

# Management of the Treatment-Experienced Patient

## Virologic Failure

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### Key Considerations and Recommendations

- Assessing and managing a patient who is experiencing antiretroviral therapy (ART) failure can be complex. Expert advice can be critical and should be sought in many instances.
- Evaluation of virologic failure should include an assessment of adherence, drug-drug and drug-food interactions, drug tolerability, HIV RNA level and CD4 T lymphocyte (CD4) cell count trends over time, ART history, and prior and current drug-resistance test results.
- 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)**. If more than 4 weeks have elapsed since ARV drugs were discontinued, resistance testing can still provide useful information to guide therapy, although it may not detect previously selected resistance mutations **(CIII)**.
- The goal of treatment for ART-experienced patients with drug resistance who are experiencing virologic failure is to establish suppression (i.e., HIV RNA levels below the lower limits of detection of currently used assays) **(AI)**.
- A new regimen can include two fully active ARV drugs if at least one with a high resistance barrier is included (e.g., dolutegravir or boosted darunavir) **(AI)**. If no fully active drug with a high resistance barrier is available, then every effort should be made to include three fully active drugs **(AI)**.
- In general, adding a single ARV agent to a virologically failing regimen **is not recommended**, because this would rarely result in full viral suppression and, therefore, may risk the development of resistance to all drugs in the regimen **(BII)**.
- 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 that are designed to minimize toxicity, preserve CD4 counts, and delay clinical progression.
- 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.
- In patients with virologic failure, it is crucial to provide continuous adherence support before and after ARV regimen changes.
- When switching an ARV regimen in a patient with hepatitis B virus (HBV)/HIV coinfection, ARV drugs that are active against HBV should be continued as part of the new regimen. Discontinuation of these drugs may lead to the reactivation of HBV, which may result in serious hepatocellular damage.
- Discontinuing or briefly interrupting therapy may lead to a rapid increase in HIV RNA, a decrease in CD4 count, and an increase in the risk of clinical progression. Therefore, this strategy **is not recommended** in the setting of virologic failure **(AI)**.

**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 that are currently recommended for initial therapy in patients with HIV have a high likelihood of achieving and maintaining plasma HIV RNA levels that are 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. Adherence to ARV regimens can be challenging for some patients, and poor adherence can result in detectable viral loads. Depending on their treatment histories, some of these patients may have minimal or no drug resistance, and 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  $\geq 200$  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:** After virologic suppression, confirmed HIV RNA level(s)  $\geq 200$  copies/mL.

**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 level <200 copies/mL.

## ***Antiretroviral Therapy 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 that are persistently suppressed below the LLOD of current assays.<sup>1</sup>

Virologic blips are not usually associated with subsequent virologic failure.<sup>2</sup> In contrast, there is controversy regarding the clinical implications of persistently low HIV RNA levels that are 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.<sup>3-5</sup> Several retrospective studies support the supposition that virologic failure is more likely to occur in patients with viral loads  $\geq 200$  copies/mL than in those with low-level viremia between 50 copies/mL and 199 copies/mL.<sup>6,7</sup> However, other studies have suggested that detectable viremia at this low level (<200 copies/mL) can be predictive of virologic failure<sup>8,9</sup> and can be associated with the evolution of drug resistance.<sup>10</sup>

Persistent HIV RNA levels  $\geq 200$  copies/mL are often associated with evidence of viral evolution and accumulation of drug-resistance mutations.<sup>11</sup> This association is particularly common when HIV RNA levels are >500 copies/mL.<sup>12</sup> Therefore, patients who have persistent HIV RNA levels  $\geq 200$  copies/mL are considered to be experiencing 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.<sup>13,14</sup> The presence of preexisting (transmitted) drug resistance also may lead to virologic failure.<sup>15</sup> Virologic failure may be associated with a variety of factors, including the following:

### **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 ARV drugs (i.e., these factors may affect the ability to access or continue therapy)
- Adverse drug 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 test results
- Prior treatment failure
- Innate resistance to prescribed ARV drugs
- Higher pretreatment HIV RNA level (some regimens may be less effective at higher levels)

### **Antiretroviral Regimen-Related Factors**

- Suboptimal pharmacokinetics (PKs) (e.g., variable absorption, metabolism, or penetration into reservoirs)
- Suboptimal virologic potency
- Low barrier to resistance
- Reduced efficacy due to prior exposure to suboptimal regimens (e.g., monotherapy, dual-nucleoside reverse transcriptase inhibitor [NRTI] therapy, or the sequential introduction of drugs)
- Food requirements
- Drug-drug interactions with concomitant medications, which may reduce concentrations of the ARV drugs
- Prescription (prescribing or dispensing) errors

### ***Managing Patients with Virologic Failure***

If virologic failure is suspected or confirmed, a thorough assessment of whether one or more of the above 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. Distinguishing among the causes of virologic failure is important, because the approaches to subsequent therapy may differ, depending on the cause. Potential causes of virologic failure should be explored in depth. Once virologic failure is confirmed, steps should be taken to improve virologic outcomes. These approaches are outlined below.

