MANAGEMENT OF PEOPLE WITH HIV AND ANTIRETROVIRAL THERAPY EXPERIENCE

Virologic Failure

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Key Considerations and Recommendations
• Assessing and managing a person with HIV 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 person is taking the failing antiretroviral (ARV) regimen **(AI)** or within 4 weeks of discontinuing 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 **(CIII).** • For people who previously received long-acting (LA) cabotegravir (CAB) plus rilpivirine (RPV), or LA CAB/RPV, and present with virologic failure, resistance testing (including integrase strand transfer inhibitor [INSTI] genotypic testing) should be performed regardless of the time since the last dose of LA CAB/RPV **(AIII).** • The goal of treatment for people with HIV 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 ARV regimen should preferably include two fully active drugs if at least one has a high resistance barrier, such as a second-generation INSTI or a boosted protease inhibitor (PI) **(AI).** • A new ARV regimen can also include a second-generation INSTI (i.e., dolutegravir [DTG]) plus a boosted PI (preferably boosted darunavir) without nucleoside reverse transcriptase inhibitors (NRTIs) if both are fully active **(AI)**. • If the above two options are not feasible, a new ARV regimen that includes at least one drug with a high resistance barrier plus two partially active NRTIs—particularly tenofovir alafenamide (TAF) or tenofovir disoproxil fumarate (TDF) with lamivudine (3TC) or emtricitabine (FTC)—can also be considered, although this is a less well-defined strategy and is based on an extrapolation of existing data. Caution with close monitoring of virologic response is advised **(BII),** as discussed below**.** • 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 new ARV regimen **(AI).** • In general, adding a single ARV drug to a virologically failing regimen **is not recommended,** because this would rarely result in full virologic suppression and may risk the development of resistance to all drugs in the regimen **(BII).** • In some rare instances, it might not be possible to achieve maximal virologic suppression in people with HIV who are highly ART-experienced and have extensive drug resistance. 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 person with multidrug-resistant HIV, the clinician should consider enrolling the person in a clinical trial of investigational agents or contacting pharmaceutical companies that may have investigational agents available.
- In people with HIV and virologic failure, it is crucial to provide continuous adherence support before and after ARV regimen changes.
- When switching an ARV regimen in a person with hepatitis B virus (HBV)/HIV coinfection, the person should remain on an ARV agent that is active against HBV and has a high resistance barrier to HBV (i.e., TAF, TDF, or entecavir) to avoid HBV rebound and hepatocellular damage **(AII)** (see Hepatitis B Virus/HIV Coinfection for more information).
- 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, discontinuing or interrupting ART **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 people 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 Initial Combination Antiretroviral Regimens for People With HIV). People 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 ARV regimen with possible cross-resistance to other ARVs. Adherence to ARV regimens can be challenging for some people with HIV, and poor adherence can result in detectable HIV RNA levels. The extent of drug resistance varies based on ARV treatment history, with some people having minimal or no resistance and others with extensive resistance. Managing people with extensive resistance is complex and usually requires consultation with an HIV expert. This section of the guidelines defines virologic failure in people 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 person who has not yet had documented virologic suppression on that regimen. A person'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 HIV RNA level above the LLOD but <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 people 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 people 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 HIV RNA platforms used in the past.[3-5] Several retrospective studies support the supposition that virologic failure is more likely to occur in people with HIV RNA levels ≥200 copies/mL than in those with low-level viremia between 50 copies/mL and 199 copies/mL.[6-8] However, other studies have suggested that detectable viremia at <200 copies/mL can be predictive of virologic failure[9] and can be associated with the evolution of drug resistance[10] and non-AIDS morbidities.[11]

Persistent HIV RNA levels ≥200 copies/mL are often associated with evidence of viral evolution and accumulation of drug-resistance mutations.[12] This association is particularly common with HIV RNA levels >500 copies/mL.[13] Therefore, people who have persistent HIV RNA levels ≥200 copies/mL are considered to be experiencing virologic failure.

Causes of Virologic Failure

Virologic failure can occur for many reasons. Data from cohorts in the earlier era of combination ART suggested that suboptimal adherence and drug intolerance/toxicity are key contributors to virologic failure and regimen discontinuations.[14,15] Current ARVs are easier to tolerate and have less pill burden, which may improve adherence.[16-18] Virologic failure may be associated with a variety of factors, including the following:

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 levels (e.g., HIV RNA >100,000 copies/mL; some regimens may be less effective at higher levels)

Antiretroviral Regimen–Related Factors

- Suboptimal pharmacokinetics (PK) (e.g., variable absorption, metabolism, 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
- Adverse drug effects
- High pill burden and/or dosing frequency
- Prescription (prescribing or dispensing) errors

Social and Adherence-Related Factors

Note: Each of the social and adherence-related factors listed below are discussed in the Adherence to the Continuum of Care section.

