

Management of the Treatment-Experienced Patient

Virologic Failure

Updated: September 21, 2022

Reviewed: September 21, 2022

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 ART 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 of **a non–long-acting ARV regimen (AII)**. If more than 4 weeks have elapsed since **non–long-acting ARV regimens were discontinued**, resistance testing still can provide useful information to guide therapy, although it may not detect previously selected resistance mutations.
- 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 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 drug 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 rare 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 maintain CD4 counts, preserve treatment options, delay clinical progression, and minimize toxicity.
- 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, the patient should remain on an ARV agent that is active against HBV and has a high resistance barrier to HBV in order to avoid HBV rebound and 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 = **Weak**

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 ARV 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 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 that 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 ≥ 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 cannot 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.¹

Virologic blips are not usually associated with subsequent virologic failure.² In contrast, there is controversy regarding the clinical implications of low-level viremia, i.e., persistent 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 Several retrospective studies support the supposition that virologic failure is more likely to occur in patients with viral load ≥ 200 copies/mL than in those with low-level viremia between 50 copies/mL and 199 copies/mL.^{6,7}

However, other studies have suggested that detectable viremia at this level (<200 copies/mL) can be predictive of virologic failure^{8,9} and can be associated with the evolution of drug resistance.¹⁰

Persistent HIV-RNA level ≥ 200 copies/mL is often associated with evidence of viral evolution and accumulation of drug-resistance mutations.¹¹ This association is particularly common when HIV-RNA level is >500 copies/mL.¹² Therefore, patients who have persistent HIV-RNA level ≥ 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.^{13,14} The presence of preexisting (transmitted) drug resistance also may lead to virologic failure.¹⁵ 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 use, 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., factors that 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 **that may or may not be** documented by current or past drug-resistance test results
- Prior ARV treatment failure
- Innate drug resistance to prescribed ARV drugs
- Higher pre-treatment 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. Approaches to designing a new ARV regimen are outlined below.

Key Factors to Consider When Designing an Antiretroviral Regimen After Virologic Failure

General Principles on Antiretroviral Use in Virologic Failure

- When designing a new ARV regimen for a patient with virologic failure, it is important to consider the factors outlined above on causes of virologic failure (including medication potency) and, if possible, consider well-tolerated and adherence-friendly regimens.
- A new regimen should be selected based on the patient’s ART history, a review of their current and previous drug-resistance test results, and whether a fully susceptible ARV drug with high barrier to resistance and **other fully active drugs** are available.^{8,16-28}
- **ARV agents with high barrier to resistance are those in which emergent resistance is uncommon in patients experiencing virologic failure, and these include boosted darunavir (DRV), dolutegravir (DTG), and bicitgravir (BIC).**
- Fully active drugs may include—
 - Drugs in classes for which the patient has not previously selected for drug-resistant virus.
 - Newer members of existing drug classes—which despite the presence of resistant mutations to some drugs in that class are predicted to be fully active against HIV isolates—such as the non-nucleoside reverse transcriptase inhibitors (NNRTIs) etravirine and possibly doravirine (DOR), the protease inhibitor DRV, and the integrase strand transfer inhibitors (INSTIs) DTG and BIC. However, clinical data supporting the use of DOR or BIC in the setting of virologic failure are limited.
 - Drugs with novel mechanisms of action which the patient has not received before, such as the post-attachment inhibitor ibalizumab (IBA), the gp120-attachment inhibitor fostemsavir (FTR), the fusion inhibitor enfuvirtide (T-20), or the CCR5 antagonist maraviroc (MVC) in patients with no detectable CXCR4-using virus.

- 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.
- Administering a drug that a patient has never used does not ensure that the drug will be fully or partially active; the potential exists for cross-resistance among drugs from the same class.
- 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**)^{29,30} (see [Discontinuation or Interruption of Antiretroviral Therapy](#)).

