CLINICAL GUIDELINES PROGRAM
NEW YORK STATE DEPARTMENT OF HEALTH AIDS INSTITUTE | HIV · HCV · SUBSTANCE USE · LGBT HEALTH

Second-Line ART After Treatment Failure or for Regimen Simplification

Guideline Information

Intended users	New York State clinicians who treat patients with HIV who require changes in their antiretroviral therapy regimens
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Updates

January 19, 2023	**Joseph P. McGowan, MD, with the MCCC:** Lenacapavir (LEN) added as a treatment option for highly treatment-experienced patients.

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Contents

Purpose and Goals of This Guideline

Purpose: This guideline was developed by the New York State Department of Health AIDS Institute (NYSDOH AI) Medical Care Criteria Committee to provide New York State clinicians with effective care management strategies for patients with HIV who require changes in their antiretroviral therapy (ART) regimens. Effective ART has allowed individuals with HIV to live longer and healthier lives than patients diagnosed earlier in the epidemic. Modern ART options are effective, safe, and simple, and guidance on their use for treatment-naive patients is available in the NYSDOH AI guideline Selecting an Initial ART Regimen and U.S. Department of Health and Human Services Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. However, clinical scenarios may arise in which a patient's ART is ineffective, leading to virologic failure, adverse effects, or drug-drug interactions with other essential medications; older ART regimens may also be burdensome for patients who may benefit from simplification.

Goals: This guideline provides information to assist clinicians in making evidence-based decisions to change ART regimens and formulate second-line and subsequent ART regimens for optimal viral suppression in patients with HIV. Toward that end, the goals of this guideline are to:

- Increase clinicians' ability to recognize ART failure
- Increase clinicians' ability to effectively manage switching a patient's initial or subsequent ART regimen when indicated to:
  - Improve viral suppression
  - Recognize and respond to virologic failure in a timely fashion
  - Improve tolerability
  - Reduce toxic effects
  - Avoid drug-drug interactions
  - Simplify (i.e., change from a multi-tablet regimen to a single-tablet regimen)
  - Ensure safety during pregnancy
- Assist clinicians in managing a patient's resumption of ART after a treatment interruption
- Assist clinicians in recognizing cases that may benefit from expert consultation, such as when choosing a new ART regimen for a patient who has already been treated with multiple ART regimens or has other complicating factors
- Encourage clinicians to seek the assistance of an experienced HIV care provider when treating patients with extensive resistance to antiretroviral drugs

Defining treatment failure: This guideline focuses on strategies for changing ART regimens to address 2 types of ART treatment failure—virologic failure and failure due to adverse effects or intolerance. The guideline also addresses modifications of suppressive therapy to avoid drug interactions with concomitant medications or to simplify ART to enhance tolerability and adherence. See the guideline section Defining Virologic Failure, for more information.

This guideline does not focus on *immunologic* failure, sometimes referred to as a "CD4/viral load disconnect," which is defined as a fully suppressed HIV viral load on ART without a restoration of CD4 cell count above a target threshold, such as 200 or 500 cells/mm^3. Immunologic failure has been associated with increased age and low CD4 cell count (nadir) at treatment initiation [Prabhakar, et al. 2011]. Studies have indicated that excess morbidity and mortality can occur if the CD4 count remains below 500 cells/mm^3 [Lewden, et al. 2012]. No specific interventions or use of immune-based therapy, such as interleukin-2, have persistently improved CD4 counts, and immune-based therapy may increase immune activation, which can be detrimental to viral reservoir control [Abrams, et al. 2009]. It is appropriate to treat active infections, including opportunistic infections, but incomplete CD4 recovery may persist if ongoing immune activation is present [Lederman, et al. 2011]. Switching ART for a patient with viral suppression would not significantly affect CD4 recovery or decrease immune activation [Hunt, et al. 2013].

Identifying and Managing Virologic Failure

☑ RECOMMENDATIONS

Identifying and Managing Virologic Failure

- When a patient's plasma HIV-1 RNA level (viral load) is not suppressed to <200 copies/mL by 24 weeks after antiretroviral therapy (ART) initiation or if it rebounds to ≥200 copies/mL after suppression has been achieved, the clinician should confirm the result with a repeat HIV RNA test within 4 weeks of the original test. (A3)
  - See the NYSDOH AI guideline Virologic and Immunologic Monitoring in HIV Care > Viral Load and CD4 Count Monitoring Intervals.
- When a patient's viral load test result indicates virologic failure (HIV RNA ≥200 copies/mL) or low-level viremia (HIV RNA 50 to 199 copies/mL) confirmed over a period of at least 1 month, the clinician should assess for and address the following factors that may reduce ART efficacy:
  - Adherence (A2)
  - Interactions between ART agents and concomitant medications, including over-the-counter medications and supplements (e.g., divalent cations, St. John's wort) (A*)
  - Adverse effects that lead to poor adherence or cessation of treatment (A2)
  - Reviews of all prior drug resistance testing results, previous treatment experience, and reason for treatment changes or discontinuation (A3)

☑ RECOMMENDATIONS

- For all cases of virologic failure, clinicians should perform genotypic resistance testing, ideally while the patient is taking the failing regimen or no longer than 4 weeks after discontinuation. (A2)
  - If the viral load is ≥500 copies/mL, clinicians should obtain a plasma RNA genotype test. (A2)
  - If the breakthrough viral load is <500 copies/mL, clinicians should obtain an archived DNA genotype test if viral suppression is not achieved after any drug-drug interactions or problems with adherence have been addressed. (B3)
- In patients with persistent low-level viremia, clinicians should consult an experienced HIV care provider; low-level viremia can have multiple causes, and its clinical effect is unclear. (A3)

Defining Virologic Failure

Virologic failure is defined as a confirmed HIV viral load ≥200 copies/mL despite a patient's use of recommended ART for at least 24 weeks or a viral load that rebounds to ≥200 copies/mL after a patient achieves viral suppression. When unsuppressed, persistent HIV replication leads to the development of resistance-associated mutations (RAMs), loss of CD4 T-helper cells, and associated clinical consequences. Table 1, below, summarizes types of HIV resistance tests and their uses.

RAMs represent alterations of HIV genetic code at specific locations, such as the gene that encodes the reverse transcriptase enzyme that copies the viral RNA into DNA, the protease gene that processes viral proteins, or the integrase gene that enables viral genes to be incorporated into host chromosomal DNA. These alterations lead to a substitution (change) in the usual amino acid pattern of that protein that has been linked to decreased activity of a drug used to block it. For example, the most common RAM is the M184V mutation of the reverse transcriptase gene selected by use of emtricitabine or lamivudine, in which the amino acid valine at position 184 of the encoding gene is substituted for the usual methionine [Shafer and Schapiro 2008]. The mutation allows the enzyme to function and the virus to replicate in the presence of the drug. Mutations that do not lead to amino acid changes or that do not affect the function of antiretroviral medications (ARVs) would be silent and not be counted as RAMs.