- Active substance use, mental health disorders, or neurocognitive impairment
- Unstable housing and other psychosocial factors
- Missed clinic appointments
- Interruption of or intermittent access to ART
- Cost and affordability of ARV drugs, which may affect the ability to access or continue therapy (see the Cost Considerations and Antiretroviral Therapy section)

Managing People With HIV and 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. The causes of virologic failure can usually be identified but may not be obvious in some cases. 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. If a new ARV regimen is needed, approaches to designing a new regimen are discussed below.

Key Factors to Consider When Designing a New Antiretroviral Regimen After Virologic Failure

General Principles on Antiretroviral Use in Virologic Failure

- When designing a new ARV regimen for a person with virologic failure, it is important to consider the factors outlined above on causes of virologic failure and, if possible, consider better tolerated and adherence-friendly regimens.
- A new ARV regimen should be selected based on ART history, current and previous drug-resistance test results, and whether a fully susceptible ARV drug with a high barrier to resistance and other fully active drugs are available.[9,19-31]
- ARV drugs with a high barrier to resistance are those in which emergent resistance is uncommon in people experiencing virologic failure. These include boosted darunavir (DRV), dolutegravir (DTG), and bictegravir (BIC).

- Fully active drugs may include—
  - Drugs in classes for which the person has not previously selected for drug-resistant virus.
  - Newer drugs in existing drug classes that are predicted to be fully active against HIV isolates despite the presence of resistance mutations for some drugs in the same drug class. For example, 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 that the person with HIV has not received before, such as the post-attachment inhibitor ibalizumab (IBA), the gp120 attachment inhibitor fostemsavir (FTR), the capsid inhibitor lenacapavir (LEN), the fusion inhibitor enfuvirtide (T-20), or the CCR5 antagonist maraviroc (MVC) in people 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 person 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 person with viremia **is not recommended** because it may increase HIV RNA levels, decrease CD4 T lymphocyte (CD4) cell count, and increase the risk of clinical progression **(AI)**[32,33] (see Discontinuation or Interruption of Antiretroviral Therapy).
- The presence of preexisting (transmitted) drug resistance also may lead to virologic failure.[34,35]

Drug-Resistance Testing to Guide New Antiretroviral Regimens

- The Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel) recommends that drug-resistance testing should be used to guide ARV regimen design and should be performed while the person with HIV is still taking the failing regimen **(AI)** 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 confirmed virologic failure, i.e., HIV RNA repeatedly >200 copies/mL (**AI** for >1,000 copies/mL, **AIII** for 501–1,000 copies/mL, **CIII** for confirmed 201–500 copies/mL), although at low HIV RNA 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 person'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 all of the person'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 protease inhibitors (PIs); INSTI-resistance testing may need to be ordered separately. INSTI-resistance testing should be ordered in people who experience virologic failure on an INSTI-based regimen. Additional drug-resistance tests for people who experience failure on a fusion inhibitor **(AII),** and viral tropism tests for people who experience failure on a CCR5 antagonist **(BIII)** are also available. There is currently no commercially available resistance test for IBA, FTR, or LEN (see Drug-Resistance Testing).

Strategies for New Antiretroviral Regimen Design

- A new ARV regimen should preferably include two fully active drugs if at least one has a high resistance barrier, such as a second-generation INSTI or a boosted PI **(AI).**[36]
- A new ARV regimen can also include a second-generation INSTI (e.g., DTG) plus a boosted PI (preferably boosted DRV) without NRTIs if both are fully active **(AI);**[37-41] see more detailed discussion in *Managing Virologic Failure in Different Clinical Scenarios* below. If this regimen is used in people with hepatitis B virus (HBV)/HIV coinfection, an HBV-active drug with a high barrier to resistance (e.g., tenofovir alafenamide [TAF], tenofovir disoproxil fumarate [TDF], or entecavir) should be continued or started to avoid HBV rebound and hepatocellular damage.
- If the above two options are not feasible, a new ARV regimen can also include a fully active drug with a high resistance barrier plus two partially active NRTIs—particularly TAF or TDF with lamivudine (3TC) or emtricitabine (FTC)—though this is less well-defined and close monitoring is advised **(BII);** this is discussed in more detail in *Managing Virologic Failure in Different Clinical Scenarios* below.[36,37,42,43]
- 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 person'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 people with relevant resistance mutations to achieve drug concentrations necessary to be at least partially active against a less sensitive virus.[44-46]
- In contrast, other agents in which resistance may be expected should be discontinued, because their continued use is unlikely to contribute to virologic suppression. These drugs include NNRTIs (especially efavirenz, nevirapine, and rilpivirine [RPV]), the first-generation INSTIs raltegravir (RAL) and elvitegravir (EVG), and T-20.[47-49]
- Long-acting (LA) cabotegravir (CAB)/rilpivirine (RPV) is currently approved as a complete ART regimen for individuals engaged in care who have good adherence to an oral regimen, sustained undetectable HIV RNA levels for >3 months, no known or suspected resistance to either drug, and no active HBV infection. To date, no large or randomized clinical trials have been published using any INSTI plus NNRTI, including LA CAB/RPV, as a complete regimen for people without viral suppression. However, a few small observational studies have shown that people with viremia despite intensive efforts on oral ART, without resistance to CAB or RPV, can achieve viral suppression with LA CAB/RPV when intensive supportive services are available.[50-53] If considering LA CAB/RPV in this population, it is important to note that data are limited, and this is not an approved indication of the regimen. If the regimen is used in people with inconsistent adherence and virologic failure, there is a high likelihood of developing acquired resistance to CAB and/or RPV, which might limit future treatment options. The approaches and considerations for the use of LA CAB/RPV in people with viremia is further outlined below.