### **Key Factors to Consider When Designing a New Antiretroviral Regimen**

- When designing a new ARV regimen for a patient with virologic failure, the expected potency of the new agent(s) is critical in predicting virologic efficacy. A fully active drug is one that is expected to have uncompromised activity after considering the patient's ART history and current and previous resistance test results, and whether an ARV drug with a new mechanistic action is available.<sup>8,16-25</sup>
- A new ARV regimen can include two fully active drugs if at least one has a high resistance barrier, such as the second-generation integrase strand transfer inhibitor (INSTI) dolutegravir (DTG) or the boosted-protease inhibitor (PI) darunavir (DRV) (AI). Bicitgravir (BIC), which is available only in a combination pill with emtricitabine/tenofovir alafenamide (FTC/TAF), also has a high resistance barrier; however, no data exist on its efficacy in this setting. If one of these drugs is fully active, they can be combined with two NRTIs if at least one is also fully active. Alternatively, if both the second-generation INSTI and boosted PI are fully active, they can be used in combination and be highly effective in those with virologic failure, without NRTIs. If no fully active drug with a high resistance barrier is available, then every effort should be made to include three fully active drugs in the regimen (AI). See the clinical scenarios below for further guidance on the number of fully active drugs a regimen should contain.
- Despite the presence of some drug-resistance mutations, some ARV drugs in the regimen may still have

partial activity against the patient's HIV and may be retained as part of a salvage regimen. These drugs may include NRTIs, PIs, and second-generation INSTIs, although dosing of some drugs (e.g., DRV and DTG) may need to be increased when treating patients with relevant resistance mutations. Other agents will likely have to be discontinued, because their continued use is unlikely to contribute to viral suppression and/or may lead to further accumulation of resistance mutations that would jeopardize future treatment options with newer drugs from the same drug class. These drugs may include non-nucleoside reverse transcriptase inhibitors (NNRTIs), especially efavirenz, nevirapine, and rilpivirine; the first-generation INSTIs raltegravir (RAL) and elvitegravir (EVG); and enfuvirtide (T-20).<sup>26-28</sup>

- Using a drug that a patient has never used does not ensure that the drug will be fully active; the potential exists 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.
- 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 (**AI**), and possibly even if it is between 500 copies/mL and 1,000 copies/mL (**BII**) (see [Drug-Resistance Testing](#)). Resistance testing should still be considered even after treatment interruptions of >4 weeks, although clinicians should recognize 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, meaning that once a mutation is detected in a resistance assay, it should be considered present in that patient's HIV thereafter, regardless of whether it appears on subsequent resistance assays; thus, clinicians should evaluate the extent of drug resistance, taking into account a patient's ART history and, importantly, prior genotypic or phenotypic resistance test results. Some assays only detect resistance to NRTIs, NNRTIs, or PIs; 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 who experience failure on a fusion inhibitor (**AII**) and viral tropism tests for patients who experience failure on a CCR5 antagonist (**BIII**) are also available. **There is currently no commercially available resistance test for the CD4 T lymphocyte (CD4) post-attachment inhibitor ibalizumab (IBA) or the gp120-attachment inhibitor fostemsavir (FTR)** (see [Drug-Resistance Testing](#)).
- Discontinuing or briefly interrupting therapy in a patient with overt or low-level viremia **is not recommended**, because it may lead to a rapid increase in HIV RNA and a decrease in CD4 T lymphocyte (CD4) cell count, and it increases the risk of clinical progression (**AI**)<sup>29,30</sup> (see [Discontinuation or Interruption of Antiretroviral Therapy](#)).
- When changing an ARV regimen in a patient with hepatitis B virus (HBV)/HIV coinfection, ARV drugs that are active against HBV should be continued as part of the new regimen. Discontinuation of these drugs may lead to the reactivation of HBV, which may result in serious hepatocellular damage (see [Hepatitis B \(HBV\)/HIV Coinfection](#)).

