, the goals of ART are to preserve immunologic function and to prevent clinical progression, even in those with ongoing viremia. There is no consensus on the optimal management of these patients. It is reasonable to observe a patient on the same regimen, rather than changing the regimen, depending on the stage of HIV disease (BII). Even partial virologic suppression of HIV RNA to >0.5 log10 copies/mL from baseline correlates with clinical benefits. Cohort studies provide evidence that continuing therapy, even in the presence of viremia and the absence of CD4 count increases, reduces the risk of disease progression. Other cohort studies suggest continued immunologic and clinical benefits if the HIV RNA level is maintained at <10,000 to 20,000 copies/mL. However, these potential benefits all must be balanced with the ongoing risk of accumulating additional resistance mutations. The management of these patients always requires expert advice. In general, adding a single fully active ARV to the regimen is not recommended because of the risk of rapid development of resistance (BII). However, in patients with a high likelihood of clinical progression (e.g., those with CD4 cell count <100 cells/mm³) and limited drug options, adding a single drug to a regimen may reduce the risk of immediate clinical progression because even transient decreases in HIV RNA and/or transient increases in CD4 cell counts have been associated with clinical benefits (CI). Weighing the risks (e.g., selection of drug resistance) and benefits (e.g., ARV activity) of adding a single active drug to the regimen of a heavily ART-experienced patient is complicated and consultation with an expert is advised.

Patients with ongoing viremia who lack sufficient treatment options to construct a fully suppressive regimen may be candidates for research studies or expanded access programs or may qualify for single-patient access of an investigational new drug(s) (IND) as specified in Food and Drug Administration (FDA) regulations: http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm163982.htm. Information about these programs may also be available from the sponsoring pharmaceutical manufacturer.

• **Previously treated patient with suspected drug resistance and in need of care but with limited information (i.e., incomplete or no self-reported history, medical records, or resistance data).** Every effort should be made to obtain the patient’s medical records and prior drug-resistance testing results; however, this may not always be possible. One strategy is to restart the most recent ARV regimen and assess drug resistance in 2 to 4 weeks to guide selection of the next regimen. Another strategy is to start two or three drugs known to be active on the basis of the patient’s treatment history (e.g., MVC if the patient has no detectable X4 virus and an INSTI if there is no prior history of treatment with drugs in this class).

In summary, the management of treatment-experienced patients with virologic failure often requires expert advice to achieve the goal of constructing virologically suppressive regimens. It is critical to carefully evaluate the cause of virologic failure including assessment of adherence, drug and food interactions, tolerability, HIV RNA and CD4 cell count changes over time, treatment history, and drug-resistance test
results before switching regimens. If HIV RNA suppression with use of currently approved agents is not possible, consider use of investigational agents that are available through clinical trials or expanded/single-patient access programs. If virologic suppression is still not achievable, the choice of regimens should focus on minimizing toxicity and preserving treatment options while maintaining CD4 cell counts to delay clinical progression.

**Suboptimal Immunologic Response Despite Viral Suppression**

After ART initiation, most patients experience improved immune function and maintain viral suppression; however, there remains a subset of patients who have suboptimal immunologic responses—defined as the failure to achieve and maintain an adequate CD4 response despite virologic suppression. In ARV-naive patients on initial ARV regimens, during the first year of ART, CD4 counts usually increase by approximately 150 cells/mm³. A CD4 count plateau may occur after 4 to 6 years of treatment with suppressed viremia.

Although there is not an accepted specific definition for suboptimal immunologic response, some studies have focused on a failure to increase CD4 counts above a specific threshold (e.g., >350 or 500 cells/mm³) over a specific period of time (e.g., 4 to 7 years). Others have focused on an inability to increase CD4 counts above pretherapy levels by a certain threshold (e.g., >50 or 100 cells/mm³) over a given time period. The former criterion may be preferable because of data linking these thresholds with the risk of non-AIDS clinical events.