Table 1: Types of HIV Resistance Tests [a]

Test	Description	Use
Genotype	• Assesses mutations in the HIV RNA genes that encode enzymes targeted by ARVs: reverse transcriptase, protease, integrase • Algorithms interpret the effect of mutations on ARV efficacy	• At diagnosis, when a patient has incomplete virologic response to ART, or when viral rebound occurs • Has utility if plasma HIV-1 RNA level (viral load) is ≥500 to 1,000 copies/mL • May not detect all RAMs
Phenotype	• Assesses the effect of HIV genes on the ARV concentration required to inhibit viral growth compared with wild-type (nonmutant) virus • Estimates a fold change	• Historically used to help assess the effect of the interplay of multiple RAMs on viral growth • Supplanted by more comprehensive genotypic interpretation algorithms
Proviral DNA genotype (archived genotype)	• Assesses genetic mutations in HIV proviral DNA genes that encode enzymes targeted by ARVs: reverse transcriptase, protease, and integrase • Algorithms interpret the effect of mutations on ARV efficacy	• When planning ART simplification or other changes, may have a role in identifying RAMs when standard genotype testing may not yield results, i.e., in patients who have prior treatment experience, have stopped taking ARVs for >4 weeks, or have an HIV viral load <500 to 1,000 copies/mL or below the limit of quantification • May not detect all RAMs or report RAMs from defective non-replication-competent proviral DNA [Li, et al. 2021]

Table 1: Types of HIV Resistance Tests [a]		
Test	**Description**	**Use**
Tropism test	Assesses the effect of HIV RNA (or proviral DNA) gp120 on the coreceptor(s) used for viral attachment: CCR5, CXCR4, or mixed/dual	• Treatment-experienced patients for whom a coreceptor antagonist is being imminently considered • RNA tropism test can be used with viral loads ≥1,000 copies/mL; proviral DNA test can be used for viral loads <1,000 copies/mL

Abbreviations: ART, antiretroviral therapy; ARV, antiretroviral medication; gp120, envelope glycoprotein 120; RAM, resistance-associated mutation.

Note:

a. All resistance assays are affected by limitations of detection; minor variants may not be present at high enough concentrations to be amplified by the assay.

Persistent low-level viremia: Persistent, even low-level, HIV viremia of >50 copies/mL for at least 1 month is associated with increased all-cause mortality, AIDS events, and development of RAMs [Elvstam, et al. 2021; Bernal, et al. 2018; Elvstam, et al. 2017; Vandenhende, et al. 2015; Ryscavage, et al. 2014; Delaugerre, et al. 2012]. At low levels of viremia, the error-prone HIV reverse transcriptase creates RAMs under the selective pressure of ART, causing ART to lose efficacy. Persistent low-level viremia has been found more often in treatment-experienced patients than in those on initial ART, suggesting that unrecognized preexisting resistance may contribute to treatment failure [Ferretti, et al. 2019; Fleming, et al. 2019].

Low-level viremia has been specifically associated with protease inhibitor (PI)-based treatment. One explanation for this finding may be prescriber bias in choosing PIs if adherence is a concern. Another explanation could be that when viral reservoirs are high (high pretreatment viral loads or prolonged unsuppressed viremia), the immature virions released on PI therapy are measurable [Sedaghat, et al. 2008]. A third possibility is that low-level viremia could result from mutations developing in the gag polyprotein gene at the protease cleavage sites, which would not be reported on standard population genotyping [Fleming, et al. 2019].

However, not all causes of low-level viremia have the same implications. Low-level viremia in patients with poor or intermittent adherence increases the risk of treatment failure, whereas the same level of viremia with consistent adherence in the absence of underlying resistance does not. Therefore, adherence is the first issue to address when low-level viremia is detected, and a change in ART is required to address any identified preexisting mutations (see the discussion of proviral DNA genotyping in Resistance-Associated Mutations in this guideline). One retrospective study of patients taking ART who had residual detected viremia (viral load 50 to 500 copies/mL) found a reduction of viral load following intensification with the CCR5 antagonist maraviroc [Dû, et al. 2016]. The underlying cause of persistent low-level viremia may be difficult to discern clinically. Therefore, instead of intensifying by adding a single agent, it is advisable to assess or, if needed, modify an existing regimen to optimize use of active agents, such as by including drugs with high barriers to resistance [Crespo-Bermejo, et al. 2021].

If adherence is not a problem and no RAMs have been identified, low-level detectable virus (viral load <200 copies/mL) may be a reflection of the viral reservoir size or the consequence of proviral DNA integration into an active, constitutively replicating gene in the CD4 chromosome that produces virus ongoing from a single infected clone [Halvas, et al. 2020; Jacobs, et al. 2019; Zhang, et al. 2019]. In these circumstances, treatment intensification would not reduce a detectable viral load and a switch to treatment with a nucleoside/nucleotide reverse transcriptase inhibitor (NRTI) plus a PI could inactivate the post-transcriptional virus and prevent the next cycle of reverse transcription.

The source of persistent low-level viremia (viral load <50 copies/mL) has been debated. It may emerge from ongoing viral replication, which is prone to reverse-transcriptase-induced development of RAMs, or it could be the result of post-integration release from the viral reservoir (clonal origin); clonal origin virus is blocked from infecting new cells by the presence of ongoing active ART. Intensifying treatment by adding a new non-nucleoside reverse transcriptase inhibitor (NNRTI), PI, CCR5 antagonist, or integrase strand transfer inhibitor (INSTI) to an ART regimen has not been shown to reduce residual viral load or immune activation in patients with a viral load <50 copies/mL [Gutiérrez, et al. 2011; Gandhi, et al. 2010; Dinoso, et al. 2009]. Studies evaluating the evolution of viral genetic mutations in proviral DNA following infection have indicated an arrest of widening diversity after the introduction of suppressive ART [Kearney, et al. 2014].

These findings demonstrate that residual viremia likely emerges from preestablished viral reservoirs through stimulation of post-integration virus rather than through replication via mutation-prone reverse transcription and would not be suppressed by adding ARVs to existing ART regimens. This is supported by several studies demonstrating that treatment intensification, such as adding an INSTI to an existing ART regimen, does not affect the viral load [Gandhi, et al. 2010; McMahon, et al. 2010; Steigbigel, et al. 2008]. Although ART modification does not decrease viremia if replication is fully suppressed, it is often clinically challenging to assess the effect of complicating factors, such as adherence and drug or food interactions, on measured low-level viremia; therefore, some experts would use only an ART regimen that contains an agent with a high genetic barrier to resistance in such situations.

