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  (Last updated October 17, 2017; last reviewed October 17, 2017)

<table>
<thead>
<tr>
<th>Panel’s Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Assessing and managing a patient experiencing failure of antiretroviral therapy (ART) is complex. Expert advice is critical and should be sought.</td>
</tr>
<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, ART history, and prior and current drug-resistance testing results.</td>
</tr>
<tr>
<td>• Drug-resistance testing should be performed while the patient is taking the failing antiretroviral (ARV) regimen (AI) or within 4 weeks of treatment discontinuation (AII). Even if more than 4 weeks have elapsed since ARVs were discontinued, resistance testing can still provide useful information to guide therapy, although it may not detect previously selected resistance mutations (CIII).</td>
</tr>
<tr>
<td>• The goal of treatment for ART-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) (AI).</td>
</tr>
<tr>
<td>• A new regimen should include at least two, and preferably three, fully active agents (AI). A fully active agent is one that is expected to have uncompromised activity on the basis of the patient’s ART history and his or her current and past drug-resistance testing results. A fully active agent may also have a novel mechanism of action.</td>
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<tr>
<td>• In general, adding a single ARV agent to a virologically failing regimen is not recommended because this may risk the development of resistance to all drugs in the regimen (BII).</td>
</tr>
<tr>
<td>• For some highly ART-experienced patients with extensive drug resistance, maximal virologic suppression may not be possible. In this case, ART should be continued (AI) with regimens designed to minimize toxicity, preserve CD4 cell counts, and delay clinical progression.</td>
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<tr>
<td>• When it is not possible to construct a viable suppressive regimen for a patient with multidrug resistant HIV, the clinician should consider enrolling the patient in a clinical trial of investigational agents or contacting pharmaceutical companies that may have investigational agents available.</td>
</tr>
<tr>
<td>• When switching an ARV regimen in a patient with hepatitis B virus (HBV)/HIV coinfection, ARV drugs active against HBV should be continued as part of the new regimen. Discontinuation of these drugs may cause serious hepatocellular damage resulting from reactivation of HBV.</td>
</tr>
<tr>
<td>• Discontinuing or briefly interrupting therapy may lead to a rapid increase in HIV RNA, a decrease in CD4 cell count, and an increase in the risk of clinical progression. Therefore, this strategy is not recommended in the setting of virologic failure (AI).</td>
</tr>
<tr>
<td>• Table 10 provides guidance on antiretroviral (ARV) regimen options in patients with virologic failure.</td>
</tr>
</tbody>
</table>

**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

Antiretroviral (ARV) regimens currently recommended for initial therapy of patients with HIV 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 antiretroviral therapy (ART) who do not achieve this treatment goal or who experience virologic rebound can develop resistance mutations to one or more components of their regimen. Many patients with detectable viral loads have challenges adhering 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 ART in these individuals.
Virologic Response Definitions

The following definitions are used in this section to describe the different levels of virologic response to ART.

**Virologic suppression:** A confirmed HIV RNA level below the LLOD of available assays.

**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 in a patient who has not yet had documented virologic suppression on this regimen. A patient’s baseline HIV RNA level may affect the time course of response, and some regimens may 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.

**Low-level viremia:** Confirmed detectable HIV RNA <200 copies/mL.

Antiretroviral Therapy Treatment Goals and Presence of Viremia While on Antiretroviral Therapy

The goal of ART is to suppress HIV replication to a level below which drug-resistance mutations do not emerge. Although not conclusive, the evidence suggests that selection of drug-resistance mutations does not occur in patients with HIV RNA levels persistently suppressed to below the LLOD of current assays.2