The proportion of patients experiencing suboptimal immunologic response depends on how suboptimal response is defined, the observation period, and the CD4 count when treatment was started. In the longest study conducted to date, the percentage of patients with suppressed viremia who reached a CD4 count >500 cells/mm³ through 6 years of treatment was 42% in those starting treatment with a CD4 count <200 cells/mm³, 66% in those starting with a CD4 count 200 to 350 cells/mm³, and 85% in those starting with a CD4 count >350 cells/mm³.

A persistently low CD4 count while on suppressive ART is associated with a small, but appreciable, risk of AIDS- and non-AIDS-related morbidity and mortality. For example, in the FIRST study, a low CD4 count on therapy was associated with an increased risk of AIDS-related complications (adjusted hazard ratio of 0.56 per 100 cells/mm³ higher CD4 count). Similarly, a low CD4 count was associated with an increased risk of non-AIDS events, including cardiovascular, hepatic, and renal disease and cancer. Other studies support these associations.

The following are some factors that have been associated with poor CD4 cell response:

- CD4 count <200/mm³ at initiation of ART
- Older age
- Coinfection (e.g., hepatitis C virus [HCV], HIV-2, human T-cell leukemia virus type 1 [HTLV-1], HTLV-2)
- ARVs (e.g., zidovudine [ZDV], tenofovir disoproxil fumarate [TDF] + didanosine [ddI]) and other medications
- Persistent immune activation
- Loss of regenerative potential of the immune system
- Concomitant medical conditions

**Assessment of Patients with Suboptimal Immunologic Responses**

CD4 count should be confirmed by repeat testing. Concomitant medications should be reviewed carefully, with a focus on those known to decrease white blood cells or, specifically, CD4 T-cells (e.g., cancer chemotherapy, interferon, prednisone, ZDV; combination of TDF and ddI), and consideration should be given to substituting or discontinuing these drugs, if possible. Untreated coinfections (e.g., HIV-2, HTLV-1,
HTLV-2) and serious medical conditions (e.g., malignancy) also should be considered. In many cases, no obvious cause for immunologic failure can be identified.

Management of Patients with Suboptimal Immunologic Response

There is no consensus with regards to when or how to manage patients with suboptimal immunologic response. Given the risk of clinical events, it is reasonable to focus on patients with CD4 counts <200 cells/mm³ because patients with higher CD4 counts have a lower risk of clinical events. It is not clear that suboptimal immunologic response in the setting of virologic suppression should prompt a change in the ARV regimen. Because ongoing immune activation occurs in some patients with suppressed HIV RNA levels, some have suggested adding a drug to an existing regimen. However, this strategy does not result in clear virologic or immunologic benefit. Others suggest changing the regimen to another regimen (e.g., from NNRTI-based to PI-based, INSTI-based, or CCR5 antagonist-based regimens), but this strategy has not shown clear benefit.

In two large randomized studies, an immune-based therapy, interleukin-2, demonstrated CD4 count increases but no clinical benefit¹⁰ and therefore is not recommended (AI). Other immune-based therapies (e.g., gene therapies, growth hormone, cyclosporine, interleukin-7) are under investigation. Currently, immune-based therapies should not be used outside the context of a clinical trial (AIII).

References


39. Tashima K, Smeaton L, Andrade A. Omitting NRTI from ARV regimens is not inferior to adding NRTI in treatment-presented at: 20th Conference on Retroviruses and Opportunistic Infections; 2013; Atlanta GA.


Regimen Switching In the Setting of Virologic Suppression  (Last updated May 1, 2014; last reviewed May 1, 2014)

With use of currently available antiretroviral therapy (ART), most HIV-infected patients are able to achieve sustained HIV viral suppression. Furthermore, advances in treatment and better understanding about drug resistance make it possible to consider switching an effective regimen to an alternative regimen in some situations (see below). When contemplating such a switch, clinicians must consider several key principles to maintain viral suppression while addressing concerns with the current treatment.