- When changing an ARV regimen in a person with HBV/HIV coinfection, ARV drugs that are active against HBV (especially TAF or TDF) should be continued as part of the new regimen or, if not possible, entecavir should be initiated **(AII).** Using 3TC or 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).
- Virologic responses should be closely monitored after regimen switch (e.g., HIV RNA level testing performed within 4 to 8 weeks), with prompt drug-resistance testing if virologic response is inadequate.

Managing Virologic Failure in Individuals With Different Levels of Viremia

People with HIV and detectable HIV RNA levels while on ART 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 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 the level of viremia are addressed below.

- **Low-level viremia (HIV RNA above the LLOD and <200 copies/mL):** People 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 individuals, the risk that drug resistance will emerge is believed to be relatively low. Therefore, these individuals 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 ≥200 copies/mL and <1,000 copies/mL:** In contrast to people with detectable HIV RNA levels that are persistently <200 copies/mL, people with levels that are persistently ≥200 copies/mL often develop drug resistance, particularly when HIV RNA levels are >500 copies/mL.[6,7] People 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 people with HIV RNA levels >500 copies/mL (at <500 copies/mL, testing may not be possible for technical reasons). Management approaches should be the same as for people 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 ≥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 evaluate 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). Assessment includes the following:

- Assessing the person'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 social determinants that may impact adherence (e.g., substance use, unstable housing, mental health challenges, etc.).
- Assessing the person's tolerance of the current ARV regimen and the severity and duration of side effects if intolerance is a concern, while considering 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 person 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 (including over-the-counter medications and dietary supplements) for possible adverse drug–drug interactions (consult the Liverpool HIV Drug Interaction Checker 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 person mostly or completely nonadherent to oral ART for >4 weeks before testing?) (see Drug-Resistance Testing).
- After a thorough assessment, the following approaches may be considered:
  - 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.
  - HIV RNA level testing should be repeated 4 to 8 weeks after treatment adherence is encouraged or treatment is modified **(AII);** if RNA levels remain >200 copies/mL, genotypic drug-resistance 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 RNA 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.[54] 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.[9,55] 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 people with HIV. 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

Note: See Table 10 below for a summary of these recommendations.

Virologic Failure on the First Antiretroviral Regimen

The Panel recommends that drug-resistance testing should be performed 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, people with HIV 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.

- **Second-generation INSTI (BIC or 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).** BIC, which is available only in a combination pill with FTC/TAF, also has a high resistance barrier and may have similar activity to that of DTG in this setting, and is also an option **(AIII);** however, no clinical trial data for this strategy with BIC is available. 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, with caution and close monitoring of viral response, as further discussed below **(BII).**

  In the DAWNING trial, participants 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 participants in the DTG arm who met virologic withdrawal criteria selected for INSTI resistance, with no PI resistance selected for in the LPV/r arm.[36]

  In the NADIA trial, participants in Uganda, Kenya, and Zimbabwe who experienced virologic failure while on a first-line NNRTI plus TDF and 3TC or FTC were randomized to receive either darunavir/ritonavir (DRV/r) or DTG, each with 3TC; participants were assigned by a second randomization to receive a third ARV, 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.[42,43] The primary study outcome was virologic suppression <400 copies/mL; at 48 and 96 weeks, >85% of participants had HIV RNA levels <400 copies/mL in all arms, and the DTG-based regimens were non-inferior to the DRV/r-based regimens. However, at 96 weeks, 9 of 35 (4%) participants in the DTG group developed DTG resistance. This represented 45% of participants in the DTG group with HIV RNA levels >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 virologic 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 virologic 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 ZDV should not be used over TDF in a public health approach. The decision to use DTG or DRV/r without another fully active drug should balance the overall efficacy data of these regimens, with considerations for potential emergent 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 populations outside of the trials due to differences in geography, HIV-1 subtype, study 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, with close monitoring **(BII).** Notably, boosted PIs as monotherapy **are not recommended (AI).**[37,39,40,42,43,56]

  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-based regimens were non-inferior at 48 and 96 weeks, with TDF being non-inferior 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 virologic 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 in the discussion about second-generation INSTI plus no estimated fully active NRTIs based on current drug-resistance algorithms, these results should be interpreted with caution within, and particularly beyond, the study populations and settings.