Virologic blips are not usually associated with subsequent virologic failure.2 In contrast, there is controversy regarding the clinical implications of persistently low HIV RNA levels between the LLOD and <200 copies/mL in patients on ART. Viremia at this threshold is detected with some frequency by commonly used real-time polymerase chain reaction (PCR) assays, which are more sensitive than the PCR-based viral load platforms used in the past.3-5 Findings from a large retrospective analysis showed that, as a threshold for virologic failure, HIV RNA levels of <200 copies/mL and <50 copies/mL had the same predictive value for subsequent rebound to >200 copies/mL.6 Two other retrospective studies also support the supposition that virologic rebound is more likely to occur in patients with viral loads >200 copies/mL than in those with low-level viremia between 50 and 199 copies/mL.7,8 However, other studies have suggested that detectable viremia at this low level (<200 copies/mL) can be predictive of progressive viral rebound9,10 and can be associated with the evolution of drug resistance.11

Persistent HIV RNA levels ≥200 copies/mL are often associated with evidence of viral evolution and accumulation of drug-resistance mutations.12 This association is particularly common when HIV RNA levels are >500 copies/mL.13 Therefore, persistent plasma HIV RNA levels ≥200 copies/mL are considered virologic failure.

Causes of Virologic Failure

Virologic failure can occur for many reasons. Data from patient cohorts in the earlier era of combination ART suggested that suboptimal adherence and drug intolerance/toxicity are key contributors to virologic failure and regimen discontinuations.14,15 The presence of pre-existing (transmitted) drug resistance may also lead to virologic failure.16 Virologic failure may be associated with various patient/adherence-, HIV-, and regimen-related factors, as listed below:

**Patient/Adherence-Related Factors** (see Adherence to the Continuum of Care)

- Comorbidities that may affect adherence (e.g., active substance abuse, mental health disorders, neurocognitive impairment)
• Unstable housing and other psychosocial factors
• Missed clinic appointments
• Interruption of or intermittent access to ART
• Cost and affordability of ARVs (i.e., may affect ability to access or continue therapy)
• Drug adverse effects
• High pill burden and/or dosing frequency

HIV-Related Factors
• Presence of transmitted or acquired drug-resistant virus documented by current or past resistance testing
• Prior treatment failure
• Innate resistance to ARVs based on tropism or the presence of HIV-2 infection/co-infection.
• Higher pretreatment HIV RNA level (some regimens may be less effective)

ARV Regimen-Related Factors
• Suboptimal pharmacokinetics (variable absorption, metabolism, or possible penetration into reservoirs)
• Suboptimal virologic potency
• Low genetic barrier to resistance
• Reduced efficacy due to prior exposure to suboptimal regimens (e.g., monotherapy, dual-nucleoside therapy, or the sequential introduction of drugs)
• Food requirements
• Adverse drug-drug interactions with concomitant medications
• Prescription errors

Managing Patients with Virologic Failure
If virologic failure is suspected or confirmed, a thorough assessment of whether one or more of the above listed factors could have been the cause(s) of failure is indicated. Often the causes of virologic failure can be identified, but in some cases, they are not obvious. It is important to distinguish among the causes of virologic failure because the approaches to subsequent therapy may differ. Potential causes of virologic failure should be explored in depth. Once virologic failure is confirmed, steps should be undertaken to improve virologic outcomes. Those approaches are outlined below.