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

• To simplify the regimen by reducing pill burden and dosing frequency to improve adherence
• To enhance tolerability and decrease short- or long-term toxicity (see Adverse Effects section)
• To change food or fluid requirements
• To avoid parenteral administration
• To minimize or address drug interaction concerns (see Drug Interactions section)
• To allow for optimal use of ART during pregnancy or should pregnancy occur (see Perinatal Guidelines)
• To reduce costs (see Cost section)

Principles and Strategies of Regimen Switching

The cardinal principle of regimen switching is to maintain viral suppression without jeopardizing future treatment options. If a regimen switch results in virologic failure with emergence of new resistance mutations, the patient may require more complex, difficult to follow, or expensive regimens. Principles for successful regimen switching are highlighted below:

• It is critical to review a patient’s full antiretroviral (ARV) history (including virologic responses, resistance test results, and past adverse events) before any treatment switch.

• Once a particular resistance mutation has been selected, it is generally archived in the HIV reservoir and is likely to reappear under the appropriate selective drug pressure, even if not detected in the most recent resistance test. If resistance data are unavailable, resistance may often be inferred from a patient’s treatment history. For example, a clinician should assume that patients who have failed a cytosine analogue (e.g., a lamivudine (3TC)- or emtricitabine (FTC)-containing regimen), likely have the M184V substitution, even if the substitution is not documented. The same assumption of resistance may also apply to patients with documented failure to a non-nucleoside reverse transcriptase inhibitor (NNRTI)-or integrase strand transfer inhibitors (INSTI)-based regimen 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 resistant virus as the suppressive regimen.

• Consultation with an HIV specialist is recommended when considering a regimen switch for a patient with a history of resistance to one or more drug classes.

• Switching from a ritonavir (RTV)-boosted protease inhibitor (PI) regimen to a regimen composed of drugs with a lower barrier to resistance generally maintains viral suppression provided there is no resistance to the other components of the regimen. However, such switches should be avoided if there is any doubt about the activity of the other agents in the regimen.

• Within-class switches prompted by adverse events usually maintain viral suppression provided that there is no drug resistance to the other ARV agents in the same drug class.
• In the absence of any likely drug resistance, switching from complex regimens, parenteral drug (i.e., enfuvirtide), or drugs known now to be more toxic (e.g., zidovudine, stavudine, or didanosine) or with higher pill burden or dosing frequency to simpler regimens (e.g., from a regimen including ritonavir-boosted saquinavir [SQV/r] to one including ritonavir-boosted darunavir [DRV/r]) or to ARVs in a new drug class (e.g., an INSTI) generally results in similar or improved adherence, continued viral suppression and possibly improved quality of life.

• More intensive monitoring of tolerability, viral suppression, adherence, and laboratory changes is recommended during the first 3 months after a regimen switch.

Alternative Switch Strategies for Patients with Virologic Suppression

RTV-Boosted PI Monotherapy
The strategy of switching virologically suppressed patients without PI resistance from one ART regimen to RTV-boosted PI monotherapy has been studied. The rationale for this strategy is to avoid nucleoside reverse transcriptase inhibitor (NRTI) toxicities and decrease costs, while taking advantage of the high barrier to resistance of RTV-boosted PIs. RTV-boosted PI monotherapy maintains virologic suppression in most patients, but at slightly lower rates than standard therapy that includes 2 NRTIs.2,3 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.

No clinical trials comparing available RTV-boosted PI monotherapy regimens have been conducted. Findings from an observational study suggest that the rate of treatment failure is higher in patients on RTV-boosted atazanavir (ATV/r) than in those on RTV-boosted lopinavir (LPV/r) or DRV/r.4 Another pilot study reported early viral rebound with use of ATV/r monotherapy.5 There are rare reports of central nervous system virologic escape, sometimes with clinical symptoms, in patients on RTV-boosted PI monotherapy.6,7

On the basis of the results from these studies, RTV-boosted PI monotherapy should generally be avoided. Other strategies to avoid use of NRTIs (i.e., use of a RTV-boosted PI plus a NNRTI, an INSTI, or maraviroc [MVC]) are also being studied, but data on these strategies are limited.