- **Boosted PI plus an INSTI:** The Panel recommends that boosted DRV plus DTG, both with high barriers to resistance, should be the preferred boosted PI plus INSTI option **(AI).** In a setting where a two-drug boosted PI and INSTI combination are being considered and both boosted DRV and DTG cannot be used, LPV/r plus RAL can be a treatment option for those who experienced virologic failure on an NNRTI-based regimen (CI).

  D^2EFT is an open-label multinational randomized controlled trial that assessed the efficacies of DRV/r plus DTG versus DTG plus two NRTIs versus standard of care (DRV/r plus two NRTIs) for participants with first-line failure of an NNRTI-based regimen.[41] In D^2EFT, TDF plus 3TC or FTC were the NRTIs used. At 48 weeks, the proportion of participants who achieved HIV RNA <50 copies/mL was 84% for the DRV/r + DTG arm, 75% for the DRV/r plus two NRTI arm, and 78% for the DTG plus two NRTI arm, showing that the DRV/r + DTG arm was non-inferior to the other two regimens, with more participants achieving viral suppression. Several other small retrospective studies have found that a regimen of boosted DRV plus DTG is effective in achieving viral suppression in people with documented resistance to multiple drug classes.[57-59] Three randomized controlled trials have found that a regimen that consisted of LPV/r plus RAL can be as effective as LPV/r plus at least two NRTIs as second-line therapy for people who failed first-line ART (mostly with an NNRTI-based regimen).[37,39,40]

  If this regimen is used in people with HBV coinfection, an HBV-active drug with a high barrier to resistance (i.e., TAF, TDF, or entecavir) should be continued or started to avoid HBV rebound and hepatocellular damage.

Boosted PI plus NRTI regimen failure: In this scenario, because boosted PI has a high barrier to resistance, most people will have either no resistance or resistance that is limited to 3TC and FTC, though additional NRTI mutations also may be present.[60,61] Failure in this setting is often attributed to poor adherence, drug–drug interactions, or drug–food interactions. Below are some management options.

- **Switch to a second-generation INSTI plus NRTIs regimen:** Second-generation INSTIs have increasingly become preferred options over boosted PIs due to lower drug–drug interaction potential, 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 based on current drug-resistance algorithms (particularly TAF or TDF with 3TC or FTC) can be considered **(CIII).** As outlined above, results from studies that may suggest such extrapolations should be interpreted with caution, as they did not involve failure of first-line boosted PI plus NRTIs regimens and 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 populations outside of the trials due to differences in geography, HIV-1 subtype, 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 ritonavir-boosted PI-based regimens showed that taking actions to improve adherence to the original regimen is as effective as changing to new regimens with or without drugs from new classes **(AII).**[62] 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 a regimen with an INSTI plus two NRTIs 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 a second-generation 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, with close monitoring of viral response **(BIII).**

INSTI plus NRTI regimen failure: Virologic failure in people 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.[63] Viruses with EVG or RAL resistance often remain susceptible to DTG and BIC.[55] However, in the presence of certain INSTI mutations, DTG dose should be increased from once daily to twice daily.[44] 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.[63-65] 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 person with HIV 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 (BIII).**

INSTI plus NNRTI regimen failure: Virologic failure in people 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.[66,67] 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 commonly used ARV drug options: Using a person'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, people 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, virologic 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 person's treatment history, past and present drug-resistance testing, and tropism testing if a CCR5 antagonist is being considered.

Multidrug resistance without fully active commonly used ARV drug options: Use of currently available ARV drugs has resulted in a dramatic decline in the number of people with HIV who have few treatment options because of multiclass drug resistance.[68,69] Despite this progress, some people have experienced toxicities with and/or developed resistance to most currently available commonly used 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 people with multidrug-resistant HIV 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, CAB, 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.[68,70] 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.[71] Other cohort studies suggest that even modest reductions in HIV RNA levels continue to confer immunologic and clinical benefits.[72,73] 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).**

People with HIV and ongoing detectable viremia who lack sufficient treatment options due to an inability to construct a fully suppressive regimen with common ARVs may be candidates for the first-in-class CD4 post-attachment inhibitor IBA,[74] the gp120-directed attachment inhibitor FTR,[75] and/or the capsid inhibitor LEN.[76]