Blips: Occasionally, the detection of low-level viremia is an isolated event, and viral suppression is confirmed on a repeat viral load test. These events are called "blips" if they are in the range of 50 to 200 copies/mL and are preceded and followed by viral load measurements of <50 copies/mL (i.e., full viral suppression). Blips have not been found to increase future risk of virologic failure [Havlir, et al. 2001]. The increased sensitivity of HIV viral load assays allows the detection of viral load levels as low as 20 copies/mL. Transient low-level viremia may also be the result of T-cell activation associated with opportunistic infections and chronic immune activation, which should be considered when clinically indicated, such as during immune reconstitution following ART initiation to diagnosed or unmasked infections [Younas, et al. 2021; Jones and Perelson 2005]. Quantifiable HIV viremia <50 copies/mL has not been associated with subsequent therapeutic failure or emergence of drug resistance [Teira, et al. 2017]. In cases of very low-level viremia or blips, adjustment of the ART regimen is not required.

→ KEY POINTS

- Virologic failure is defined as a confirmed HIV viral load ≥200 copies/mL despite a patient's use of recommended ART for at least 24 weeks or an HIV viral load that rebounds to ≥200 copies/mL after a patient achieves viral suppression.
- Persistent low-level viremia (HIV RNA 50 to 199 copies/mL) confirmed over a period of at least 1 month may be the cause or result of chronic immune activation and should prompt a clinician to assess for adherence, preexisting resistance, or drug-drug interactions.
- Once underlying drug resistance, potential drug-drug interactions, and adherence have been addressed, persistent low-level viremia may reflect a large viral reservoir size or the consequence of constitutive, post-integration virus production from a single infected clone.
- Identifying and addressing adherence problems causing virologic failure can prevent unnecessary ART intensification. Treatment intensification can further complicate adherence and expose additional classes of ARVs to the risk of resistance development.

Causes of Virologic Failure

Virologic failure may occur for several reasons, and a timely investigation is imperative to prevent RAMs and subsequent loss of immune function. The most likely causes of ART-associated virologic failure are poor adherence, pharmacokinetic drug-drug interactions that lead to subtherapeutic target drug concentrations, and the presence (through transmission) or development of drug resistance mutations (see the NYSDOH AI resource ART Drug-Drug Interactions). The time it takes for drug resistance to emerge is related to several factors, including the height of the residual viral load, the level of drug exposure, the specific medications used, and the patient's pattern of adherence. Virologic failure can occur within months or within weeks, especially because a single RAM can lead to failure for some medications [Feder(b), et al. 2021].

Adherence: Poor or incomplete adherence, commonly defined as less than 90% to 95% of doses taken, is one of the most common reasons for virologic failure or relapse [Ortego, et al. 2011]. It is important to verify that the patient can identify their ART medications and confirm pharmacy refills to ensure proper access as part of an adherence assessment. Poor ART adherence has been associated with younger age, male sex, Black race, low income and education level, injection drug use, alcohol use, and lack of effective adherence support [Papageorgiou, et al. 2022; Benson, et al. 2020]. Patients who experience adverse effects may not adhere to their ART regimen or may stop taking the medications altogether. Other barriers to adherence include inability to pay for medications, substance use, housing instability, health literacy, language barriers, and mental illness. Identifying and addressing modifiable barriers and providing support for optimal adherence are crucial. Socioeconomic barriers, stigma, financial limitations, unstable housing, and disbelief in treatment value may also reduce adherence. Young adults and adolescents are at particularly high risk of poor ART adherence [Kim, et al. 2014]. Routine patient education and a multidisciplinary approach are key to addressing these issues. Inclusion of

peers to facilitate adherence to ART regimens is effective, and peers are viewed as credible sources for health information [Enriquez, et al. 2019; Houston, et al. 2015].

Forgetfulness is a modifiable factor that can be addressed by dispensing ART medications in pre-filled pill trays or dose packs, monitoring pharmacy refill patterns; setting up digital alerts; sending messages from healthcare providers, peers, or case managers; encouraging support from family or friends; linking medication timing to routine daily activities; or using long-acting injectable medications.

Management of chronic comorbidities and coinfections often adds a significant number of daily medications, which may complicate a patient's ability to adhere to an ART regimen. ART simplification to lower pill burden is addressed in ART Changes for Regimen Simplification.

Identifying and addressing adherence problems causing virologic failure can prevent unnecessary ART intensification. Treatment intensification can further complicate adherence and expose additional classes of ARVs to the risk of resistance development.

If virologic failure is detected in a patient taking a complete ART regimen who does not report missing doses, genotypic resistance testing should be performed. A standard genotype test is appropriate if the patient's HIV viral load is ≥500 copies/mL [Swenson, et al. 2014]; an archive genotype test may be considered if persistently detectable viral load below that level is found.

The hallmark of nonadherence as the cause of virologic failure is the presence of wild-type virus (i.e., no pertinent RAMs) or a genotype test result indicating that the prevalent viral population is fully susceptible to the prescribed ART regimen. Susceptible virus should be suppressed; resistant virus predominates in the presence of full selective pressure. In these cases, it is essential to identify and address adherence challenges. It may be appropriate to select a single-tablet regimen with higher forgiveness for incomplete adherence (or higher "genetic barrier"), such as a boosted PI or second-generation INSTI-based regimen [Anstett, et al. 2017]. The preferred agents from these classes in the absence of baseline resistance are:

- Abacavir/lamivudine/dolutegravir (ABC/3TC/DTG; Triumeq); *or*
- Tenofovir alafenamide/emtricitabine/bictegravir (TAF 25 mg/FTC/BIC; Biktarvy); *or*
- Tenofovir alafenamide/emtricitabine/cobicistat/darunavir (TAF 10 mg/FTC/COBI/ DRV; Symtuza).

Resistance-Associated Mutations

"Transmitted resistance" refers to RAMs present at the time of HIV acquisition (see Table 2, below, for prevalence of transmitted RAMs). To construct a fully suppressive ART regimen, clinicians have to first recognize these mutations, which requires baseline genotypic resistance testing before ART initiation to identify any highly represented strains. Recommendations for same-day "rapid initiation" of ART regimens have been selected for activity against virus containing the most prevalent transmitted RAMs.

Table 2: Prevalence of Transmitted HIV Drug Resistance-Associated Mutations

Population	Prevalence of RAMs
36,288 genotype sequences from individuals who acquired HIV in the United States between 2013 and 2016 [McClung, et al. 2019]	**Transmitted: 19.0%** • NNRTI: 11.9% • NRTI: 6.8% • PI: 4.3% • INSTI: 0.8%
3,616 genotype sequences acquired from ART-naive individuals in California from 2008 to 2018 [Feng, et al. 2020]	**Transmitted: 20.0%** • NNRTI: 11.7% • NRTI: 7.5% • PI: 4.3% • INSTI: 1.5%

Abbreviations: INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; PI, protease inhibitor; RAM, resistance-associated mutation.