Key Factors to Consider When Designing a New Antiretroviral Regimen
• Ideally, a new ARV regimen should contain at least two, and preferably three, fully active drugs whose predicted activity is based on the patient’s ART history, current and previous resistance testing, or a new mechanistic action (AI).
• Despite drug resistance, some ARV drugs may contribute partial ARV activity to a regimen and may be retained as part of a salvage regimen. These drugs may include nucleoside reverse transcriptase inhibitors (NRTIs) or protease inhibitors (PIs). Other agents will likely have to be discontinued, as their continued use may lead to further accumulation of resistance mutations and jeopardize treatment options with newer drugs from the same drug class. These drugs may include enfuvirtide (T20); non-nucleoside reverse transcriptase inhibitors (NNRTIs), especially efavirenz (EFV), nevirapine (NVP), and rilpivirine (RPV); and the first-generation integrase strands transfer inhibitors (INSTIs) raltegravir (RAL) or elvitegravir (EVG).
• Using a “new” drug that a patient has never used previously does not ensure that the drug will be fully active; there is a potential for cross-resistance among drugs from the same class.
• 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.
• Drug potency and viral susceptibility based on cumulative genotype data are more important factors to consider when constructing a salvage regimen than the number of component drugs.
• Resistance testing should be performed while the patient is still taking the failing regimen or within 4 weeks of regimen discontinuation if the patient’s plasma HIV RNA level is >1,000 copies/mL (A1), and possibly even if it is between 500 to 1,000 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). Drug resistance is cumulative; thus, evaluate the extent of drug resistance, taking into account prior ART history and, importantly, prior genotypic or phenotypic resistance-test results. Some assays only detect resistance to NRTIs, NNRTIs, or PIs, whereas INSTI-resistance testing may need to be ordered separately. INSTI-resistance testing should be ordered in patients who experience virologic failure on an INSTI-based regimen. Additional drug-resistance tests for patients experiencing failure on a fusion inhibitor (AII) and viral tropism tests for patients experiencing failure on a CCR5 antagonist (BIII) are also available (see Drug-Resistance Testing).
• Discontinuing or briefly interrupting therapy in a patient with overt or low-level viremia is not recommended, as it may lead to a rapid increase in HIV RNA and a decrease in CD4 T lymphocyte (CD4) cell count and increases the risk of clinical progression (A1). See Discontinuation or Interruption of Antiretroviral Therapy.

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

Antiretroviral Strategies
• In general, patients who receive at least three active drugs experience better and more sustained virologic response than those receiving fewer active drugs in the regimen. These three drugs should be selected based on the patient’s ART history and a review of their drug-resistance test results, both past and present.18,19,21,22,32,33
• Active drugs are ARVs that, based on current and previous resistance test results and ART history, are expected to have antiviral activity equivalent to that seen when there is no resistance to the specific drugs. ARVs with partial activity are those predicted to reduce HIV RNA, but to a lesser extent than when there is no underlying drug resistance.
• Active drugs may be newer members of existing drug classes that are active against HIV isolates that are resistant to older drugs in the same classes (e.g., etravirine [ETR], darunavir [DRV], and dolutegravir [DTG]).
• An active drug may also be one with a unique mechanism of action compared to prior therapy in that individual (e.g., the fusion inhibitor T20, the CCR5 antagonist maraviroc in patients with no detectable CXCR4-using virus, and some investigational ARV drugs).
• Increasing data in treatment-naive and treatment-experienced patients show that an active pharmacokinetically-enhanced PI plus one other active drug or plus several partially-active drugs will effectively reduce viral load in most patients.34-37
• In the presence of certain drug resistance mutations, some ARVs, such as DTG, ritonavir-boosted DRV (DRV/r), and ritonavir-boosted lopinavir (LPV/r), need to be given twice daily instead of once daily to achieve the higher drug concentrations necessary to be active against a less-sensitive virus.38,39
Addressing Patients with Different Levels of Viremia

Patients with detectable viral loads comprise a heterogenous group of individuals with different ART exposure history, extents of drug resistance, duration of virologic failure, and levels of plasma viremia. Management strategies should be individualized. The first steps for all patients with detectable viral loads are to confirm the level of HIV viremia and assess and address adherence and potential drug-drug interactions (including those with over-the-counter products and supplements) and drug-food interactions. Some general approaches based on level of viremia are addressed below.