- **Ibalizumab (IBA)** is a long-acting CD4 post-attachment inhibitor that is given intravenously every 2 weeks. 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 IBA infusions every 2 weeks, in addition to an optimized background regimen (OBR) 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% achieved HIV RNA <200 copies/mL.[77] 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 participants who had HIV RNA <50 copies/mL at Week 24 maintained virologic suppression up to Week 48.[78]
- **Fostemsavir (FTR)** is a gp120 attachment inhibitor that is given orally twice daily. 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 OBR. In the nonrandomized cohort (n = 99), participants with no remaining ARV options were started on open-label FTR (oral 600 mg twice daily) plus OBR on Day 1. The primary endpoint for the randomized cohort was a change in HIV RNA level from baseline at Day 8. In the FTR group, the mean RNA level decrease was 0.79 $\log_{10}$ copies/mL compared to 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 nonrandomized cohort had HIV RNA levels <40 copies/mL, with mean CD4 increases of 205 cells/mm^3 and 119 cells/mm^3, respectively.[79,80] 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.
- **Lenacapavir (LEN)** is a LA HIV capsid inhibitor that can be given by one of two initiation schemes (oral plus subcutaneous [SQ] dosing), followed by SQ injections every 6 months (see Appendix A, Table 7 for dosing details).

  A Phase 3 multicenter trial (CAPELLA) enrolled 72 heavily ART-experienced participants who had multidrug-resistant HIV-1 and experienced virologic failure into two cohorts.[81] Cohort 1 (n = 36) included participants who had a <0.5 $\log_{10}$ HIV-1 RNA decline between screening and baseline (i.e., stable viremia at ≥400 copies/mL, confirming lack of response to the failing therapy). The participants were randomized 2:1 to either oral LEN or placebo (on Days 1, 2, and 8) and continued to receive the failing ARV regimen for 14 days to evaluate the virologic effect of LEN functional monotherapy. Starting on Day 15, all participants began on an OBR; those randomized to oral LEN began SQ LEN every 6 months, whereas participants in the placebo arm received oral LEN on Days 15, 16, and 22 followed by SQ LEN on Day 29 (14 days after the

first oral LEN dose) and then every 6 months. On Day 15, 88% of participants in the LEN arm and 17% in the placebo arm had HIV RNA level reduction of ≥0.5 $\log_{10}$ copies/mL, with least-squares mean change in HIV RNA level of −2.1 $\log_{10}$ copies/mL versus −0.07 $\log_{10}$ copies/mL for the LEN and placebo arms, respectively ($P < 0.001$). At the end of 26 weeks (i.e., after one dose of SQ LEN), 81% of participants had RNA levels <50 copies/mL, and 89% had RNA levels <200 copies/mL, with a mean change in RNA level of −2.58 ± 1.04 $\log_{10}$ copies/mL.[81] At the end of 52 weeks (i.e., after two doses of SQ LEN), 83% of participants had RNA levels <50 copies/mL, with 94% of those with at least two active OBR drugs and 67% with no active OBR drugs. The mean CD4 cell count change at 52 weeks[76] was +82 cells/mm^3.

Cohort 2 (n = 36) was a nonrandomized cohort that included participants who either had a ≥0.5 $\log_{10}$ HIV-1 RNA decline from screening to baseline visit or were enrolled after Cohort 1 reached its planned sample size. All participants were started on an OBR and received oral LEN on Days 1, 2, and 8; on Day 15, SQ LEN was started and given every 6 months. After 26 weeks, 83% of the participants had HIV RNA levels <50 copies/mL, and 86% had HIV RNA levels <200 copies/mL. At Week 52, 72% had RNA levels <50 copies/mL, and the mean CD4 cell count change was +113 cells/mm^3.

Oral lead-in therapy was well tolerated overall, with nausea reported in 13% of participants who received LEN. Injection site reactions, which were generally mild and transient, were reported in 63% of the participants.[81]

Twenty-two of 72 (31%) participants met the criteria for resistance testing at confirmed virologic failure through Week 52.[76] LEN-associated capsid resistance mutations were found in 9 of the 22 (41%) participants with confirmed virologic failure. The M66I mutation was the most common mutation, reported in six participants. Four of the nine participants with LEN-associated capsid resistance mutations had no active agent in the OBR. Four others had low plasma concentrations of the OBR drugs at Week 26, suggesting poor adherence of the self-administered OBR, resulting in an unfavorable LEN functional monotherapy.[82]

Taken together, these data[76,82,83] highlight the importance of selecting a robust OBR to support LEN and counseling about adherence to the OBR. Additionally, LEN is a moderate CYP3A4 inhibitor and may increase concentrations of some coadministered drugs, whereas LEN concentration may be significantly decreased in the presence of a strong CYP3A4 inducer (see the Liverpool HIV Drug Interaction Checker for further details). Therefore, people with HIV should be routinely counseled to inform all their health care providers of all medications they are taking, including LEN, even though it is not taken daily. Potential drug–drug interactions should be discussed, particularly before a new drug is started, to minimize the risk of toxicities, nonadherence, and drug resistance.