Drug-Resistance Testing to Guide New Antiretroviral Regimens

- Drug-resistance testing should guide ARV regimen design and should be performed while the patient is still taking the failing regimen or **within 4 weeks of discontinuation of a non-long-acting regimen (AII)**. If more than 4 weeks have elapsed since **discontinuation of a non-long-acting regimen**, drug-resistance testing still may provide useful information to guide therapy, although it may not detect previously selected resistance mutations (**CIII**).
- Drug-resistance testing is recommended in persons with virologic failure and HIV RNA >200 copies/mL (**AI** for >1,000 copies/mL, **AIII** for 501–1,000 copies/mL, **CIII** for confirmed 201–500 copies/mL); though at low viral load levels, testing may be difficult to obtain outside of a research setting. In persons with HIV RNA >200 copies/mL but <500 copies/mL, testing may be unsuccessful, but it still should be considered.
- 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 (**this is sometimes referred to as “archived” resistance**), regardless of whether it appears on subsequent drug-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.
- **Activity of ART based on current and cumulative genotypic mutations can be estimated by tools and interpretation algorithms, such as the [Stanford University HIV Drug-Resistance Database](#). Also see [Drug-Resistance Testing](#).**
- Some drug-resistance 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**) also are available. There is currently no commercially available resistance test for IBA or FTR (see [Drug-Resistance Testing](#)).

Strategies for New Antiretroviral Regimen Design

- A new ARV regimen can include two fully active drugs if at least one has a high resistance barrier, such as the second-generation INSTI DTG or the boosted-PI DRV (**AI**).³¹⁻³⁹
- A new ARV regimen can include an INSTI (preferably the second-generation DTG) plus boosted PI (preferably boosted DRV), without NRTIs, if both are fully active (**AII**); this is discussed in more detail below.^{33,34,38,39}

- If no fully active drug with a high resistance barrier is available, 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 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 to achieve drug concentrations necessary to be at least partially active against a less-sensitive virus.⁴⁰⁻⁴²
- In contrast, other agents in which resistance may be expected should be discontinued, because their continued use is unlikely to contribute to viral suppression. These drugs may include NNRTIs, especially efavirenz, nevirapine, and rilpivirine (RPV); the first-generation INSTIs raltegravir (RAL) and elvitegravir (EVG); and T-20.⁴³⁻⁴⁵
- The long-acting ARV combination of injectable cabotegravir (CAB) and RPV is **not currently recommended** for people with virologic failure.
- When changing an ARV regimen in a patient with hepatitis B virus (HBV)/HIV coinfection, ARV drugs that are active against HBV (especially tenofovir disoproxil fumarate [TDF] or tenofovir alafenamide [TAF]) should be continued as part of the new regimen or, if not possible, entecavir should be initiated (**BI**). Using lamivudine (3TC) or emtricitabine (FTC) as the only drug with HBV activity in a regimen **is not recommended (AII)**, because HBV resistance to these drugs can emerge. Discontinuation of these drugs may lead to the reactivation of HBV, which may result in serious hepatocellular damage (see [Hepatitis B Virus/HIV Coinfection](#)).
- Patients should be closely monitored for virologic responses after regimen switch (e.g., HIV viral load testing performed within **4 to 8 weeks**), with prompt drug-resistance testing if virologic response is inadequate.

Managing Virologic Failure in 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 to 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.

- **Low-level viremia (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**).⁴ Although there is no consensus on how to manage these patients, the risk that drug resistance will emerge is believed to be relatively low. Therefore, these patients should continue their current regimens and have their HIV-RNA levels monitored at least every 3 months to assess the need for changes to ART in the future (**AIII**).
- **HIV RNA \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.^{6,7} 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 drug-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 drug-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 the following:
 - 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 an 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 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 (e.g., when used with rifamycin) or impaired drug absorption (e.g., using polyvalent cations with an INSTI) 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?) (see [Drug-Resistance Testing](#)).
 - If the current regimen is well tolerated, with no significant drug–drug or drug–food interactions, it is reasonable to continue the same regimen while focusing on improving adherence.