### The Use of Integrase Strand Transfer Inhibitors in Persons of Childbearing Potential

Because preliminary data from a birth outcome surveillance study in Botswana raised concern that DTG use around the time of conception may be associated with an increased risk of infant neural tube defects (NTDs),<sup>31</sup> the Panel previously recommended DTG as an *alternative* ARV drug in individuals of childbearing potential who are trying to conceive or who are sexually active and not using effective contraception. Additional results from the same study have shown that the prevalence of infant NTDs in association with DTG exposure at conception is substantially lower than in the preliminary data,<sup>32</sup> but still higher than with non-DTG containing regimens; however, the difference was not statistically significant. Based on these newer data, the Panel now considers DTG a *recommended* option for persons of childbearing potential. Before initiating a DTG-based

regimen, clinicians should discuss the risks and benefits of using DTG with persons of childbearing potential to allow them make an informed decision. Clinicians should refer to the [Perinatal Guidelines](#) for more detailed recommendations on the safety and effectiveness of ARV drugs during conception and throughout pregnancy.

## Antiretroviral Drug Strategies

- In general, ART-experienced patients who receive at least two fully active agents, at least one of which has a high resistance barrier, or three fully active drugs experience better and more sustained virologic response than those who receive fewer fully active drugs. Drugs should be selected based on the patient's ART history and a review of their drug-resistance test results, both past and present.<sup>17, 18, 20, 21, 33-35</sup> See the clinical scenarios below for further guidance on the number of fully active drugs a regimen should contain.
- If a high resistance barrier, second-generation INSTI (e.g., DTG or possibly BIC), or boosted PI (e.g., DRV) is expected to be fully active, one of these can be combined with two NRTIs if at least one also is fully active (AI). Alternatively, if both the second-generation INSTI and boosted PI are fully active, studies have found that these two drugs in combination can result in high levels of viral suppression in those with virologic failure (AI).<sup>36-40</sup>
- A fully active ARV is one that, based on current and previous resistance test results and ART history, is expected to have antiviral activity equivalent to that seen when there is no resistance to the specific drug. ARV drugs with partial activity are those predicted to have antiviral activity but to a lesser extent than when there is no underlying drug resistance.
- Fully active drugs may be newer members of existing drug classes that are fully active against HIV isolates that are resistant to older drugs in the same classes, such as etravirine, DRV, DTG, and possibly doravirine (DOR) and BIC. Clinical data supporting the use of DOR or BIC are limited, and close monitoring of HIV RNA is advised if these drugs are used as part of a new regimen.
- A fully active drug may also be one with a mechanism of action that differs from the mechanisms of the ARV drugs that were previously used in that individual, such as the fusion inhibitor T-20, the CCR5 antagonist maraviroc (MVC) in patients with no detectable CXCR4-using virus, the post-attachment inhibitor IBA, the gp120-attachment inhibitor FTR, and other investigational ARV drugs with new mechanisms of action.
- An increasing number of studies in ART-naïve and early stage ART-experienced patients have shown that a fully active, PK-enhanced PI plus one other fully active drug or several partially active drugs will effectively reduce viral load in most patients.<sup>37, 39, 41, 42</sup>
- In the presence of certain resistance mutations, some ARV drugs, such as DTG, DRV/r, and lopinavir/ritonavir (LPV/r), need to be given twice daily instead of once daily to achieve the higher drug concentrations necessary to be fully active against a less-sensitive virus.<sup>43-45</sup>

## Addressing Patients with Different Levels of Viremia

Patients with detectable viral loads comprise a heterogeneous group of individuals with different ART exposure histories, degrees of drug resistance, durations 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 interactions 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 have these HIV RNA levels do not typically require a change in treatment (AII).<sup>4</sup> Although there is no consensus on how to manage these patients, the risk that resistance will emerge is believed to be relatively low. Therefore, these patients should continue their current regimens and have HIV RNA levels monitored at least every 3 months to assess the need for changes to ART in the future (AIII).

- HIV RNA Levels  $\geq 200$  copies/mL and  $< 1,000$  copies/mL:** In contrast to patients with detectable HIV RNA levels that are persistently  $< 200$  copies/mL, those with levels that are persistently  $\geq 200$  copies/mL often develop drug resistance, particularly when HIV RNA levels are  $> 500$  copies/mL.<sup>6,7</sup> Patients who have persistent plasma HIV RNA levels in the range of 200 copies/mL to 1,000 copies/mL are considered to be experiencing virologic failure, and resistance testing should be attempted, particularly in patients with HIV RNA levels  $> 500$  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 HIV RNA levels, the decision of whether to empirically change ARV drugs should be made on a case-by-case basis, taking into account whether a new regimen that is expected to fully suppress viremia can be constructed. **If genotypic resistance test results cannot be obtained because of low HIV RNA levels, proviral DNA genotypic testing may be considered. Results from this test should be interpreted with caution because these assays might miss some or all previously existing drug-resistance mutations. However, mutations that are detected using proviral DNA genotypic testing may be significant and can affect the effectiveness of future regimens (see [Drug-Resistance Testing](#)).**
- HIV RNA  $\geq 1,000$  copies/mL and No Drug Resistance Mutations Identified Using Current or Previous Genotypic Resistance Test Results:** This scenario is almost always associated with suboptimal adherence. A thorough assessment should be conducted 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:

  - Assessing the patient's access to ART, including access to pharmacy, refills, and copays or patient assistance programs, and seeking assistance to overcome any barriers to consistent access to ART.**
  - Assessing 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.
  - Addressing intolerance by treating symptoms (e.g., with antiemetics or antidiarrheals), switching one ARV agent in a regimen to another agent in the same drug class, or switching from one drug class to another class (e.g., from a NNRTI to a PI or an INSTI; see [Adverse Effects of Antiretroviral Agents](#)).
  - Reviewing food requirements for each medication and assessing whether the patient adheres to the requirements.
  - Assessing whether there is a recent history of gastrointestinal symptoms (e.g., vomiting, diarrhea) may result in short-term malabsorption.
  - Reviewing concomitant medications and dietary supplements for possible adverse drug-drug interactions (consult [Drug-Drug Interactions](#) and Tables [24a](#) through [25b](#) for common interactions) and, if possible, making appropriate substitutions for ARV agents and/or concomitant medications.
  - Considering therapeutic drug monitoring if PK drug-drug interactions or impaired drug absorption leading to decreased ARV drug exposure is suspected.
  - Considering the timing of the drug-resistance test (e.g., was the patient mostly or completely ART-nonadherent for  $> 4$  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 have important drug-drug or drug-food interactions, changing the regimen to an equally effective but more tolerable regimen should be considered.
    - Viral load testing 2 to 4 weeks after treatment is resumed or started should be repeated; if viral load remains  $> 500$  copies/mL, genotypic testing to determine whether a resistant viral strain has emerged should be performed (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.<sup>46</sup> In addition, several studies have shown that virologic responses to new and fully active regimens are greater in individuals with lower HIV RNA levels and/or higher CD4 counts at the time of regimen changes; thus, the change is best done before viremia worsens or CD4 count declines.<sup>8,47</sup> The availability of newer ARV drugs, 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 and are addressed in the clinical scenarios outlined below.

## ***Managing Virologic Failure in Different Clinical Scenarios***

See Table 11 below for a summary of these recommendations.

### **Virologic Failure with First Antiretroviral Regimen**

**NNRTI plus NRTI Regimen Failure:** These patients often have viral resistance to the NNRTI, with or without the M184V/I mutation, which confers high-level resistance to lamivudine (3TC) and FTC. Additional NRTI mutations may also be present. Below are some switch options.

- **DTG plus One or Two Fully Active NRTIs:** In the DAWNING trial, patients who experienced virologic failure while on a first-line, NNRTI-based regimen were randomized to receive either LPV/r or DTG; each of these drugs was given with two NRTIs, one of which had to be fully active based on real-time resistance testing. The study was stopped early after an interim analysis showed that the DTG arm was superior to the LPV/r arm.<sup>48</sup> Thus, DTG plus two NRTIs (at least one of which is fully active) can be an option after failure of a first-line, NNRTI-based therapy (**AI**). BIC may have activity that is similar to that of DTG in this setting; however, no data currently support its use. Not enough data exist on the efficacy of EVG or RAL to recommend the use of these INSTIs in the setting of first-line, NNRTI-based therapy failure.
- **Boosted PI plus Two NRTIs:** Three large randomized controlled trials (primarily conducted in resource-limited settings where NNRTI-based regimens have been used as first-line therapy) have explored different second-line regimen options. The studies found that regimens that contained LPV/r plus two NRTIs were as effective as regimens that contained LPV/r plus RAL. However, LPV/r alone, and probably other ritonavir-boosted PIs (PI/r) as monotherapy, **cannot be recommended (AI)**.<sup>37, 39, 40, 49</sup> Participants in some of these studies did not undergo resistance testing before randomization. Thus, based on these data and those of the prior section, the Panel recommends that a boosted PI plus two NRTIs can be an option after failure of a first-line NNRTI-based regimen in settings with no access to second-generation INSTIs or to genotypic resistance testing (**AI**). However, in settings where second-generation INSTIs are not available but genotypic resistance tests can be conducted, the Panel favors using a boosted PI plus two NRTIs with at least one being fully active (**AIII**). Even though LPV/r was the PI used in these studies, other boosted PIs (e.g., DRV) would likely have similar activities and may be better tolerated.
- **Boosted PI plus an INSTI:** As noted earlier, a regimen that consisted of LPV/r plus RAL was found to be as effective as LPV/r plus two NRTIs.<sup>37, 39, 40</sup> Thus, LPV/r plus RAL can also be a treatment option for those who experienced virologic failure on an NNRTI-based regimen (**AI**). Although data are limited, another boosted PI (e.g., DRV) combined with RAL or an alternative INSTI (e.g., DTG) may also be an option in this setting (**AIII**). BIC (which is only available in a combination pill with FTC/TAF) combined with a boosted PI in the setting of first-line, NNRTI-based therapy failure may have activity that is similar to DTG; however, there are currently no data to support its use in this situation.