People with HIV 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-person access to an investigational new drug, as specified in the U.S. Food and Drug Administration's Physician Request for a Single Patient Investigational New Drug for Compassionate or Emergency Use. Information about ARV agents that are in clinical studies can be found in the drug database available on the Clinicalinfo website.

People With HIV on ART With Suspected Drug Resistance Who Present With Limited Information (Incomplete or No Self-Reported ARV History, Medical Records, or Drug-Resistance Test Results)

Every effort should be made to obtain the person'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

person'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 for which dosage in this setting is unclear), and/or twice-daily boosted DRV—as part of the regimen. Regardless of which strategy is employed, people should be closely monitored for virologic response (e.g., HIV RNA level testing approximately 4 to 8 weeks after reinitiation of therapy), with prompt drug-resistance testing performed if virologic response is inadequate.

People With HIV Who Are Unable to Achieve Viral Suppression Due to Poor Adherence to Oral ART and Who Do Not Have Resistance to Cabotegravir and Rilpivirine

Based on very limited data discussed below, the Panel recommends the use of LA CAB/RPV on a case-by-case basis in select individuals with persistent virologic failure despite intensive adherence support on oral ART, who have no evidence of resistance to RPV or CAB, and with shared decision-making between providers and people with HIV **(CIII).**

Some people with HIV cannot reach or maintain viral suppression on oral ART despite intensive adherence support. Although a complete LA injectable regimen may overcome some adherence obstacles for people with viremia, long-term clinical efficacy data are limited in these circumstances and the regimen is only approved for people who are virologically suppressed for at least 3 months. No large, published randomized controlled trial has demonstrated the efficacy of a complete regimen of any INSTI plus NNRTI, including LA CAB/RPV, in people with viremia. However, cohort data are emerging, resulting in two possible approaches to use LA CAB/RPV in this population. If achieving viral suppression with oral ART is possible with intensive adherence support to oral ART, switching to LA CAB/RPV after viral suppression can serve as a goal to incentivize the person to adhere to the oral regimen. Data from the Long-Acting Therapy to Improve Treatment Success in Daily Life (LATITUDE) AIDS Clinical Trial Group (ACTG) A5359 study using this strategy is discussed in Approach #1 below.[84] If achieving viral suppression with oral ART is not possible despite intensive adherence support to oral ART, switching to LA CAB/RPV without viral suppression may be an option in certain circumstances, as discussed in Approach #2 below.

Approach #1: Intensive efforts to achieve viral suppression prior to switching to LA CAB/RPV

Because all of the large LA CAB/RPV studies enrolled participants who were adherent to ART with sustained viral suppression, every effort should be made to achieve viral suppression before considering a switch to LA CAB/RPV, even in people with poor adherence. The Phase 3 prospective, randomized, open-label LATITUDE study was designed to assess this strategy in people who faced challenges with ART adherence. Preliminary data have been presented from this study that enrolled individuals without resistance to CAB or RPV from 33 sites in the United States and Puerto Rico.[84] Participants received adherence support and conditional economic incentives to assist in achieving viral suppression on oral ART. Study participants who experienced viral suppression were randomized to continue oral ART or switch to LA CAB/RPV every 4 weeks. At a planned data safety monitoring board (DSMB) interim efficacy analysis, only 294 (68%) of the 434 participants enrolled achieved viral suppression and were eligible for randomization, with 146 assigned LA CAB/RPV and 148 continuing standard of care (SOC) oral ART. At randomization, it was noted that despite the intensive adherence support, 17% in the LA CAB/RPV arm and 7% in the SOC arm had HIV RNA >200 copies/mL. At Week 48 of the randomized phase, 24% in the LA CAB/RPV arm and 39% in the SOC arm met the primary endpoint of earliest confirmed virologic failure or treatment discontinuation, which did not meet the predefined stringent stopping criteria. However, two secondary endpoints—virologic failure alone (7% in LA CAB/RPV vs. 25% in SOC)

and treatment-related failure (defined as first virologic failure or discontinuation due to adverse events) (10% in LA CAB/RPV vs. 26% in SOC)—met the predefined stopping criteria and were statistically significant. Based upon the totality of the data, in February 2024, the DSMB recommended halting randomization and offering all eligible participants LA CAB/RPV. Of the six participants with virologic failure on LA CAB/RPV, two had new drug-resistance mutations (one conferring high-level resistance to CAB and one conferring high-level resistance to both CAB and RPV). The available data suggest that an intensive effort to achieve viral suppression followed by a switch to LA CAB/RPV may be a viable option for individuals who cannot adhere to an oral ARV regimen. Further analyses and formal publication of LATITUDE study results are pending.