Switching from a Ritonavir-Boosted Protease Inhibitor to Unboosted Atazanavir
Several clinical studies have evaluated switching a RTV-boosted PI to unboosted atazanavir (ATV) in virologically suppressed patients without NRTI resistance. Two comparative clinical trials reported that ATV/r and ATV, both in combination with 2 NRTIs (mostly ABC/3TC), demonstrated comparable levels of virologic suppression and a similar lack of treatment-emergent resistance. The benefits of the unboosted ATV regimen included a slightly improved lipid profile and a lower incidence of hyperbilirubinemia.8,9 An additional study of 296 patients with virologic suppression on tenofovir disoproxil fumarate (TDF)/FTC plus ATV/r showed that patients switched to ABC/3TC plus ATV maintained viral suppression and showed improvements in certain bone and renal biomarkers.10 The results of these and other non-comparative studies suggest that a regimen of ABC/3TC plus ATV can be considered in virologically suppressed patients, especially in those who have adverse effects from TDF or RTV.

Switching to Maraviroc
Co-receptor usage in virologically suppressed patients can be determined from proviral DNA obtained from peripheral blood mononuclear cells. Individuals found to have R5-tropic virus by this technique could potentially have a component of their regimens switched to MVC.11,12 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 Tropism Testing section).
De-intensification of a standard RTV-boosted PI regimen from three to two active drugs (e.g., to a boosted PI plus one NRTI, a boosted PI plus an INSTI, or an NNRTI such as etravirine or the CCR5 antagonist MVC) may be more effective virologically than RTV-boosted PI monotherapy, but, thus far, comparative data on this approach are limited. In general, switching a regimen—even in a patient without known drug resistance—from an effective three-drug regimen to a two-drug regimen has not been validated and is not recommended.

Monitoring After Treatment Changes

Patients should be evaluated more closely for several months after a treatment switch (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 goal of the 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 are a concern with the new regimen, fasting cholesterol subsets and triglycerides should be assessed within 3 months after the change in therapy. Absent any specific 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 section).

References


Knowledge of the relationship between systemic exposure (or concentration) and drug responses (beneficial and/or adverse) is key in selecting the dose of a drug, in understanding the variability in the response of patients to a drug, and in designing strategies to optimize response and tolerability.

TDM is a strategy applied to certain antiarrhythmics, anticonvulsants, antineoplastics, and antibiotics that utilizes measured drug concentrations to design dosing regimens to improve the likelihood of the desired therapeutic and safety outcomes. The key characteristic of a drug that is a candidate for TDM is knowledge of the exposure-response relationship and a therapeutic range of concentrations. The therapeutic range is a range of concentrations established through clinical investigations that are associated with a greater likelihood of achieving the desired therapeutic response and/or reducing the frequency of drug-associated adverse reactions.

Several ARV agents meet most of the characteristics of agents that can be considered candidates for a TDM strategy. The rationale for TDM in managing antiretroviral therapy (ART) derives from the following:

- data showing that considerable interpatient variability in drug concentrations exists among patients who take the same dose;
- data indicating that relationships exist between the concentration of drug in the body and anti-HIV effect and, in some cases, toxicities; and
- data from small prospective studies demonstrating that TDM improved virologic response and/or decreased the incidence of concentration-related drug toxicities.

**TDM for ARV agents, however, is not recommended for routine use in the management of the HIV-infected adult (CIII).**

Multiple factors limit the routine use of TDM in HIV-infected adults. These factors include:

- lack of large prospective studies demonstrating that TDM improves clinical and virologic outcomes. (This is the most important limiting factor for the implementation of TDM at present.);
- lack of established therapeutic range of concentrations for all ARV drugs that is associated with achieving the desired therapeutic response and/or reducing the frequency of drug-associated adverse reactions;
- intrapatient variability in ARV drug concentrations;
- lack of widespread availability of clinical laboratories that perform quantitation of ARV concentrations under rigorous quality assurance/quality control standards; and
- shortage of experts to assist with interpretation of ARV concentration data and application of such data to revise patients’ dosing regimens.