**Boosted PI plus NRTI Regimen Failure:** In this scenario, most patients will have either no resistance or resistance that is limited to 3TC and FTC.<sup>50, 51</sup> Failure in this setting is often attributed to poor adherence, drug-drug interactions, or drug-food interactions. Below are some management options.

- **Maintain on the Same Regimen:** A systematic review of multiple randomized trials that investigated the failures of first-line, PI/r-based regimens showed that maintaining the same regimen while making efforts to enhance adherence is as effective as changing to new regimens with or without drugs from new classes (AII).<sup>52</sup> If the regimen is well tolerated and there are no concerns about drug-drug or drug-food interactions or drug resistance, then the regimen can be continued with adherence support and viral monitoring.
- **Switch to Another Regimen:** If poor tolerability, drug interactions, or drug resistance may be contributing to virologic failure, then the regimen can be modified to:
  - A different boosted PI plus two NRTIs (at least one of which is active) (AIII); *or*
  - DTG, or possibly BIC plus two NRTIs (at least one of which is fully active) (AIII). As noted above, if only one of the NRTIs is fully active or if adherence is a concern, DTG is currently preferred over BIC (AIII). There are limited to no data on the efficacy of BIC or EVG in this setting. **However, considering the high resistance barrier of BIC, it might also be considered a viable option in this setting, despite limited supportive data; or**
  - A different boosted PI (with no evidence for cross-resistance) plus an INSTI (AIII).

**INSTI plus NRTI Regimen Failure:** Virologic failure in patients on a regimen that consists of RAL or EVG plus two NRTIs may be associated with emergent resistance to 3TC or FTC and, possibly, the INSTI.<sup>53</sup> Viruses with EVG or RAL resistance often remain susceptible to DTG and BIC.<sup>47</sup> In contrast, in clinical trials, persons who experienced virologic failure while receiving DTG or BIC plus two NRTIs as first-line therapy were unlikely to develop resistance to DTG or BIC.<sup>53-55</sup> No existing clinical trial data guide therapy for first-line INSTI failures; therefore, treatment strategy should be based on resistance test results and the potential potency of the next regimen. Below are some treatment options, based on resistance pattern considerations.

- **Virologic Failure without Any Resistance Mutations:** The patient should be managed as outlined above in the section on virologic failure without resistance.
- **Virologic Failure without INSTI Resistance:** The regimen can be modified to
  - A boosted PI plus two NRTIs (at least one of which is active) (AIII); *or*
  - A boosted PI plus an INSTI (AIII); *or*
  - DTG plus two NRTIs (at least one of which is active) (AIII).
- **Virologic Failure with Resistance to RAL and EVG but Susceptibility to DTG:** The regimen can be modified to one of the following:
  - A boosted PI plus two NRTIs (at least one of which is fully active) (AIII); *or*
  - DTG, (twice daily) or possibly BIC plus two NRTIs (at least one of which is fully active) (BIII); *or*
  - DTG, (twice daily) or possibly BIC plus a boosted PI (AIII).

Currently no data exist on the efficacy of BIC in patients who experience virologic failure while on an EVG- or RAL-based regimen. **Considering the high resistance barrier of BIC, it might be considered a viable option,** although its use cannot be formally recommended in these settings currently.