- **HIV RNA above the LLOD and <200 copies/mL:** Patients who typically have these HIV RNA levels (i.e., blips) do not require a change in treatment (AII).4 Although there is no consensus on how to manage these patients, the risk of emerging resistance is believed to be relatively low. Therefore, these patients should maintain on their current regimens and have 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 <1,000 copies/mL:** In contrast to patients with detectable HIV RNA levels persistently <200 copies/mL, those with levels persistently ≥200 copies/mL often develop drug resistance, particularly when HIV RNA levels are >500 copies/mL.7,8 Persistent plasma HIV RNA levels in the 200 to 1,000 copies/mL range should be considered virologic failure, and resistance testing should be attempted, particularly with HIV RNA >500 copies/mL. Management approaches should be the same as for patients with HIV RNA >1,000 copies/mL (as outlined below). When resistance testing cannot be performed because of low RNA levels, the decision of whether to empirically change ARVs should be made on a case-by-case basis, taking into account whether a new regimen expected to fully suppress viremia can be constructed.

- **HIV RNA ≥1,000 copies/mL and no current or previous drug resistance identified:** This scenario is almost always associated with suboptimal adherence. Conduct a thorough assessment to determine the level of adherence, identify and address the underlying cause(s) for incomplete adherence and, if possible, simplify the regimen (e.g., decrease pill count, simplify food requirement or dosing frequency) (see Adherence to the Continuum of Care). Approaches include:
  - 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.
  - Address intolerance by symptomatic treatment (e.g., antiemetics, antidiarrheals), switch from one ARV in a regimen to another agent in the same drug class, or switch from one drug class to another class (e.g., from a NNRTI to a PI or an INSTI) (see Adverse Effects).
  - Review food requirement for each medication, and assess whether the patient adheres to the requirement.
  - Assess if there is a 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 and Tables 18a-18b for common interactions) and, if possible, make appropriate substitutions for ARV agents and/or concomitant medications.
  - Consider therapeutic drug monitoring 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).
  - Consider the timing of the drug-resistance test (e.g., was the patient mostly or completely ART-nonadherent for more than 4 weeks before testing?). If the current regimen is well tolerated and there are no significant drug-drug or drug-food interactions, it is reasonable to continue the same regimen. If the agents are poorly tolerated or there are important drug-drug or drug-food interactions, consider changing the regimen to an equally effective, more tolerable regimen. Two to four weeks...
after treatment is resumed or started, repeat viral load testing; if viral load remains >500 copies/mL, perform genotypic testing to determine whether a resistant viral strain has emerged (CIII).

- **HIV RNA >1,000 copies/mL and drug resistance identified:** If new or previously detected resistance mutations compromise the regimen, the regimen should be modified as soon as possible in order to avoid progressive accumulation of resistance mutations. In addition, several studies have shown that virologic responses to new and active regimens are greater in individuals with lower HIV RNA levels and/or higher CD4 cell counts at the time of regimen changes, thus the change is best done before worsening of viremia or decline in CD4 count. The availability of newer ARVs, including some with new mechanisms of action, makes it possible to suppress HIV RNA levels to below the LLOD in most of these patients. The options in this setting depend on the extent of drug resistance present and are addressed in the clinical scenarios outlined below.

### Managing Virologic Failure in Different Clinical Scenarios

See Table 10 for a summary of these recommendations.

### Virologic Failure with First Antiretroviral Regimen

- **NNRTI plus NRTI regimen:** Patients with virologic failure while on an NNRTI-based regimen often have viral resistance to the NNRTI, with or without the M184V/I mutation, which confers high-level resistance to lamivudine (3TC) and emtricitabine (FTC). Several studies have explored the efficacy of a pharmacokinetically boosted PI or an INSTI with at least one active NRTI, or of a boosted PI with an INSTI. Two studies found that regimens containing a ritonavir-boosted PI (PI/r) combined with at least one active NRTI were as active as regimens containing the PI/r combined with RAL. Two studies also demonstrated higher rates of virologic suppression with use of a PI/r plus at least one active NRTI than with a PI/r alone. Although LPV/r was the PI used in these studies, it is likely that other pharmacokinetically boosted PIs would have similar activities, but this has not been demonstrated in large clinical trials. On the basis of these studies, even patients with NRTI resistance can often be treated with a pharmacokinetically boosted PI plus at least one active NRTI or RAL (AIII). Although data are limited, the other INSTIs (i.e., EVG or DTG) combined with a pharmacokinetically boosted PI may also be options in this setting (AIII). In an interim analysis comparing DTG versus LPV/r, both administered with two NRTIs in patients who experienced virologic failure while receiving a first-line NNRTI regimen, the DTG arm was superior to the LPV/r arm (AII). Thus, an INSTI with two NRTIs is also an option after failure of first-line NNRTI-based therapy. If only one of the NRTIs is fully active or if adherence is a concern, DTG is preferred over EVG or RAL (AIII).