- 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 should be repeated **4 to 8** weeks after treatment adherence is reinforced or treatment is modified (**AII**); if viral load remains **>200 copies/mL**, genotypic testing should be performed to determine whether a resistant viral strain has emerged (**AI** for **>1,000 copies/mL**, **AIII** for 501–1,000 copies/mL, **CIII** for 201–500 copies/mL); though at low viral load levels, testing may be difficult to obtain outside of a research setting.
- **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 to avoid progressive accumulation of resistance mutations.⁴⁶ 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 before CD4 count declines.^{8,47} 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 on the First Antiretroviral Regimen

The Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel) recommends that drug-resistance testing should be used upon treatment failure to inform regimen design (**AI**).

NNRTI plus NRTI regimen failure: Although an NNRTI plus NRTI regimen is no longer considered a preferred first-line ART option in treatment guidelines, data from clinical trials comparing different ARV regimens after NNRTI plus NRTI failure provide the most robust evidence to inform second-line treatment strategies and, therefore, are included here.

In this setting, patients often have viral resistance to the NNRTI, with or without the M184V/I mutation, which confers high-level resistance to 3TC and FTC. Additional NRTI mutations also may be present. Below are some treatment options.

- **DTG plus NRTIs:** The Panel recommends that fully active DTG plus two NRTIs, at least one of which is fully active, can be a treatment option after failure of a first-line NNRTI-based therapy (**AI**). If at least one fully active NRTI cannot be assured and a clinician wants to avoid using a boosted PI or a drug from other classes, a regimen that includes fully active DTG plus two NRTIs that are estimated to be only partially active (particularly TAF or TDF with 3TC or FTC) can be considered (**BII**). BIC, which is available only in a combination pill with FTC/TAF, also has a high resistance barrier and may have activity that is similar to that of DTG in this setting; however, no clinical trial data for this strategy is available and, therefore, it is **not currently recommended (CIII)**.

In the DAWNING trial, patients from 13 countries who experienced virologic failure while on a first-line NNRTI-based regimen were randomized to receive either lopinavir/ritonavir (LPV/r) or DTG; each with two NRTIs, one of which had to be fully active based on real-time drug-

resistance testing. The study was stopped early after an interim analysis showed that the DTG arm was superior to the LPV/r arm. The superiority of DTG was somewhat counterbalanced by the finding that 2 of 11 patients in the DTG arm selected for INSTI resistance, with no PI resistance selected for in the LPV/r arm.³⁷

In the NADIA trial, participants in Uganda, Kenya, and Zimbabwe who experienced virologic failure while on a first-line NNRTI plus 3TC or FTC with TDF regimen were randomized to receive either darunavir/ritonavir (DRV/r) or DTG, each with 3TC; participants were assigned by a second randomization to receive either TDF or zidovudine (ZDV). Unlike the DAWNING study, full activity of the NRTIs based on genotype testing at the time of switch was not required.^{35,36} The primary study outcome was viral suppression <400 copies/mL: at 48 and 96 weeks, >85% of participants had viral load <400 copies/mL in all arms, and the DTG-based regimens were noninferior to the DRV/r-based regimens. However, at 96 weeks, 9 of 235 (4%) participants in the DTG group developed DTG resistance. This represented 45% of participants in the DTG group with viral load >400 copies/mL, six of whom were assigned to ZDV. In contrast, no PI resistance was selected for in the DRV/r group. When comparing TDF with ZDV, the two NRTIs demonstrated viral suppression noninferiority at 48 weeks, but TDF was superior to ZDV at 96 weeks. These results included 84 of 92 (91%) participants in the DTG group who had viral suppression <400 copies/mL despite no predicted active NRTIs at the time of failure of first-line NNRTI-based regimens, and a large proportion of this group had the K65R and M184V/I mutations. Individual-level drug-resistance data would have enabled further examination of specific mutation patterns and their association with patient characteristics and treatment outcomes. Although such data are not available, these results suggest that in a public health approach, ZDV should not be used over tenofovir. The decision to use DTG or DRV/r without another fully active drug should balance the overall efficacy data of these regimens, with considerations to the potential for emerging drug resistance, drug–drug interactions, convenience, and tolerability. The results from these studies should be interpreted with caution, as individual-level drug-resistance data and their linkage to patient characteristics and outcomes were not available; thus, preventing full interpretation of these results. Additionally, these results may not be generalizable to settings and patient populations outside of the trials due to differences in geography, patient population, ART availability, and treatment monitoring practice.