Approach #2: Administer LA CAB/RPV in people with viremia who are unable to achieve viral suppression despite intensive adherence support

Emerging data show that select people with HIV who are unable to achieve viral suppression on an oral ARV regimen despite intensive support might benefit from use of LA CAB/RPV, which is currently not approved for use in this population. Available data with this strategy include an initial case report,[85] followed by outcome data from a compassionate use program,[86] showing that 16 of 28 (57%) people with viremia achieved virologic suppression after a median of 5 months with LA CAB/RPV. Among those with virologic failure and for whom resistance data were available, all had new NNRTI mutations conferring RPV resistance and 50% had new integrase mutations, two of which conferred CAB resistance. Since then, three small observational studies have suggested that LA CAB/RPV may achieve viral suppression in select people with viremia and poor adherence to oral ART.[50-52] In these studies, select people with viremia who were unable to adhere to daily oral ART were initiated on monthly or twice-monthly LA CAB/RPV with or without oral lead-in therapy. At up to 10 months of follow-up, 95% achieved HIV RNA <50 copies/mL. Of those with virologic failure for whom genotypes were available, new reverse transcriptase (e.g., L100I, E138K, Y181I) and/or integrase (e.g., G140S, Q148R, R263K) mutations were detected, conferring intermediate to high resistance to RPV and/or CAB, respectively. Various levels of multidisciplinary support and intensive case management were utilized throughout these studies (e.g., provision of injections in field sites, financial incentives, appointment reminders, and transportation assistance). Despite the intensive support, not all injections were given on time.

In the multisite U.S. Observational Pharmacoepidemiology Research and Analysis (OPERA) cohort,[87] clinical data on the use of LA CAB/RPV were prospectively captured from electronic health records from 84 clinics in 18 U.S. states and territories. Among the 36 individuals who had HIV RNA >200 copies/mL before starting LA CAB/RPV and had at least one follow-up HIV RNA test, 94% had an HIV RNA <200 copies/mL at their last follow-up visit.

Taken together, until additional data are available, these approaches may provide alternatives for individuals with viremia and difficulties with adherence to oral ART, especially for those at the highest risk for disease progression or death. If either of the above approaches are employed, close monitoring is recommended with drug-resistance testing performed if virologic response is inadequate. Importantly, beyond conventional and intensive multidisciplinary team involvement, case management and outreach support are needed to ensure adherence and adequate monitoring while on LA CAB/RPV (see the Adherence to the Continuum of Care section for discussion on strategies to improve adherence in these situations). Caution with close monitoring is advised, as data are unavailable for detailed guidance regarding the need for specific adherence or intensive case management services or whether every 4- or every 8-week LA CAB/RPV will yield similar virologic outcomes in people with viremia before switching. Every 4-week dosing was used in the LATITUDE study. In the published case series to date in people with viremia, every 4-week dosing was prescribed for most, with the option of switching to every 8 weeks after achieving viral suppression. Until further data are available, it may be prudent to use similar strategies when LA CAB/RPV is

being considered. People with HIV and providers need to be aware of the significant risk of developing resistance to NNRTIs, and particularly INSTIs if virologic failure occurs on LA CAB/RPV. Such resistance may limit future treatment options and may also lead to its transmission, which should be balanced with the individual's HIV-related risk for disease progression and death.[88] Closely monitoring for viral responses is advised if LA CAB/RPV is used in people with viremia and who have challenges with adherence.

Summary

The goal of treatment for people with HIV and virologic failure is to establish virologic suppression. The management of people 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 10. Antiretroviral Options for People With HIV and Virologic Failure

Designing a new regimen for people with HIV 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 people 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 before and after regimen changes.

Clinical Scenario	Type of Failing Regimen	Resistance Considerations	New Regimen Options[a]	Goal
First Regimen Failure	NNRTI plus two NRTIs	Most likely resistant to NNRTI +/– 3TC or FTC (i.e., NNRTI mutations +/– M184V/I).[b] Additional NRTI mutations also may be present.	DTG (or possibly BIC) plus two NRTIs (preferably at least one fully active[c]) **(AI);** *or* Boosted PI plus two NRTIs (preferably at least one fully active) **(AI);** *or* Boosted PI plus INSTI (boosted DRV plus DTG **[AI]**; LPV/r plus RAL **[CI]**)	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)[b]	DTG, or possibly BIC, plus two NRTIs (preferably at least one fully active; if only one of the NRTIs is fully active[c] or if adherence is a concern, DTG is currently preferred over other INSTIs) **(AIII);** *or* Continue same regimen **(AII);** *or* Boosted PI plus INSTI (boosted DRV plus DTG **[AIII]**; LPV/r plus RAL **[CI]**); *or* Another boosted PI plus two NRTIs (at least one fully active[c]) **(AIII).**	Resuppression
	INSTI plus two NRTIs	If failure with no INSTI resistance	Boosted PI plus two NRTIs (preferably at least one fully active[c]) **(AIII);** *or* DTG, or likely BIC, plus two NRTIs (preferably at least one fully active[c]) **(AIII);** *or* DRV/r plus DTG **(AIII)**	Resuppression