## Second-Line Regimen Failure and Beyond

### Drug Resistance with Fully Active Antiretroviral Therapy Options

Using a patient's treatment history and drug-resistance data, a clinician can decide whether to include a fully active, boosted PI or INSTI in future regimens. For example, those who have no documented PI resistance and who have never been treated with an unboosted PI likely harbor virus that is fully susceptible to PIs. **Similarly, patients who have no documented INSTI resistance and who have never been treated with an INSTI, or even those who have been treated with only RAL or EVG, may have virus susceptible to DTG or BIC.** In this setting, viral suppression should be achievable using a boosted PI combined with either



two NRTIs (at least one of which is fully active), a boosted PI combined with an INSTI, or DTG or BIC combined with two NRTIs (at least one of which is fully active)—provided the virus is susceptible to these drugs. If a fully active, boosted PI or DTG or BIC 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 fully 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 Antiretroviral Therapy Options**

Use of currently available ARV drugs has resulted in a dramatic decline in the number of patients who have few treatment options because of multiclass drug resistance.<sup>56, 57</sup> Despite this progress, some patients remain who have experienced toxicities with and/or developed resistance to most currently available drugs. Maximal virologic suppression should remain the goal; however, if it cannot be achieved, the goals of ART will be to preserve immunologic function, prevent clinical progression, and minimize the development of further resistance that may compromise future regimens.

Consensus on the optimal management of these patients is lacking. If resistance to NNRTIs, T-20, MVC, BIC, DTG, EVG, or RAL are identified, there is rarely a reason to continue using these drugs, because there is little evidence that keeping them in the regimen helps delay disease progression (BII). Moreover, continuing these drugs (in particular, early-generation INSTIs) may allow selection of additional resistance mutations and development of within-class cross-resistance that may limit future treatment options. It should be noted that even partial virologic suppression of HIV RNA to  $>0.5 \log_{10}$  copies/mL from baseline correlates with clinical benefit.<sup>56, 58</sup> Cohort studies provide evidence that continuing ART even in the presence of viremia and the absence of CD4 count increases reduces the risk of disease progression.<sup>59</sup> Other cohort studies suggest that even modest reductions in HIV RNA levels continue to confer immunologic and clinical benefits.<sup>60, 61</sup> However, these potential benefits must be balanced with the ongoing risk of accumulating additional resistance mutations. In general, adding a single, fully active ARV drug 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 the first-in-class CD4 post-attachment inhibitor IBA<sup>62</sup> and/or the gp120-directed attachment inhibitor FTR.

- IBA: A single-arm, multicenter clinical trial enrolled 40 heavily ART-experienced participants who had multidrug-resistant HIV-1 and who were experiencing virologic failure on an ARV regimen. Subjects received intravenous infusions of IBA every 2 weeks, in addition to an optimized background regimen that included at least one additional agent to which the subject’s virus was susceptible. At Week 24, 43% of participants achieved HIV RNA  $<50$  copies/mL, and 50% of participants achieved HIV RNA  $<200$  copies/mL.<sup>63</sup> Of the 27 participants who continued to the 48-week follow-up study, 59% and 63% had HIV RNA  $<50$  copies/mL and  $<200$  copies/mL, respectively. All 15 patients who had HIV RNA  $<50$  copies/mL at Week 24 maintained viral suppression up to Week 48.<sup>64</sup>
- FTR: A Phase 3 multicenter trial enrolled 371 heavily ART-experienced participants who had multidrug-resistant HIV-1 and who were experiencing virologic failure. Participants were enrolled into two cohorts, according to their remaining treatment options. The randomized cohort (n = 272) included those with at least one fully active, approved ARV drug in at least one but no more than two classes. These individuals were randomized to FTR (oral 600 mg twice daily) or placebo for 8 days, followed by open-label FTR plus optimized background ART. In the non-randomized cohort (n = 99), participants with no remaining ARV options were started on open-label FTR (oral 600 mg twice daily) plus optimized background ART on Day 1. The primary endpoint for the randomized cohort was change in viral load from baseline at Day 8. In the FTR group, the mean viral load decrease was  $0.79 \log_{10}$  copies/mL versus  $0.17 \log_{10}$  copies/mL in the placebo group (P < 0.001). At Week 96, 60% of participants in the randomized cohort and 37%

of those in the non-randomized cohort had viral load <40 copies/mL, with mean CD4 increases of 205 cells/mm<sup>3</sup> and 119 cells/mm<sup>3</sup>, respectively.<sup>65,66</sup> In this study, 15 individuals in the non-randomized cohort used the CD4 post-attachment inhibitor IBA in combination with FTR and other ARVs. The virological response rate for these participants by snapshot analysis was 53% at Week 48 and 33% at Week 96.

Patients who continue to have detectable viremia and who lack sufficient treatment options to construct a fully suppressive regimen may also be candidates for research studies or expanded access programs, or they may qualify for single-patient access to an investigational new drug as specified in the [Food and Drug Administration regulations](#). Information about agents that are in clinical studies (e.g., [lenacapavir](#), [leronimab](#), [islatravir](#)) can be found in the [drug fact sheets](#) available on the [HIVinfo](#) website.