- **Boosted PI plus NRTIs:** The Panel recommends that a boosted PI (preferably boosted DRV) 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**). However, if full activity of at least one NRTI in the regimen cannot be assured, fully active boosted DRV plus two NRTIs estimated to be only partially active (particularly TAF or TDF with 3TC or FTC) can be considered (**BII**). Notably, boosted PIs as monotherapy **are not recommended (AI)**.^{33-36,39,48}

Several 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 or DRV/r plus at least two NRTIs were as effective as regimens that contained LPV/r plus RAL or DTG plus two NRTIs. Participants in some of these studies did not undergo drug-resistance testing before randomization. In the NADIA trial (summarized above), virologic efficacy of DTG and DRV/r were noninferior at 48 and 96 weeks, with TDF being noninferior at 48 weeks and superior at 96 weeks compared with ZDV. Although there were nine participants in the DTG group who developed DTG resistance (six on ZDV and three on TDF), no participant in the DRV/r group developed PI resistance. Additionally, 74 of 80 (93%) participants in the DRV/r group had viral suppression <400 copies/mL at 96 weeks despite no predicted active NRTIs at

the time of failure of first-line NNRTI-based regimens. As outlined above, these results should be interpreted with caution within, and particularly beyond, the study patient populations and settings.

- **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 at least two NRTIs.^{33,34,39} Thus, LPV/r plus RAL can be a treatment option for those who experienced virologic failure on an NNRTI-based regimen (**CI**). Although data are limited, a boosted PI (e.g., DRV) that is a preferred option combined with DTG would be a viable option in this setting (**AIII**).

Boosted PI plus NRTI regimen failure: In this scenario, because boosted PI has a high barrier to resistance, most patients will have either no resistance or resistance that is limited to 3TC and FTC; though additional NRTI mutations also may be present.^{49,50} Failure in this setting is often attributed to poor adherence, drug–drug interactions, or drug–food interactions. Below are some management options.

- **Switch to an INSTI-based regimen:** Second-generation INSTIs have increasingly become preferred options over boosted PIs due to the lack of drug–drug interactions, improved tolerability, comparable efficacy, and a high barrier to resistance. Therefore, consideration should be given to switching to DTG or possibly BIC plus two NRTIs (if at least one of them is fully active) (**AIII**). If only one of the NRTIs is fully active or if adherence is a concern, DTG is currently preferred over BIC (**AIII**). If full activity of at least one NRTI in the regimen cannot be assured, DTG plus two NRTIs estimated to be only partially active (particularly TAF or TDF with 3TC or FTC) can be considered (**BIII**). As outlined above, the results from these studies should be interpreted with caution, as individual-level drug-resistance data and their linkage to patient characteristics and outcomes were not available; thus, preventing full interpretation of these results. Additionally, these results may not be generalizable to settings and patient populations outside of the trials, due to differences in geography, patient population, ART availability, and treatment monitoring practice.
- **Maintain 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**).⁵¹ If the regimen is well tolerated with 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 PI-based regimen:** If an INSTI-based regimen is not an option and poor tolerability is contributing to virologic failure, the regimen can be modified with a different boosted PI that has no evidence for cross-resistance, plus an INSTI (**AIII**), or plus two NRTIs (at least one of which is fully active) (**AIII**). If full activity of at least one NRTI in the regimen cannot be assured, another fully active boosted PI plus two NRTIs estimated to be only partially active (particularly TAF or TDF with 3TC or FTC) can be considered (**BIII**).

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 (with/without additional NRTI mutations) and, possibly, the INSTI.⁵² Viruses with EVG or RAL resistance often remain susceptible to DTG and BIC.⁴⁷ However, in the presence of certain INSTI mutations, DTG dose should be increased from once daily to twice daily.⁴⁰ The effective dose of BIC in these situations is unknown. In contrast, in clinical trials, people 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.⁵²⁻⁵⁴ No existing clinical trial data guide therapy for first-line INSTI failures; therefore, treatment strategy should be based on drug-resistance test results and the potential potency of the next regimen. Below are some treatment options, based on drug-resistance pattern considerations.