Panel's Recommendations

- Therapeutic drug monitoring (TDM) for antiretroviral (ARV) agents is not recommended for routine use in the management of the HIV-infected adult (CIII).
- TDM may be considered in selected clinical scenarios, as discussed in the text below.

**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
Exposure-Response Relationships and TDM with Different ARV Classes

Protease Inhibitors (PIs), Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs), and Integrase Inhibitors. Relationships between the systemic exposure to PIs and NNRTIs and treatment response have been reviewed in various publications. Although there are limitations and unanswered questions, the consensus among clinical pharmacologists from the United States and Europe is that the data provide a framework for the potential implementation of TDM for PIs and NNRTIs. However, information on relationships between concentrations and drug-associated toxicities are sparse. Clinicians who use TDM as a strategy to manage either ARV response or toxicities should consult the most current data on the proposed therapeutic concentration range. Exposure-response data for darunavir (DRV), etravirine (ETR), and raltegravir (RAL) are accumulating but are not sufficient to recommend minimum trough concentrations. The median trough concentrations for these agents in HIV-infected persons receiving the recommended dose are included in Table 10b.

CCR5 Antagonists. Trough maraviroc (MVC) concentrations have been shown to be an important predictor of virologic success in studies conducted in ART-experienced persons. Clinical experience in the use of TDM for MVC, however, is very limited. Nonetheless, as with PIs and NNRTIs, the exposure-response data provide a framework for TDM, and that information is presented in these guidelines (Table 10b).

Nucleoside Reverse Transcriptase Inhibitors (NRTIs). Relationships between plasma concentrations of NRTIs and their intracellular pharmacologically active moieties have not yet been established. Therefore, monitoring of plasma or intracellular NRTI concentrations for an individual patient largely remains a research tool. Measurement of plasma concentrations, however, is routinely used for studies of drug-drug interactions.

Scenarios for Use of TDM. Multiple scenarios exist in which both ARV concentration data and expert opinion may be useful in patient management. Consultation with a clinical pharmacologist or a clinical pharmacist with HIV expertise may be advisable in these cases. These scenarios include the following:

- Suspect clinically significant drug-drug or drug-food interactions that may result in reduced efficacy or increased dose-related toxicities;
- Changes in pathophysiologic states that may impair gastrointestinal, hepatic, or renal function, thereby potentially altering drug absorption, distribution, metabolism, or elimination;
- Pregnant women who may be at risk of virologic failure as a result of changes in their pharmacokinetic parameters during the later stage of pregnancy, which may result in plasma concentrations lower than those achieved in the earlier stages of pregnancy and in the nonpregnant patient;
- Heavily pretreated patients experiencing virologic failure and who may have viral isolates with reduced susceptibility to ARVs;
- Use of alternative dosing regimens and ARV combinations for which safety and efficacy have not been established in clinical trials;
- Concentration-dependent, drug-associated toxicities; and
- Lack of expected virologic response in medication-adherent persons.

TDM

- **For patients who have drug-susceptible virus.** Table 10a includes a synthesis of recommendations for minimum target trough PI and NNRTI concentrations in persons with drug-susceptible virus.

- **For ART-experienced patients with virologic failure** (see Table 10b). Fewer data are available to formulate suggestions for minimum target trough concentrations in ART-experienced patients who have viral isolates with reduced susceptibility to ARV agents. Concentration recommendations for tipranavir...
(TPV) and MVC were derived only from studies in ART-experienced persons. It is likely that use of PIs and NNRTIs in the setting of reduced viral susceptibility may require higher trough concentrations than those needed for wild-type virus. The inhibitory quotient (IQ), which is the ratio of ARV drug concentration to a measure of susceptibility (genotype or phenotype) of the patient’s strain of HIV to that drug, may additionally improve prediction of virologic response—as has been shown, for example, with DRV in ART-experienced persons.\textsuperscript{10-11} Exposure-response data for DRV, ETR, and RAL are accumulating but are not sufficient to recommend minimum trough concentrations. The median trough concentrations for these agents in HIV-infected persons receiving the recommended dose are included in Table 10b.