#### **Antiretroviral Therapy-Experienced Patients with Suspected Drug Resistance Who Present with Limited Information (Incomplete or No Self-Reported History, Medical Records, or Resistance Test Results)**

Every effort should be made to obtain the patient’s ARV history and prior drug-resistance test 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 the selection of the next regimen. Another strategy is to start two or three drugs that are predicted to be fully active based on the patient’s treatment history. If no ARV history is available, a clinician may consider using agents with a high barrier to resistance—such as twice-daily DTG, BIC (which is available only in a combination pill with FTC/TAF), and/or boosted DRV—as part of the regimen. Patients should be closely monitored for virologic responses, e.g., HIV viral load testing approximately 2 to 4 weeks after re-initiation of therapy with prompt drug-resistance testing performed if virologic response is inadequate.

#### ***Summary***

The goal of treatment for ART-experienced patients with virologic failure is to establish virologic suppression. The management of ART-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 potential cause(s) of virologic failure, including incomplete adherence, poor tolerability, and drug-drug and drug-food interactions, as well as to review HIV RNA and CD4 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 the 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 counts to delay clinical progression.

**Table 11. Antiretroviral Options for Patients with Virologic Failure (Last updated June 3, 2021; last reviewed June 3, 2021)** (page 1 of 2)

Designing a new regimen for patients who are experiencing treatment failure should always be guided by ARV history and results from current and past resistance testing. This table summarizes the text above and displays the most common or likely clinical scenarios seen in patients with virologic failure. 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. It is also crucial to provide continuous adherence support to all patients before and

Clinical Scenario	Type of Failing Regimen	Resistance Considerations	New Regimen Options <sup>a,b</sup>	Goal
First Regimen Failure	NNRTI plus two NRTIs	Most likely resistant to NNRTI +/- 3TC or FTC (i.e., NNRTI mutations +/- M184V/I). <sup>c</sup> Additional NRTI mutations may also be present.	DTG <sup>d</sup> (or possibly BIC) plus two NRTIs (at least one active) <b>(AI)</b> ; or Boosted PI plus two NRTIs (at least one active) <b>(AIII)</b> ; or Boosted PI plus INSTI <sup>e</sup>	Resuppression
	Boosted PI plus two NRTIs	Most likely no resistance, or resistance only to 3TC or FTC (i.e., M184V/I, without resistance to other NRTIs) <sup>c</sup>	Continue same regimen <b>(AII)</b> ; or Another boosted PI plus two NRTIs (at least one active) <b>(AIII)</b> ; or DTG, or possibly BIC, plus two NRTIs (at least one fully active; if only one of the NRTIs is fully active or if adherence is a concern, DTG <sup>d</sup> is currently preferred over other INSTIs) <b>(AIII)</b> ; or Another boosted PI plus INSTI <b>(AIII)</b>	Resuppression
	INSTI plus two NRTIs	No INSTI resistance (can have 3TC or FTC resistance, i.e., only M184V/I, usually without resistance to other NRTIs) <sup>c</sup>	Boosted PI plus two NRTIs (at least one fully active) <b>(AIII)</b> ; or DTG <sup>d</sup> , or possibly BIC, plus two NRTIs (at least one fully active) <b>(AIII)</b> ; or Boosted PI plus INSTI <b>(AIII)</b>	Resuppression
		EVG or RAL +/- 3TC or FTC resistance but susceptible to DTG	Boosted PI plus two NRTIs (at least one fully active) <b>(AIII)</b> ; or DTG <sup>d,f</sup> , twice daily or possibly BIC (if HIV is sensitive) plus two fully active NRTIs <b>(BIII)</b> ; or DTG <sup>d,e</sup> twice daily or possibly BIC (if HIV is sensitive) plus a boosted PI <b>(AIII)</b>	Resuppression

**Table 11. Antiretroviral Options for Patients with Virologic Failure, (Last updated June 3, 2021; last reviewed June 3, 2021)** (page 2 of 2)