Multiclass drug resistance: The emergence of multiclass drug-resistant virus presents challenges in managing ART. Rates of "triple class" (NRTI, NNRTI, and PI) resistance were found in 10% of longitudinal care patients at a U.S. HIV specialty center, where multiclass drug resistance was associated with low CD4 count and high viral load at ART initiation, prolonged ART use, initiation with non-highly active ART regimens, or use of many different ARVs over many years [Davy-Mendez, et al. 2018; Napravnik, et al. 2007]. In the multicenter Pediatric HIV/AIDS Cohort Study, the rate of triple-class-resistant virus was 18% among individuals with perinatally acquired HIV [Van Dyke, et al. 2016].

With the advent of INSTIs, many individuals with triple-class-resistant virus can now achieve viral suppression. Treatment failure with first-generation INSTIs (raltegravir or elvitegravir) has been associated with significant cross-resistance to the second-generation INSTIs dolutegravir and bictegravir [Orta-Resendiz, et al. 2020]. As ART regimens have been simplified, it appears that rates of resistance to NRTIs, NNRTIs, and PIs peaked around 2005 and may be on the decline while rates of INSTI resistance have been increasing over time [Davy-Mendez, et al. 2018], to the extent that 5-class resistant viruses have now been reported [Puertas, et al. 2020; Magambo, et al. 2014].

Genotypic resistance testing: Genotypic resistance testing should be performed in all cases of virologic failure [Weinstein, et al. 2001] (see the NYSDOH AI guideline HIV Resistance Assays). If a patient's plasma HIV-1 plasma viral load is ≥500 copies/mL, a standard plasma RNA genotype should be obtained; if the breakthrough viral load is <500 copies/mL, an archived DNA genotype test may be considered if viral suppression is not achieved after addressing adherence and drug-drug interaction issues.

Timing: The timing of genotyping with HIV RNA is important. A viral load ≥500 copies/mL is typically necessary to detect RAMs. A lower level of viremia may lead to assay failure. Ideally, the test should be performed while the patient is taking a failing regimen. Stopping ART would remove selective pressure and allow wild-type (nonmutated) HIV to repopulate and dilute out the resistant strain of HIV, hindering the chance to identify RAMs that may have developed. If ART is stopped, resistance testing should be performed within 4 weeks. Beyond week 4, the ability to detect mutations may decay at a variable rate (transmitted mutations and those that have less effect on viral growth fitness may persist longer), making standard genotyping less reliable, in which case HIV DNA testing may be more informative [Ellis, et al. 2020; Iarikov, et al. 2010].

Even with appropriate timing, these assays may not provide complete information because resistant strains may only be represented as a minority species and evade amplification. Therefore, it is crucial to review prior testing results for RAMs (genotypes) and phenotypic resistance test results and inquire about prior nonsuppressive ART regimens to identify likely resistance and cross-resistance patterns. Factors that increase the likelihood of virologic failure and potential RAM development include virologic breakthrough on an ART regimen with a low genetic barrier, longer time with unsuppressed viremia, treatment with an incomplete ART regimen, or partial adherence to ART [Cohen, et al. 2013; Daar, et al. 2011; Riddler, et al. 2008].

RAMs can be detected by sequencing circulating plasma HIV RNA or, less commonly, by sequencing proviral DNA in CD4 cells (archive genotype test). Caution is advised in interpreting results of proviral DNA genotype testing because it may not amplify all previously existing archived resistant strains, especially after long-term viral suppression when the density of residually infected CD4 cells may be sparse (i.e., founder effect) [Derache, et al. 2015], and it may identify mutations that are not associated with replication-defective proviral DNA [Li, et al. 2021]. The utility of next-generation DNA sequencing is also challenged by the identification of RAMs from minor variants predictive of virologic failure from patients fully suppressed on the jeopardized regimen [Inzaule, et al. 2018]. The proportion of archived minor variants in the population that might affect viral suppression is unknown.

Currently, no genotypic tropism assay is available commercially, although algorithms to predict viral tropism from genotypic sequences are under investigation. For patients with a plasma viral load ≥500 copies/mL and for whom use of a coreceptor antagonist is being imminently considered, phenotypic testing (Trofile) can be used to assess RNA tropism; in patients with lower or undetectable plasma viral loads, a DNA tropism assay (Trofile DNA) may be used.

Table 3: Genotypic Resistance Testing Based on Viral Load

HIV RNA (Viral Load)	Indicated Genotypic Resistance Test
0 to 500 copies/mL	HIV proviral DNA genotype (RT, PR, INT) or phenotype (tropism)
500 to 1,000 copies/mL	HIV RNA genotype (RT, PR, INT) or phenotype (tropism) at assay amplification threshold; may use HIV proviral DNA test if nonamplifiable
≥1,000 copies/mL	HIV RNA genotype if currently or recently (within 4 weeks) on ART; DNA proviral genotype may be considered for patients who are currently not taking ART but have in the past

Abbreviations: ART, antiretroviral therapy; INT, integrase; PR, protease; RT, reverse transcriptase.

ART Changes to Address Drug Resistance

☑ RECOMMENDATIONS

ART Changes to Address Drug Resistance

- When choosing a new ART regimen for a patient with drug-resistant virus, clinicians should:
  - Choose a regimen that is likely to fully suppress viral replication, even if it may require multi-tablet dosing. (A1)
  - Document and evaluate the importance of all RAMs and identify the most tolerable regimen to suppress drug-resistant HIV effectively. (A3)
- Clinicians should address barriers to ART adherence that may have contributed to failure of a patient's first-line regimen. (A2)
- In constructing a new regimen to replace a failed ART regimen, the clinician should:
  - Review all prior genotype or phenotype resistance assay results that are retrievable and previous instances of virologic treatment failure to assist in identifying potentially active medications. (A2)
  - Select agents to which the patient is naive or active second-generation agents within a previously prescribed class to avoid potential within-class cross-resistance. (A2)
  - Select a regimen containing an agent with a high barrier to resistance, such as DRV, DTG, or BIC, if the M184V RAM is present and FTC/3TC will be used in conjunction with TAF/TDF. (A*)
  - Avoid monotherapy (i.e., an ART regimen with fewer than 2 fully active agents). (A1)
  - Choose the equivalent of 3 fully active ARVs; a 2-drug regimen may be prescribed when both are fully active and at least 1 is an agent with a high resistance barrier, i.e., a boosted PI or a second-generation INSTI. (A2)
  - Consult with an experienced HIV care provider when planning treatment regimens for patients with multiclass drug-resistant virus. (A3)
  - If a patient has chronic HBV infection, include TAF/TDF in conjunction with 3TC/FTC or another agent with activity against HBV (e.g., ETV) in the patient's ART regimen. (A2)
- Clinicians should closely monitor the patient's response to ART by obtaining an HIV RNA test within 4 weeks of a change in regimen and at least every 8 weeks thereafter until virologic suppression is achieved. (A3)
  - See the NYSDOH AI guideline Virologic and Immunologic Monitoring in HIV Care.