Table 10. Antiretroviral Options for People with HIV and Virologic Failure

Clinical Scenario	Type of Failing Regimen	Resistance Considerations	New Regimen Options[a]	Goal
		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[c]) **(AIII);** *or* DTG[d] twice daily or possibly BIC (if HIV is sensitive) plus two fully active NRTIs **(BIII);** *or* DTG[d] twice daily or possibly BIC (if HIV is sensitive) plus a boosted PI (preferably DRV/r) **(AIII).**	Resuppression
	INSTI plus NNRTI (DTG/RPV or LA CAB/RPV)	INSTI and/or NNRTI resistance possible	Use ART history and past and current resistance testing to design a new regimen. Consult an expert in drug resistance as needed.	Resuppression
Second Regimen Failure and Beyond	Drug resistance with fully active treatment options—	Use past and current genotypic- +/– phenotypic-resistance testing and ART history when designing new regimen.	New regimen according to original treatment type—	Resuppression
	(i) Boosted PI, but not second-generation INSTI, fully active		(i) Boosted PI with two NRTIs (preferably at least one fully active)	
	(ii) Second-generation INSTI, but not boosted PI, fully active		(ii) DTG or BIC with two NRTIs (preferably at least one fully active)	
	(iii) Both PI and INSTI fully active		(iii) The two options above or boosted PI with INSTI	
	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.	New regimen should include at least two, and preferably three, fully active agents, including those with novel mechanisms of action (e.g., IBA, FTR, LEN). If fewer than three fully active drugs, include as many fully active drugs as possible, along with potentially partially active drugs **(BII).**	Resuppression if possible; otherwise, keep viral RNA levels as low as possible and CD4 count as high as possible.

Table 10. Antiretroviral Options for People with HIV and Virologic Failure

Clinical Scenario	Type of Failing Regimen	Resistance Considerations	New Regimen Options[a]	Goal
		Consult an expert in drug resistance if needed.	Consider enrollment into clinical trials or expanded access programs for investigational agents if available. Discontinuation of all ARV drugs **is not recommended (AI).**	
People 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 person has been off ART. Keep in mind that resistance mutations may not be detected in the absence of drug pressure.	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 monitoring of virologic response and early resistance testing, if inadequate virologic suppression.	Resuppression

[a] When switching an ARV regimen in a person with HBV/HIV coinfection, ARV drugs that are active against HBV and have a high resistance barrier to HBV (i.e., tenofovir) should be continued as part of the new regimen, or another HBV drug (i.e., entecavir) should be started. Discontinuation of these drugs may lead to the reactivation of HBV, which may result in serious hepatocellular damage.

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

[c] See text for details and additional options in special settings.

[d] Response to DTG depends on the type and number of INSTI mutations.

Key: 3TC = lamivudine; ART = antiretroviral therapy; ARV = antiretroviral; BIC = bictegravir; CD4 = CD4 T lymphocyte; DRV = darunavir; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EVG = elvitegravir; FTC = emtricitabine; FTR = fostemsavir; HBV = hepatitis B virus; IBA = ibalizumab; INSTI = integrase strand transfer inhibitor; LEN = lenacapavir; 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. People experiencing this present with new, usually subacute, neurological symptoms that are associated with a 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.[89-91] Clinical evaluation frequently shows abnormalities on magnetic resonance imaging (MRI) and abnormal CSF findings with characteristic lymphocytic pleocytosis.[92] In most (though not all) people, drug-resistant CSF virus is evident.[93] 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).**[94] 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 person's treatment history or on predicted drug penetration into the CNS **(CIII).**[95-98]

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[99-101]; *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).[102]

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 person with this condition are recommended to monitor for the emergence of neurologic symptoms or systemic viremia.[94] 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 people with HIV who show no evidence of CNS viral breakthrough.[103]

Neurological Symptoms in People With HIV on Antiretroviral Therapy

Evidence is currently not available to support empiric intensification or switch of ARV regimens in people on systemically suppressive ART with mild neurological and/or cognitive symptoms who do not have documented CSF escape. Such individuals 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 multinational randomized, double-blinded, placebo-controlled trial randomized 191 ART-experienced participants—with cognitive impairment and suppressed plasma HIV RNA level 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.[104]

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