Using Drug Concentrations to Guide Therapy. There are several challenges and considerations for implementation of TDM in the clinical setting. Use of TDM to monitor ARV concentrations in a patient requires multiple steps:

- quantification of the concentration of the drug, usually in plasma or serum;
- determination of the patient’s pharmacokinetic characteristics;
- integration of information on patient adherence;
- interpretation of the concentrations; and
- adjustment of the drug dose to achieve concentrations within the therapeutic range, if necessary.

Guidelines for the collection of blood samples and other practical suggestions can be found in a position paper by the Adult AIDS Clinical Trials Group Pharmacology Committee.\textsuperscript{4}

A final caveat to the use of measured drug concentrations in patient management is a general one—drug concentration information cannot be used alone; it must be integrated with other clinical information. In addition, as knowledge of associations between ARV concentrations and virologic response continues to accumulate, clinicians who employ a TDM strategy for patient management should consult the most current literature.

\begin{table}[h]
\centering
\begin{tabular}{|l|c|}
\hline
Drug & Concentration (ng/mL) \\
\hline
Suggested minimum target trough concentrations in patients with HIV-1 susceptible to the ARV drugs\textsuperscript{2-9} & \\
\hline
Fosamprenavir (FPV) & 400 (measured as amprenavir concentration) \\
\hline
Atazanavir (ATV) & 150 \\
\hline
Indinavir (IDV) & 100 \\
\hline
Lopinavir (LPV) & 1000 \\
\hline
Nelfinavir\textsuperscript{a} (NFV) & 800 \\
\hline
Saquinavir (SQV) & 100–250 \\
\hline
Efavirenz (EFV) & 1000 \\
\hline
Nevirapine (NVP) & 3000 \\
\hline
\end{tabular}
\caption{Trough Concentrations of Antiretroviral Drugs for Patients Who Have Drug-Susceptible Virus}
\end{table}

\textsuperscript{a} Measurable active (M8) metabolite
Table 10b. Trough Concentrations of Antiretroviral Drugs for Treatment-Experienced Patients with Virologic Failure

<table>
<thead>
<tr>
<th>Drug</th>
<th>Concentration (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Suggested minimum target trough concentrations for ART-experienced patients who have resistant HIV-1 strains</strong></td>
<td></td>
</tr>
<tr>
<td>Maraviroc (MVC)</td>
<td>&gt;50</td>
</tr>
<tr>
<td>Tipranavir (TPV)</td>
<td>20,500</td>
</tr>
<tr>
<td><strong>Median (Range) Trough Concentrations from Clinical Trials</strong>&lt;sup&gt;12-14&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Darunavir (DRV) (600 mg twice daily)</td>
<td>3300 (1255–7368)</td>
</tr>
<tr>
<td>Etravirine (ETR)</td>
<td>275 (81–2980)</td>
</tr>
<tr>
<td>Raltegravir (RAL)</td>
<td>72 (29–118)</td>
</tr>
</tbody>
</table>

References

**Discontinuation or Interruption of Antiretroviral Therapy** (Last updated January 10, 2011; last reviewed January 10, 2011)

Discontinuation of antiretroviral therapy (ART) may result in viral rebound, immune decompensation, and clinical progression. Unplanned interruption of ART may become necessary because of severe drug toxicity, intervening illness, surgery that precludes oral therapy, or unavailability of antiretroviral (ARV) medication. Some investigators have studied planned treatment discontinuation strategies in situations or for reasons that include: in patients who achieve viral suppression and wish to enhance adherence; to reduce inconvenience, long-term toxicities, and costs for patients; or in extensively treated patients who experience treatment failure due to resistant HIV, to allow reversion to wild-type virus. Potential risks and benefits of interruption vary according to a number of factors, including the clinical and immunologic status of the patient, the reason for the interruption, the type and duration of the interruption, and the presence or absence of resistant HIV at the time of interruption. Below are brief discussions on what is currently known about the risks and benefits of treatment interruption in some of these circumstances.