Abbreviations: 3TC, lamivudine; ART, antiretroviral therapy; ARV, antiretroviral medication; DRV, darunavir; DTG, dolutegravir; ETV, entecavir; FTC, emtricitabine; HBV, hepatitis B virus; INSTI, integrase strand transfer inhibitor; PI, protease inhibitor; RAM, resistance-associated mutation; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

Guiding Principles

Selection of an effective ART regimen for patients with preexisting or selected ARV drug resistance can be challenging but is achievable by following 4 guiding principles:

- Address the barriers to adherence that may have contributed to first-line treatment failure [Schaecher 2013].
- Do not compromise treatment efficacy for convenience.
- Account for all RAMs that may have been transmitted or selected during prior treatment courses.
- Strive to construct the most tolerable and acceptable treatment regimen to suppress preexisting drug-resistant HIV effectively.

The ideal: The ideal ART regimen optimizes pharmacokinetics and adverse effect profiles, is easy to adhere to, and accounts for RAMs. One resource for assessing the effect of RAMs is the Stanford University HIV Drug Resistance Database. Importing RAMs into this algorithm allows clinicians to weigh the efficacy of different ARVs and avoid those with limited activity due to high resistance levels. It is crucial to review all previous genotypic and phenotypic resistance test results, to the extent possible, to identify any RAMs that have been present at any time during a patient's treatment history. RAMs that may have been identified on historical resistance test reports that are not reported on subsequent testing should be considered to be archived within integrated HIV genomes. That is, these resistant strains remain

dormant (latent) within long-lived CD4 cells and can reemerge during subsequent therapy that does not contain medications that remain active in their presence. Therefore, constructing a composite genotype of all identified RAMs to account for any present or archived strains may help in selecting subsequent ART regimens. HIV-ASSIST offers a free online tool for selecting ART regimens based on HIV drug resistance mutations and comorbidities. Creating a fully suppressive treatment regimen is the goal, but HIV can evolve resistance to all existing classes of ARVs, especially in long-term survivors who were adherent to serial treatment intensifications as new agents were developed. Management of such cases requires expertise in identifying partially active agents that, when combined, can slow viral growth and fitness to replicate [Buckheit 2004]. For highly treatment-experienced patients with limited options, clinicians can search ClinicalTrials.gov for active studies of novel therapeutics for HIV, which may include monoclonal antibodies, long-acting agents, and agents with unique mechanisms of action and next-generation molecules.

Identifying Switch Options

Strains: In some cases of high-level multidrug-resistant virus with few evident treatment options in which a number of previously obtained genotypic or phenotypic test results are available, it is helpful to look at patterns of mutational sequences to identify strains that may have been selected by past treatment sequences to construct regimens that have at least 2 drugs with activity for each strain. For example, there may be a genotype test result demonstrating 1 or more thymidine analog resistance mutations (TAMs) from prior zidovudine (ZDV) use along with non-nucleoside reverse transcriptase inhibitor (NNRTI) mutations from past efavirenz (EFV) use, but a subsequent genotype test result may show a nucleoside/nucleotide reverse transcriptase inhibitor (NRTI) RAM such as K65R selected by tenofovir (TFV) and PI mutations. An archive genotype test may show all of the NRTI, NNRTI, and PI mutations; however, interpretation of the sequences from serial past genotypes may clarify that these mutations may not all be present on any single strain, but rather an earlier strain that is susceptible to both PIs and INSTIs and a latter strain susceptible to NNRTIs and INSTIs. Therefore, a regimen of a PI/INSTI/NNRTI would provide 2 fully active drugs, 1 of which has a high genetic barrier, for both strains.

Potency and resistance barrier: Because of the variety of ARV therapeutic classes available and the availability of later-generation agents that are effective against virus otherwise resistant to older drugs within a class, multiple treatment options may remain after RAMs have developed. In these cases, potency and barrier to resistance should determine drug choices. Generally, agents with a higher barrier to resistance include bictegravir (BIC) and DTG among the INSTIs, ritonavir-boosted DRV (DRV/RTV) among PIs, and etravirine (ETR) and doravirine (DOR) among NNRTIs. For example, a meta-analysis of 7 randomized clinical trials that included 1,686 treatment-naive and -experienced participants who used a once-daily boosted DRV regimen found that only 4 (0.2%) developed a PI or DRV RAM and only 1 (<0.1%) developed DRV resistance [Lathouwers, et al. 2017]. Including a drug with a high resistance barrier not only protects against development of RAMs after treatment failure but also reduces the likelihood that resistance to other drugs in the regimen will develop [Luber 2005].

The effect of resistance barrier on viral suppression was illustrated in the SWITCHMRK trial, in which treatment-experienced participants who were virally suppressed on a high genetic barrier boosted PI-based regimen of RTV-boosted lopinavir (LPV/RTV) were randomized to continue their current regimen or switch to a raltegravir (RAL)-based regimen, an INSTI with a low genetic barrier, to assess effect on lipid control [Eron, et al. 2010]. Virologic control was not maintained to the same extent in those who switched to RAL as in those who continued LPV/RTV.

Resistance barrier can be defined by the number of mutations that must be accumulated to incur resistance or the relative ease with which a mutation will emerge in the virus under selective pressure. Some mutations, such as the NRTI mutation K65R associated with TFV use, are rarely selected compared with others, such as the NRTI mutation M184V associated with 3TC or FTC use. Factors such as drug effectiveness, preexisting RAMs, and effect on viral growth capacity (fitness) can affect the relative ease of mutation selection during therapy [Brenner and Coutsinos 2009]. The NADIA trial conducted in sub-Saharan Africa demonstrated the benefit of using a boosted PI or an INSTI with a high genetic barrier after NNRTI failure in individuals with NRTI resistance [Paton, et al. 2022]. Participants were randomized to receive DRV/RTV once daily or DTG once daily with either TDF/FTC or ZDV/3TC. At 96 weeks, DTG was noninferior to DRV/RTV, although 4% of participants developed DTG RAMs and none developed DRV RAMs on their respective treatments. Continuing TDF/FTC was superior to switching to ZDV/3TC despite nearly 58% of those assigned to the TDF/FTC arm having no predicted NRTI activity. The benefit of retaining TDF/FTC may be related to the low fitness of virus containing K65R and M184V mutations, as well as lower adherence due to twice daily dosing and poorer tolerability of ZDV.

Table 4, below, lists ARVs categorized by their level of genetic barrier to resistance.