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

Although BIC has a high resistance barrier, there are no data on whether the current BIC dose is efficacious in settings with RAL or EVG resistance and, therefore, it **is not currently recommended**.

INSTI plus NNRTI regimen failure: Virologic failure in patients on a regimen that consists of an INSTI (e.g., DTG or CAB) plus an NNRTI (e.g., RPV) may be associated with resistance to one or both of the medications in the regimen.^{55,56} Experience to guide therapy upon failure of these regimens is limited. Therefore, treatment strategies should be based on past treatment history; drug-resistance test results; and the potential potency of the next regimen, based on the guidance provided above.

Second-Line Regimen Failure and Beyond

Drug resistance with fully active antiretroviral therapy options: Using a patient's complete ARV 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 are likely to have virus susceptible to DTG or BIC. In this setting, viral suppression should be achievable using a boosted PI plus either two NRTIs (preferably at least one of which is fully active), a boosted PI plus an active INSTI, or DTG or BIC plus two NRTIs (preferably at least one of which is fully active). 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.^{57,58} Despite this progress, some patients have experienced toxicities with and/or developed resistance to most currently available ARV 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 neither a fully active boosted PI nor a second-generation INSTI (e.g., DTG or BIC) is available, the new regimen should include at least two, and preferably three, fully active agents. If less than three fully active drugs are available, the regimen should include as many fully active drugs as possible, along with potentially partially active agents (**BII**). 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.^{57,59} Cohort studies provide evidence that even in the presence of viremia and no improvement in CD4 count, continuing ART reduces the risk of disease progression.⁶⁰ Other cohort studies suggest that even modest reductions in HIV-RNA levels continue to confer immunologic and clinical benefits.^{61,62} 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 IBA⁶³ 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.⁶⁴ 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 48.⁶⁵
- **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 nonrandomized 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 log₁₀ copies/mL versus 0.17 log₁₀ 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 nonrandomized cohort had viral load <40 copies/mL, with mean CD4 increases of 205 cells/mm³ and 119 cells/mm³, respectively.^{66,67} In this study, 15 individuals in the nonrandomized 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 also may 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 [U.S. Food and Drug Administration regulations](#). Information about ARV agents that are in clinical studies (e.g., lenacapavir) can be found in the [drug database](#) available on the [Clinical Info](#) website.

Antiretroviral Therapy-Experienced Patients with Suspected Drug Resistance Who Present with Limited Information (Incomplete or No Self-Reported History, Medical Records, or Drug-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. Regardless of which strategy is employed, patients should be closely monitored for virologic response (e.g., HIV viral load testing approximately 4 to 8 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 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

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 texts above and/or consult an expert in HIV 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 after regimen changes.

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

Table 11. Antiretroviral Options for Patients with Virologic Failure

Clinical Scenario	Type of Failing Regimen	Resistance Considerations	New Regimen Options ^{a,b}	Goal
			DTG ^e twice daily or possibly BIC (if HIV is sensitive) plus a boosted PI (AIII)	
Second Regimen Failure and Beyond	Drug resistance with fully active treatment options— (i) Boosted PI, but not second-generation INSTI, fully active (ii) Second-generation INSTI, but not boosted PI, fully active (iii) Both PI and INSTI fully active	Use past and current genotypic- +/- phenotypic-resistance testing and ART history when designing new regimen.	(i) Boosted PI with two NRTIs (preferably at least one fully active) (ii) DTG or BIC with two NRTIs (preferably at least one fully active) (iii) The two options above or boosted PI with INSTI	Resuppression
	Multiple or extensive drug resistance with few treatment options (e.g., fully active boosted PI or second-generation INSTI unavailable)	Use past and current genotypic- and phenotypic-resistance testing to guide therapy. Confirm with a viral tropism assay when use of MVC is considered. Consult an expert in drug resistance if needed.	New regimen should include at least two, and preferably three, fully active agents, including those with novel mechanisms of action (e.g., IBA or FTR). If <3 fully active drugs as possible, along with potentially partially active drugs. Consider enrollment into clinical trials or expanded access programs for investigational agents if available. Discontinuation of all ARV drugs is not recommended .	Resuppression if possible; otherwise, keep viral load as low as possible and CD4 count as high as possible.
ART-Experienced Patients with Suspected Drug Resistance and Limited or Incomplete ARV and Resistance History	Unknown	Obtain medical records if possible. 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	Consider restarting the old regimen with careful monitoring of virologic response and early resistance testing if inadequate virologic suppression. If no ARV history is available, consider initiating a regimen with drugs with high genetic barriers to resistance (e.g., DTG, BIC, and/or boosted DRV) with careful	Resuppression