<b>Second Regimen Failure and Beyond</b>	Drug resistance with fully active treatment options	Use past and current genotypic +/- phenotypic resistance testing and ART history when designing new regimen.	<p>Boosted PI, DTG, or BIC with two NRTIs (at least one fully active);</p> <p>Boosted PI with INSTI; <i>or</i></p> <p>DTG or BIC with two NRTIs (at least one fully active)</p> <p>Partially active drugs may be used when no other options are available.</p> <p>Consider using an ARV drug with a different mechanism of action.</p>	Resuppression
<b>Clinical Scenario</b>	<b>Type of Failing Regimen</b>	<b>Resistance Considerations</b>	<b>New Regimen Options<sup>a,b</sup></b>	<b>Goal</b>
<b>Second Regimen Failure and Beyond, continued</b>	Multiple or extensive drug resistance with few treatment options	<p>Use past and current genotypic and phenotypic resistance testing to guide therapy.</p> <p>Confirm with a viral tropism assay when use of MVC is considered.</p> <p>Consult an expert in drug resistance, if needed.</p>	<p>Identify as many fully active or partially active drugs as possible, based on resistance test results.</p> <p>Consider using an ARV drug with a different mechanism of action (e.g., IBA or FTR).</p> <p>Consider enrollment into clinical trials or expanded access programs for investigational agents, if available.</p> <p><b>Discontinuation of all ARV drugs is not recommended.</b></p>	Resuppression, if possible; otherwise, keeping viral load as low as possible and CD4 count as high as possible.
<b>ART-Experienced Patients with Suspected Drug Resistance and Limited or Incomplete ARV and Resistance History</b>	Unknown	<p>Obtain medical records, if possible.</p> <p>Resistance testing may be helpful in identifying drug resistance mutations, even if the patient has been off ART. Keep in mind that resistance mutations may not be detected in the absence of drug pressure.</p>	<p>Consider restarting the old regimen with careful monitoring of virologic response and early resistance testing, if inadequate virologic suppression.</p> <p>If no ARV history is available, consider initiating a regimen with drugs with high genetic barriers to resistance (e.g., DTG<sup>d,e</sup>, BIC, and/or boosted DRV) with careful monitoring of virologic response and early resistance testing, if inadequate virologic suppression.</p>	Resuppression

<sup>a</sup> Data are insufficient to provide a recommendation for the continuation of 3TC or FTC in the presence of M184V/I.

<sup>b</sup> When switching an ARV regimen in a patient with HBV/HIV coinfection, ARV drugs that are active against HBV should be continued as part of the new regimen. Discontinuation of these drugs may lead to the reactivation of HBV, which may result in serious hepatocellular damage.

<sup>c</sup> If other NRTI-resistance mutations are present, use resistance test results to guide NRTI usage in the new regimen.

<sup>d</sup> Based on newer data on DTG and risk of neural tube defects outlined in the text, clinicians should discuss with patients the risks and benefits of using DTG to allow them to make an informed decision.

<sup>e</sup> AI for LPV/r + RAL; AIII for other boosted PI (e.g., DRV) or INSTI (e.g., DTG).

<sup>f</sup> Response to DTG depends on the type and number of INSTI mutations.

**Key:** 3TC = lamivudine; ART = antiretroviral therapy; ARV = antiretroviral; BIC = bicitegravir; CD4 = CD4 T lymphocyte; DRV = darunavir; DTG = dolutegravir; EVG = elvitegravir; FTC = emtricitabine; FTR = fostemsavir; HBV = hepatitis B virus; IBA = ibalizumab; INSTI = integrase strand transfer inhibitor; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NTD = neural tube defect; PI = protease inhibitor; RAL = raltegravir

## ***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 that are associated with breakthrough of HIV infection within the CNS compartment despite plasma HIV RNA suppression.<sup>67-69</sup> Clinical evaluation frequently shows abnormalities on magnetic resonance imaging and abnormal cerebrospinal fluid (CSF) findings with characteristic lymphocytic pleocytosis.<sup>70</sup> Measurement of CSF HIV RNA shows higher concentrations in the CSF than in plasma, and in most (though not all) patients, drug-resistant CSF virus is evident. Drug-resistance testing of HIV in CSF can be used to guide changes in the treatment regimen, according to the principles outlined above for plasma HIV RNA resistance (**CIII**). In these patients, it may also be useful to consider CNS PKs during drug selection 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**).<sup>71-74</sup>

This “neurosymptomatic” CNS viral escape should be distinguished from—

- The incidental detection of asymptomatic and mild CSF HIV RNA elevation, which is similar to plasma blips in that it is usually transient with low levels of CSF HIV RNA;<sup>75, 76</sup> *or*
- A transient increase in CSF HIV RNA that is related to other CNS infections that can induce a brief increase in CSF HIV RNA (e.g., herpes zoster).<sup>77</sup>

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.<sup>78</sup> Unlike the “neurosymptomatic” CNS viral escape, these latter conditions do not currently warrant a change in ART.<sup>79</sup>

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