**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 unavailability of drugs. Stopping ARV drugs for a short time (i.e., <1 to 2 days) due to medical/surgical procedures can usually be done by holding all drugs in the regimen. Recommendations for some other scenarios are listed below:

**Unanticipated Need for Short-Term 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 Interruption (>2–3 days)**

- **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 sustained period of 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 ARV regimen contains drugs with differing 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]). Options in this circumstance are discussed below. (See Discontinuation of efavirenz, etravirine, or nevirapine.)

**Interruption of Therapy after Pregnancy**

ARV drugs for prevention of perinatal transmission of HIV are recommended for all pregnant women, regardless of whether they have indications for ART for their own health. Following delivery, considerations regarding continuation of the ARV regimen for maternal therapeutic indications are the same as for other nonpregnant individuals. The decision of whether to continue therapy after delivery should take into account current recommendations for initiation of ART, current and nadir CD4 T-cell counts and trajectory, HIV RNA levels, adherence issues, and patient preference.
Planned Long-Term Therapy Interruptions

Planned therapy interruptions have been contemplated in various scenarios, listed below. Research is ongoing in several of the scenarios. Therapy interruptions cannot be recommended at this time outside of controlled clinical trials (AI).

- **In patients who initiated therapy during acute HIV infection and achieved virologic suppression**—the optimal duration of treatment and the consequences of treatment interruption are not known at this time. (See Acute HIV Infection.)

- **In patients who have had exposure to multiple ARV agents, have experienced ARV treatment failure, and have few treatment options available because of extensive resistance mutations**—interruption is not recommended unless done in a clinical trial setting (AI). Several clinical trials, largely yielding negative results, but some with conflicting results, have been conducted to better understand the role of treatment interruption in these patients. The largest of these studies showed negative clinical impact of treatment interruption in these patients. The Panel notes that partial virologic suppression from combination therapy has been associated with clinical benefit; therefore, interruption of therapy is not recommended.

- **In patients on ART who have maintained a CD4 count above the level currently recommended for treatment initiation and irrespective of whether their baseline CD4 counts were either above or below that recommended threshold**—interruption is also not recommended unless done in a clinical trial setting (BI). (See discussion below highlighting potential adverse outcomes seen in some treatment interruption trials.)

Temporary treatment interruption to reduce inconvenience, potential long-term toxicity, and/or overall treatment cost has been considered as a strategy for patients on ART who have maintained CD4 counts above those currently recommended for initiating therapy. Several clinical trials have been designed to determine the safety of such interruptions, in which reinitiation is triggered by predetermined CD4 count thresholds. In these trials, various CD4 count levels have been set to guide both treatment interruption and reinitiation. In the SMART study, the largest of such trials with more than 5,000 subjects, interrupting treatment with CD4 counts >350 cells/mm³ and reinitiating when <250 cells/mm³ was associated with an increased risk of disease progression and all cause mortality compared with the trial arm of continuous ART. In the TRIVACAN study, the same CD4 count thresholds were used for stopping and restarting treatment. This study also showed that interruption was an inferior strategy; the interventions in both trials were stopped early because of these findings. Data from the DART trial reported a twofold increase in rates of World Health Organization (WHO) Stage 4 events/deaths in the 12-week ART cycling group among African patients achieving a CD4 count >300/mm³ compared with the continuous ART group. Observational data from the EuroSIDA cohort noted a twofold increase in risk of death after a treatment interruption of >3 months. Factors linked to increased risk of death or progression included lower CD4 counts, higher viral loads, and a prior history of AIDS. Other studies have reported no major safety concerns, but these studies had smaller sample sizes. Results have been reported from several small observational studies evaluating treatment interruption in patients doing well with nadir CD4 counts >350/mm³, but further studies are needed to determine the safety of treatment interruption in this population. There is concern that CD4 counts <500 cells/mm³ are associated with a range of non-AIDS clinical events (e.g., cancer and heart, liver, and kidney disease).