Table 4: Antiretroviral Medications by Level of Genetic Barrier to Resistance [a,b]		
Low Resistance (single mutation)	**Intermediate Resistance (1 or 2 mutations)**	**High Resistance (>2 mutations)**
• Lamivudine • Emtricitabine • Efavirenz • Nevirapine • Rilpivirine • Raltegravir • Elvitegravir	• Tenofovir disoproxil fumarate • Tenofovir alafenamide • Zidovudine • Abacavir • Doravirine • Cabotegravir • Fostemsavir • Enfuvirtide	• Etravirine • Dolutegravir • Bictegravir • Darunavir [c] • Atazanavir [c] • Maraviroc
Notes: a. Derived from [Lataillade, et al. 2018; Oliveira, et al. 2018; Tang and Shafer 2012] b. For group M, subtype B HIV c. Combined with ritonavir or cobicistat		

Selecting the most effective ART regimen to suppress an HIV strain with established RAMs requires an understanding of the available treatment options, appreciation of cross-class resistance among related agents, and avoidance of combinations that have not demonstrated potency in clinical trials.

Available ARV classes: The box below lists the 7 currently available classes of ARVs in the order of their position in interruption of the HIV life cycle.

Box: Antiretroviral Medication Classes in Order of Position in Interruption of HIV Life Cycle

- **Attachment inhibitors:** Fostemsavir (FTR; Rukobia), ibalizumab (IBA; Trogarzo)
- **Coreceptor antagonist:** Maraviroc (MVC; Selzentry)
- **Fusion inhibitor:** Enfuvirtide (T20; Fuzeon)
- **Capsid inhibitor:** Lenacapavir (LEN, Sunlenca)
- **Nucleoside/nucleotide reverse transcriptase inhibitors:** Abacavir (ABC; Ziagen), emtricitabine (FTC; Emtriva), lamivudine (3TC; Epivir), tenofovir (TFV)
- **Non-nucleoside reverse transcriptase inhibitors:** Doravirine (DOR; Pifeltro), efavirenz (EFV; Sustiva), etravirine (ETR; Intelence), rilpivirine (RPV; Edurant)
- **Integrase strand transfer inhibitors:** Bictegravir (BIC; Biktarvy), dolutegravir (DTG; Tivicay), raltegravir (RAL; Isentress), elvitegravir/cobicistat (EVG/COBI; Genvoya or Stribild), cabotegravir (CAB; Cabenuva)
- **Protease inhibitors:** Atazanavir (ATV; Reyataz), darunavir (DRV; Prezista), ritonavir (RTV; Norvir; as a pharmacokinetic booster), tipranavir (TPV; Aptivus)

Cross-resistance within ARV classes: Although an ARV class may include several drugs, they often share resistance profiles, which may limit options for a switch within a class. For example, among NRTIs, FTC and 3TC share complete resistance. Some drugs within a class can retain activity after failure of related compounds. For example, EFV treatment may fail with the development of the K103N mutation, but rilpivirine (RPV), DOR, and ETR would still retain activity. Drugs developed later that have higher resistance barriers are referred to as second (or later) generation and include ETR (NNRTI), DTG and BIC (INSTIs), and DRV and TPV (PIs). The International Antiviral Society-USA has developed tables of the major and minor mutations associated with ARV resistance that illustrate the overlap across drugs within classes. Major mutations are those with a more profound effect on virus susceptibility. In general, HIV resistance develops stepwise, with the primary mutation appearing first. This mutation allows the virus to survive and continue to replicate under the pressure of drug treatment. If HIV is not resuppressed, additional mutations will emerge that increase viral growth fitness and also increase the potential for cross-class resistance. For example, the initial RAM usually selected by RPV is E138K,

which would have little effect on other NNRTIs [Hayashida, et al. 2016]. Understanding the unique patterns of resistance selection by drugs and responding rapidly to virologic failure can be useful in selecting the most effective ART options.

HIV resistance evolves in a predictable manner over time, with drugs with a lower resistance barrier affected first, allowing viral replication and further selection pressure to reduce effectiveness of other drugs in the regimen and enhance growth capacity. RAMs can evolve rapidly; for example, half of a population of virus will become resistant to 3TC (from selection of a single mutation) within 5 weeks of 3TC monotherapy [Feder(a), et al. 2021]. Resistance to currently preferred combinations takes longer and depends on several factors, including resistance barrier, regimen potency, medication exposure, and viral load, making it unlikely that resistance will emerge while resistance testing results are pending. That time affords the opportunity to address adherence barriers that might be contributing to poor viral response.

Patients who have viral breakthrough or suppressed viral load despite having virus that is resistant to a single therapeutic class can still have options for simplified therapy, including single-tablet regimens (see Table 5). To adopt this approach, therapy regimens must be based on a complete history of previous treatment failures, resistance testing, and tolerability.

Table 5: ART Options After First-Line Treatment Failure With Single-Class Drug Resistance [a]

Failed First-Line Regimen Drug Classes	Classes and Medication Options for Switch
2 NRTIs + 1 NNRTI [a]	• 2 NRTIs + 1 boosted PI: – TAF/FTC/DRV/COBI (single tablet) – TAF/FTC + DRV/RTV • 2 NRTIs + 1 INSTI: – TAF/FTC/BIC (single tablet) – TAF/FTC + DTG
2 NRTIs + 1 PI [a]	• 2 NRTIs + 1 INSTI: – TAF/FTC/BIC (single tablet) – TAF/FTC + DTG • 1 INSTI + 1 NNRTI: RPV/DTG (single tablet) • 2 NRTIs + 1 twice-daily boosted PI
2 NRTIs + 1 INSTI [a]	• 2 NRTIs + 1 boosted PI: – TAF/FTC/DRV/COBI (single tablet) – TAF/FTC + DRV/RTV
Multiclass	• 2 NRTIs + 1 INSTI + 1 boosted PI +/- 1 NNRTI (based on genotype): – Consider: MVC [b], FTR, IBA, LEN, ETR, DOR, RPV, TPV

Abbreviations: ART, antiretroviral therapy; BIC, bictegravir; COBI, cobicistat; DOR, doravirine; DRV, darunavir; DTG, dolutegravir; ETR, etravirine; FTC, emtricitabine; FTR, fostemsavir; IBA, ibalizumab; INSTI, integrase strand transfer inhibitor; LEN, lenacapavir; MVC, maraviroc; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; PI, protease inhibitor; RAM, resistance-associated mutation; RPV, rilpivirine; RTV, ritonavir; TAF, tenofovir alafenamide; TPV, tipranavir.

Notes:

a. Single-class resistance, with no major NRTI RAMs other than M184V
b. If current tropism assay indicates exclusive R5 tropic virus

Alternative strategy: It has been a general principle of ART strategy to include new medication classes when constructing second-line and subsequent ART regimens following virologic failure and drug resistance selection. In particular, the addition of high genetic barrier agents, such as a PI (boosted with either RTV or COBI) or a second-generation INSTI, can improve successful viral suppression.