- **Pharmacokinetically boosted PI plus NRTI regimen:** In this scenario, most patients will have either no resistance or resistance limited to 3TC and FTC. Failure in this setting is often attributed to poor adherence, drug-drug interactions, or drug-food interactions. A systematic review of multiple randomized trials of PI/r first-line failure showed that maintaining the same regimen, with efforts to enhance adherence, is as effective as changing to new regimens with or without drugs from new classes (AII). If the regimen is well tolerated and there are no concerns regarding drug-drug or drug-food interactions or drug resistance, the regimen can be continued with adherence support and viral monitoring. Alternatively, if poor tolerability or drug interactions may be contributing to virologic failure, the regimen can be modified to include a different pharmacokinetically boosted PI plus either at least one active NRTI (AIII), or an INSTI (BIII). The regimen can also be switched to a new non-PI-based regimen that includes at least two fully active agents, such as an INSTI plus two NRTIs (AIII). As noted above, if only one of the NRTIs is fully active or if adherence is a concern, DTG is preferred over EVG or RAL (AIII).

- **INSTI plus NRTI regimen:** Virologic failure with a regimen consisting of RAL or EVG plus two NRTIs may be associated with emergent resistance to 3TC/FTC and possibly the INSTI. Viruses with EVG or RAL resistance often remain susceptible to DTG. In contrast, in clinical trials, persons who experienced
virologic failure while receiving DTG plus two NRTIs as first-line therapy were unlikely to develop
phenotypic resistance to DTG.49 There are no clinical trial data to guide therapy for first-line INSTI
failures, although one might extrapolate from the data for NNRTI-based failures. Thus, patients with
first-line INSTI plus NRTIs failure without INSTI resistance should respond to a pharmacokinetically
boosted PI plus two NRTIs (at least one active) (AIII), a pharmacokinetically boosted PI plus an INSTI
(BII), or DTG plus two NRTIs (at least one active) (AII). If the virus is found to have resistance to RAL
and EVG but remains susceptible to DTG, regimen options include a pharmacokinetically boosted PI
plus two NRTIs (at least one active) (AIII), twice-daily DTG plus two active NRTIs (AIII), or twice-
daily DTG plus a pharmacokinetically boosted PI (AIII). If no resistance is identified, the patient should
be managed as outlined above in the section on virologic failure without resistance.

Second-Line Regimen Failure and Beyond

• Drug resistance with fully active ART options: Depending on treatment history and drug-resistance
data, one can predict whether or not to include a fully active pharmacokinetically boosted PI in
future regimens. For example, those who have no documented PI resistance and previously have
never been treated with an unboosted PI likely harbor virus that is fully susceptible to PIs. In this
setting, viral suppression should be achievable using a pharmacokinetically boosted PI combined
with either two NRTIs or an INSTI—provided the virus is susceptible to these drugs. If a fully active
pharmacokinetically boosted PI is not an option, the new regimen should include at least two, and
preferably three, fully active agents. Drugs should be selected based on the likelihood that they will be
active, as determined by the patient’s treatment history, past and present drug-resistance testing, and
tropism testing if a CCR5 antagonist is being considered.