Planned long-term therapy interruption strategies cannot be recommended at this time outside of controlled clinical trials (BI) based on available data and a range of ongoing concerns.

If therapy has to be discontinued, patients should be counseled about the need for close clinical and laboratory monitoring. They should also be aware of the risks of viral rebound, acute retroviral syndrome,
increased risk of HIV transmission, decline of CD4 count, HIV disease progression or death, development of minor HIV-associated manifestations such as oral thrush, development of serious non-AIDS complications, development of drug resistance, and the need for chemoprophylaxis against opportunistic infections depending on the CD4 count. Treatment interruptions often result in rapid reductions in CD4 counts.

Prior to any planned treatment interruption, a number of ARV-specific issues should be taken into consideration. These include:

- **Discontinuation of efavirenz (EFV), etravirine (ETR), or nevirapine (NVP).** The optimal interval between stopping EFV, ETR, or NVP and other ARV drugs is not known. The duration of detectable levels of EFV or NVP after discontinuation ranges from less than 1 week to more than 3 weeks. Simultaneously stopping all drugs in a regimen containing these agents may result in functional monotherapy with the NNRTIs because NNRTIs have much longer half-lives than other agents. This may increase the risk of selection of NNRTI-resistant mutations. It is further complicated by evidence that certain host genetic polymorphisms may result in slower rates of clearance. Such polymorphisms may be more common among specific ethnic groups, such as African Americans and Hispanics. Some experts recommend stopping the NNRTI but continuing the other ARV drugs for a period of time. The optimal time sequence for staggered component discontinuation has not been determined. A study in South Africa demonstrated that giving 4 or 7 days of zidovudine (ZDV) + lamivudine (3TC) after a single dose of NVP reduced the risk of postnatal NVP resistance from 60% to 10%-12%. Use of nucleoside reverse transcriptase inhibitors (NRTIs) with a longer half-life such as tenofovir (TDF) plus emtricitabine (FTC) has also been shown to decrease NVP resistance after single-dose treatment. The findings may, however, differ in patients on chronic NVP treatment. An alternative strategy is to substitute a protease inhibitor (PI) for the NNRTI and to continue the PI with dual NRTIs for a period of time. In a post-study analysis of the patients who interrupted therapy in the SMART trial, patients who were switched from an NNRTI- to a PI-based regimen prior to interruption had a lower rate of NNRTI-resistant mutation after interruption and a greater chance of resuppression of HIV RNA after restarting therapy than those who stopped all the drugs simultaneously or stopped the NNRTI before the 2-NRTI. The optimal duration needed to continue the PI-based regimen after stopping the NNRTI is not known. Given the potential of prolonged detectable NNRTI concentrations for more than 3 weeks, some suggest that the PI-based regimen may need to be continued for up to 4 weeks. Further research to determine the best approach to discontinuing NNRTIs is needed. Clinical data on ETR and treatment interruption is lacking but its long half-life of approximately 40 hours suggests that stopping ETR needs to be done carefully using the same suggestions for NVP and EFV for the time being.

- **Discontinuation and reintroduction of NVP.** Because NVP is an inducer of the drug-metabolizing hepatic enzymes, administration of full therapeutic doses of NVP without a 2-week, low-dose escalation phase will result in excess plasma drug levels and potentially increase the risk of toxicity. Therefore, in a patient who has interrupted treatment with NVP for more than 2 weeks, NVP should be reintroduced with a dose escalation period of 200 mg once daily for 14 days and then a 200 mg twice-daily regimen.

- **Discontinuation of FTC, 3TC, or TDF in patients with hepatitis B virus (HBV) coinfection.** Patients with HBV coinfection (hepatitis B surface antigen [HbsAg] or hepatitis B e antigen [HBeAg] positive) and receiving one or a combination of these NRTIs may experience an exacerbation of hepatitis upon drug discontinuation. (See **Hepatitis B (HBV)/HIV Coinfection**.)

**References**


2. Ruiz L, Ribera E, Bonjoch A, et al. Role of structured treatment interruption before a 5-drug salvage antiretroviral