An alternative or complementary strategy is to include later-generation agents within a class that may retain activity against the resistant strain, such as the boosted PIs DRV or TPV; the NNRTI ETR, and in some instances RPV (with K103N only) or DOR; and the INSTIs DTG and BIC. For example, in the DUET 1 and 2 trials, which enrolled adults on failing therapy with NNRTI and PI resistance mutations, the combination of a second-generation NNRTI (ETR) and boosted PI (DRV/RTV)

achieved sustained viral suppression for 96 weeks [Katlama, et al. 2010]. TFV may retain activity due to its barrier to resistance related to viral hindrance from selecting its primary resistance mutation K65R (discussed above). Likewise, 3TC has been demonstrated to retain clinical activity (as discussed below) even in the presence of its signature drug resistance mutation M184V [Ciaffi, et al. 2017].

→ KEY POINT

- If a patient has evidence of chronic or active HBV infection, ARVs with activity against HBV (e.g., TFV, 3TC, and FTC) should be maintained in new ART regimens to avoid a flare of HBV due to treatment interruption.

How Many Active Drugs Are Enough?

The traditional answer is 3 (see below for the exception). Based on this principle, ARVs are added to a regimen until it accumulates the equivalent of 3 fully active drugs. New classes of therapy add a count of 1 since there is no preexisting resistance. Partially active agents may add only a fraction depending on their relative resistance (partial, low-level). This can lead to fairly complex regimens.

Genotypic susceptibility score: The activity of a second-line or subsequent ART regimen can be predicted by its genotypic susceptibility score (GSS), a rating system in which each active drug (based on the Stanford University HIV Drug Resistance Database genotypic resistance interpretation system) contributes a full (1) or partial (fraction) to the score [Gonzalez-Serna, et al. 2017]. Improved viral suppression rates have been demonstrated to correlate with increased GSS in short-term follow-up (16 to 24 weeks) after regimen switches [Anderson, et al. 2008].

Typically, the GSS is calculated by adding up mutations or using the Stanford University HIV Drug Resistance Database to identify potentially active agents. However, for some medications that may be considered for highly treatment-experienced patients, such as DRV [de Meyer, et al. 2008; de Meyer, et al. 2005], TPV/RTV [Marcelin, et al. 2008], and ETR [Vingerhoets, et al. 2010], a weighted genotypic score in which certain mutations have a greater effect than others in achieving viral suppression may be used. These algorithms can be useful in interpreting genotypes for cases in which more complicated regimens may be needed. In addition, therapeutic drug monitoring has been used to assess a genotypic inhibitory quotient to represent the extent to which the measured trough drug concentration exceeds the amount needed to suppress virus based on the weighted GSS [Gonzalez de Requena, et al. 2011]. This method demonstrates the value of weighted scores in interpreting resistance in highly treatment-experienced patients, but it is not readily available for clinical practice.

2-NRTI backbone: An established practice based on the evolution of ART has been to start building regimens on a "backbone" of 2 NRTIs and adding a third, fourth, or additional agent as needed. However, the combination of DRV/RTV, ETR, and RAL without NRTIs among triple-class-experienced participants whose previous ART failed demonstrated significant long-term activity (88% suppression at 96 weeks) in an open-label, multicenter clinical trial in Europe and rural treatment sites in the United States where monitoring was more difficult [Ebers, et al. 2017; Fagard, et al. 2012].

Some studies indicate that retention of NRTIs in constructing regimens after virologic failure contributed additional benefit even when resistance assays predicted limited residual activity [Scherrer, et al. 2011]. The presence of the M184V mutation, in particular, which contributes high-level resistance to 3TC and FTC, has properties that may be advantageous in a second-line regimen, including improving the susceptibility of coadministered NRTIs (such as TFV) even when resistance mutations are present, reducing viral fitness to replicate, and decreasing the rate of viral mutation by improving the fidelity of the HIV reverse transcriptase and making it less error-prone [Wainberg 2004]. A randomized clinical trial with treatment-experienced participants, however, demonstrated that when an ART regimen could be constructed that had a phenotypic susceptibility score >2 (i.e., containing at least 2 fully active agents not counting NRTIs), omitting NRTIs was noninferior to adding NRTIs with regard to viral suppression rates (HIV RNA <50 copies/mL) at week 96 [Gandhi, et al. 2020; Tashima, et al. 2015]. Therefore, if a fully active regimen (at least 2 fully active agents, including at least 1 with a high genetic barrier such as a PI or an INSTI) can be constructed for a highly treatment-experienced patient without including an NRTI, there would be no need to add one. However, if it is possible to construct only a partially active regimen, then inclusion of 1 or 2 NRTIs based on their unique characteristics may be beneficial.

The results of the BENCHMRK-1 and BENCHMRK-2 clinical trials of the INSTI RAL demonstrate some of the key principles for constructing ART regimens in a highly treatment-experienced patient with multiclass drug-resistant virus [Eron, et al. 2013]. The study recruited participants who were RAL-naive with HIV resistant to ARVs from 3 or more classes and randomized them to receive RAL or placebo added to an optimized background therapy chosen from all available treatment options at that time. The results demonstrated that use of the new class of drug (INSTI) led to higher viral

suppression rates at week 156 than placebo (51% vs. 22% with HIV RNA <50 copies/mL). It also demonstrated that inclusion of the fully active PI DRV in the optimized background regimen improved response to 72% and the new class fusion inhibitor enfuvirtide to 79% viral suppression. The optimized background therapy in the study was rated by a GSS in which 0 = no fully active agents, 1 = 1 fully active agent, 2 = 2 fully active agents, and ≥3 = 3 or more fully active agents in the background therapy. The addition of RAL improved viral response for all GSS background regimens, with additional benefit diminishing as the GSS score increased [Eron, et al. 2013].

Three fully active ARVs may not be needed in a second-line or subsequent regimen if 1 of the agents is a fully active agent with a high genetic barrier. In a large cohort study, patients who had failed NRTI/NNRTI-based first-line therapy responded well to RTV-boosted PI-based therapy regardless of the number of active NRTIs used and the overall GSS of the regimen [Waters, et al. 2013]. The second-generation INSTI DTG plus 2 NRTIs was demonstrated in a randomized trial to have a 48-week viral suppression rate (84%) superior to that of RTV-boosted LPV (70%) in resource-limited settings among participants who had experienced virologic failure on 2 NRTI/1 NNRTI-based therapy in which the GSS of the NRTI background regimen was <2 among 81% of the participants [Aboud(a), et al. 2019]. Similarly, the VISEND study from Zambia confirmed the effectiveness of using DTG, an INSTI with a high genetic barrier, with recycled NRTIs [Mulenga, et al. 2022]. In this trial, 1,201 participants with HIV taking TDF/3TC plus an NNRTI (EFV or nevirapine [NVP]) were randomly switched to receive TDF/3TC or TAF/FTC plus DTG or ZDV/3TC plus either LPV/RTV or ATV/RTV. Among 783 participants with viral loads >1,000 copies/mL at the time of the switch, both DTG/TAF/FTC and DTG/TDF/3TC were superior to the 2 boosted PI-based regimens in achieving viral loads <1,000 and <50 copies/mL, and these regimens were noninferior to each other.