• Multidrug resistance without fully active ART options: Use of currently available ARVs has resulted
in a dramatic decline in the number of patients who have few treatment options because of multiclass
drug resistance.50,51 Despite this progress, there remain patients who have experienced toxicities and/or
developed resistance to all or most currently available drugs. If maximal virologic suppression cannot
be achieved, the goals of ART will be to preserve immunologic function, prevent clinical progression,
and minimize increasing resistance which may compromise future regimens. Consensus on the optimal
management of these patients is lacking. If resistance to NNRTIs, T20, DTG, EVG, or RAL are identified,
there is rarely a reason to continue these drugs, as there is little evidence that keeping them on the regimen
helps delay disease progression (BII). Moreover, continuing these drugs, in particular INSTIs, may allow
for increasing resistance and within-class cross resistance that may limit future treatment options. It should
be noted that even partial virologic suppression of HIV RNA to >0.5 log10 copies/mL from baseline
correlates with clinical benefit.50,52 Cohort studies provide evidence that continuing therapy, even in the
presence of viremia and the absence of CD4 cell count increases, reduces the risk of disease progression.53
Other cohort studies suggest continued immunologic and clinical benefits with even modest reductions
in HIV RNA levels.54,55 However, these potential benefits must be balanced with the ongoing risk of
accumulating additional resistance mutations. In general, adding a single fully active ARV to the regimen
is not recommended because of the risk of rapid development of resistance (BII).

Patients with ongoing detectable 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 to an investigational new drug as specified in Food and Drug Administration
regulations: http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm163982.htm. Information about two agents that are in late-stage clinical studies, ibalizumab
and fostemsavir, can be found at https://aidsinfo.nih.gov/drugs/511/ibalizumab/0/professional and https://aidsinfo.nih.gov/drugs/508/fostemsavir/0/professional.

• Previously treated patients with suspected drug resistance who present with limited information
(i.e., incomplete or no self-reported history, medical records, or resistance-testing results): Every
effort should be made to obtain the patient’s ARV history and prior drug-resistance testing results;

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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 predicted to be active on the basis of the patient’s treatment history. If there is no available ARV history, a clinician may consider using agents with high barrier to resistance, such as DTG and/or boosted DRV, as part of the regimen. HIV RNA and resistance testing should be obtained approximately 2 to 4 weeks after re-initiation of therapy and patients should be closely monitored for virologic responses.

Table 10. Antiretroviral Options for Patients with Virologic Failure  (page 1 of 2)

Designing a new regimen for patients with treatment failure should always be guided by results from current and past resistance testing and ARV history. This table summarizes the text above and displays the most common or likely clinical scenarios seen in patients with virologic failure. It is also crucial to provide continuous adherence support to all patients before and after regimen changes. For more detailed descriptions, please refer to the text above and/or consult an expert in drug resistance to assist in the design of a new regimen.