Table 11. Antiretroviral Options for Patients with Virologic Failure

Clinical Scenario	Type of Failing Regimen	Resistance Considerations	New Regimen Options ^{a,b}	Goal
		not be detected in the absence of drug pressure.	monitoring of virologic response and early resistance testing, if inadequate virologic suppression.	

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

^b When switching an ARV regimen in a patient with HBV/HIV coinfection, ARV drugs that are active against HBV and have high resistance barrier to 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.

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

^d CI for LPV/r + RAL; AIII for other boosted PIs (e.g., DRV) or INSTIs (e.g., DTG).

^e Response to DTG depends on the type and number of INSTI mutations.

*See text for details and additional options in special settings.

Key: 3TC = lamivudine; ART = antiretroviral therapy; ARV = antiretroviral; BIC = bictegravir; 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; LPV/r = lopinavir/ritonavir; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; RAL = raltegravir

Isolated Central Nervous System Virologic Failure and Neurologic Symptoms

Cerebrospinal Fluid Viral Escape

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 replication within the CNS compartment, despite relative plasma HIV RNA suppression. In this case, cerebrospinal fluid (CSF) HIV RNA shows higher concentrations than in plasma.⁶⁸⁻⁷⁰ Clinical evaluation frequently shows abnormalities on magnetic resonance imaging (MRI) and abnormal CSF findings with characteristic lymphocytic pleocytosis.⁷¹ In most (though not all) patients, drug-resistant CSF virus is evident.⁷² Consensus among experts is that this “neurosymptomatic” form of CNS viral escape should be treated through optimization of ARV regimens based on drug-resistance testing results if available (CIII).⁷³ Although drug-resistance testing of HIV in CSF can be used to guide changes in the ARV regimen, according to the principles outlined above for plasma HIV RNA resistance, such testing typically needs to be conducted in a research setting. If CSF HIV drug-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).⁷⁴⁻⁷⁷

This “neurosymptomatic” CNS viral escape should be distinguished from “neuroasymptomatic” escape, defined as—

- The incidental detection of asymptomatic and mild CSF HIV RNA elevation, which is similar to plasma viral blips in that it is usually transient with low levels of CSF HIV RNA and has been associated with PI-based regimens;⁷⁸⁻⁸⁰ 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).⁸¹

There is not clear evidence to support a change in an ARV regimen for incidentally detected “neuroasymptomatic” escape, although careful clinical review and follow up of each individual patient with this condition is recommended to monitor for emergence of neurologic symptoms or systemic viremia.⁷³ 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.⁸²

Neurological Symptoms in People with HIV on Antiretroviral Therapy

Evidence is currently not available to support empiric intensification or switch of ARV regimens in patients on systemically suppressive ART with mild neurological and/or cognitive symptoms who do not have documented CSF escape. Such patients should be referred for neurological evaluation to determine if further evaluation is indicated. This may include blood laboratory testing, lumbar puncture, neuropsychological testing, and MRI to evaluate for CSF escape, as well as other causes of neurological symptoms. A recent multi-national randomized, double-blinded, placebo-controlled trial randomized 191 ART-experienced participants—with cognitive impairment and suppressed plasma HIV viral load and not taking an INSTI—to one of three arms: dual placebo, addition of DTG plus placebo, or DTG plus MVC. Compared with placebo, ART intensification with DTG or DTG plus MVC did not alter neuropsychological performance or depressive symptoms over time in participants with cognitive impairment.⁸³

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