<table>
<thead>
<tr>
<th>Clinical Scenario</th>
<th>Type of Failing Regimen</th>
<th>Resistance Considerations</th>
<th>New Regimen Options1,2</th>
<th>Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>First Regimen Failure</td>
<td>NNRTI + 2 NRTIs</td>
<td>Most likely resistant to NNRTI +/- 3TC/FTC (i.e., NNRTI mutations +/- M184V/I, without resistance to other NRTIs)3</td>
<td>• Boosted PI + 2 NRTIs (at least 1 active) (AIII); or • INSTI + 2 NRTIs (if only 1 of the NRTIs is fully active, or if adherence is a concern, DTG is preferred over EVG or RAL) (AIII); or • Boosted PI + INSTI (AIII)</td>
<td>Resuppression</td>
</tr>
<tr>
<td></td>
<td>Boosted PI + 2 NRTIs</td>
<td>Most likely no resistance or resistance only to 3TC/FTC (i.e., M184V/I, without resistance to other NRTIs)3</td>
<td>• Continue same regimen (AII); or • Another boosted PI + 2 NRTIs (at least 1 active) (AII); or • INSTI + 2 NRTIs (at least 1 active) (if only 1 of the NRTIs is fully active, or if adherence is a concern, DTG is preferred over EVG or RAL) (AII); or • Boosted PI + INSTI (BII)</td>
<td>Resuppression</td>
</tr>
<tr>
<td></td>
<td>INSTI + 2 NRTIs</td>
<td>3TC/FTC (i.e., only M184V/I, without resistance to other NRTIs)3 No INSTI resistance</td>
<td>• Boosted PI + 2 NRTIs (at least 1 active) (AII); or • DTG + 2 NRTIs (at least 1 active) (AII); or • Boosted PI + INSTI (BII)</td>
<td>Resuppression</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Resistance to first-line DTG is rare</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>EVG or RAL +/- 3TC/FTC (i.e., INSTI mutations +/- M184V/I, without resistance to other NRTIs)3</td>
<td></td>
<td>Boosted PI + 2 NRTIs (at least 1 active) (AII); or DTG4 twice daily (if sensitive to DTG) + 2 active NRTIs (AII); or DTG4 twice daily (if sensitive to DTG) + a pharmacokinetically boosted PI (AII)</td>
<td>Resuppression</td>
</tr>
<tr>
<td>Second Regimen Failure and Beyond</td>
<td>Drug resistance with active treatment options</td>
<td>Use past and current genotypic +/- phenotypic resistance testing and ART history in designing new regimen</td>
<td>• At least 2, and preferably 3, fully active agents (AII) • Partially active drugs may be used if no other options are available • Consider using ARV with a different mechanism of action</td>
<td>Resuppression</td>
</tr>
</tbody>
</table>
**Isolated Central Nervous System Virologic Failure and Neurologic Symptoms**

Presentation with new-onset central nervous system (CNS) signs and symptoms has been reported as a rare form of “compartmentalized” virologic failure. These patients present with new, usually subacute, neurological symptoms associated with breakthrough of HIV infection within the CNS compartment despite plasma HIV RNA suppression.\(^{56-58}\) Clinical evaluation frequently shows abnormalities on magnetic resonance imaging (MRI) and abnormal cerebrospinal fluid (CSF) findings with characteristic lymphocytic pleocytosis.\(^{59}\) Measurement of CSF HIV RNA shows higher concentrations in the CSF than in plasma, and in most (though not all) patients, evidence of drug-resistant CSF virus. Drug-resistance testing of HIV in CSF can be used to guide changes in the treatment regimen according to principles outlined above for plasma HIV RNA resistance (CIII). In these patients it may also be useful to consider CNS pharmacokinetics in drug selection in order to assure adequate concentrations of drugs within the CNS (CIII). If CSF HIV resistance testing is not available, the regimen may be changed based on the patient’s treatment history or on predicted drug penetration into the CNS (CIII).\(^{60-63}\)

This “neurosymptomatic” CNS viral escape should be distinguished from: (1) incidental detection of asymptomatic mild CSF HIV RNA elevation that is usually transient with low levels of CSF HIV RNA, likely equivalent to plasma blips;\(^{54,65}\) or (2) transient increase in CSF HIV RNA related to other CNS

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infections that can induce a brief increase in CSF HIV RNA (e.g., herpes zoster). There does not appear to be an association between these asymptomatic CSF HIV RNA elevations and the relatively common chronic, usually mild, neurocognitive impairment in patients with HIV who show no evidence of CNS viral breakthrough. Unlike the “neurosymptomatic” CNS viral escape, these latter conditions do not currently warrant a change in ART.

Summary
The management of treatment-experienced patients with virologic failure often requires expert advice to construct virologically suppressive regimens. Before modifying a regimen, it is critical to carefully evaluate the cause(s) of virologic failure, including incomplete adherence, poor tolerability, and drug and food interactions, as well as review HIV RNA and CD4 cell count changes over time, complete treatment history, and current and previous drug-resistance test results. If HIV RNA suppression is not possible with currently approved agents, consider use of investigational agents through participation in 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.

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