Single-Tablet or Once-Daily Regimen After Virologic Failure

In the past, virologic failure often required construction of increasingly complex ART regimens, including use of medications dosed twice daily, which exacerbated the adherence problems that were frequently the cause of the initial treatment failure.

Agents with a high resistance barrier can often be used to anchor second-line and later ART regimens and make once-daily and, at times, single-tablet regimens viable options.

The ODIN trial demonstrated that among participants with a history of ART treatment failure (54% of whom had PI experience, including 28% with prior use of 2 or more PIs) and no primary DRV resistance mutations (V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V, and L89V), no difference was found in virologic suppression between use of once- or twice-daily DRV/RTV [Cahn, et al. 2011].

In another study, adults who were virally suppressed on a TAF/FTC/DTG regimen successfully maintained viral suppression after switching to TAF/FTC/BIC stratified by known or suspected prior NRTI resistance (K65R or ≥3 TAMS vs. other NRTI RAMs vs. no NRTI RAMs) [Sax(a), et al. 2020]. Similarly, viral suppression was maintained among Black participants after switching from regimens of 2 NRTIs plus a third agent to TAF/FTC/BIC, regardless of prior drug resistance (10% with M184V/I, 7% with TAMs, 21% with NNRTI resistance, and 13% with PI resistance) [Andreatta, et al. 2020]. Participants whose previous resistance test results demonstrated the presence of K65R/E/N, ≥3 TAMs, T69 insertion, or INSTI RAMs were excluded from the study.

Agents for Use in Highly Treatment-Experienced Patients

As noted above, some patients, usually those who have had HIV for many years and have been at least partly adherent to multiple sequential nonsuppressive therapies or younger individuals who acquired HIV perinatally and, similarly, used multiple sequential therapies, have developed multiclass drug-resistant virus, which limits options in trying to construct a fully active ART regimen from the 4 major drug classes alone. The proportion of such patients has declined over time, and they currently represent less than 1% of people with HIV in care, but these patients also present unique treatment challenges [Bajema, et al. 2020]. To construct regimens with 3 fully active agents (or at least 2 active drugs with 1 that is fully active and has a high resistance barrier, such as a boosted PI or second-generation INSTI), the use of novel drug classes described below may be necessary.

Ibalizumab (IBA): IBA is the first monoclonal antibody therapy approved by the U.S. Food and Drug Administration (FDA) for the treatment of HIV. IBA attaches to the CD4 binding site for HIV envelope glycoprotein 120 (gp120), inhibiting viral attachment. After the initial loading dose, the medication is administered intravenously every 2 weeks and may be given over 30 seconds intravenous push. A phase 3 study of highly treatment-experienced participants (>90% with NRTI, NNRTI, and PI resistance and 68% with resistance to at least 1 agent per class) demonstrated that 83% achieved a 0.5-log and

60% a 1.0-log reduction in viral load after 7 days of effective monotherapy and 43% had a viral load <50 copies/mL at week 25 [Chahine and Durham 2021; Emu, et al. 2018]. Of note, 9 of 10 participants with virologic failure or rebound (25% of participants) had HIV that demonstrated reduced IBA susceptibility, indicating a low resistance barrier to this agent. When taking IBA combined with at least 1 other fully active agent, 71% of participants achieved a viral load <50 copies/mL, and when combined with at least 2 fully active drugs, 56% achieved viral loads <50 copies/mL at week 25. Responses were better if the fully active agent was DTG; 75% and 78% of participants achieved viral suppression <50 copies/mL when DTG was the only or 1 of 2 fully active agents in the regimen [Chahine and Durham 2021; DeJesus, et al. 2020]. As ibalizumab will be a single component of a mixed oral/injectable regimen, it is critically important that adherence to the other agents in the combination be strict because the risk of monotherapy with the potential for development of resistance is high.

Fostemsavir (FTR): FTR has been approved by the FDA for treatment of multidrug-resistant HIV. FTR functions as a CD4 attachment inhibitor by binding to HIV gp120. The registrational study included a randomized arm (for optimized background therapy with at least 1 other active agent) and a nonrandomized arm (when no additional fully active agent was available) [Kozal, et al. 2020]. The randomized arm included an 8-day effective monotherapy period in which 68% and 50% of participants achieved 0.5-log and 1.0-log reductions in viral load, respectively. In the randomized arm, 53% achieved viral load suppression (HIV RNA <40 copies/mL) by week 24, with poorer responses among those with viral loads >100,000 copies/mL or CD4 counts <20 cells/mm^3 (35%). In the nonrandomized cohort, 37% achieved viral load suppression (HIV RNA <40 copies/mL) at week 24, with an improved response among 15 patients (53%) who also received IBA, which was allowed per study protocol.

Maraviroc (MVC): MVC is an oral attachment inhibitor that blocks HIV gp120 from binding to the CCR5 coreceptor on the T-cell surface following CD4 binding. HIV tropism is dynamic, and most transmitted HIV is CCR5 (macrophage, or M) tropic. However, over time, viral phenotype may adapt during the course of uncontrolled viremia to develop the capacity to bind to an alternative (or additional) coreceptor CXCR4 (T-cell, or T-tropic). This shift in tropism occurs independent of ARV pressure but coincides with a longer time of infection and higher levels of treatment experience [Mosier 2009]. Therefore, when a novel, fully active agent may be needed, MVC as a purely CCR5 active agent may be less likely to contribute to treatment response. Before switching to a regimen that includes MVC, a tropism assay that demonstrates only CCR5 (not dual or X4-tropic) virus in the population should be confirmed. RNA tropism can be assessed if the plasma viral load is ≥500 copies/mL, and DNA tropism assays may be used when viral loads are lower or undetectable. However, historical tropism results may not be reliable if a period of viral replication ensued after the assay was obtained, so when viremia is present, a tropism assay should be performed as soon as possible proximate to the planned use of MVC. Among patients with prior treatment and failure with 3 ARV classes and R5-tropic virus in 2 randomized, placebo-controlled clinical trials, adults who received MVC in addition to an optimized background therapy had significantly improved viral suppression rates and improvement in CD4 cell counts at 48 weeks [Gulick, et al. 2008].

Enfuvirtide (T20): T20 is an injectable (subcutaneous, twice daily) fusion inhibitor with a novel mechanism and site of action (blockage of gp41-mediated membrane fusion). Because of a high incidence of adverse effects (injection site reactions), T20 has been used mainly as a "bridging" agent to fill the gap pending the availability of new active ARVs to supplant its place in the regimen. In a clinical trial in which 501 participants with a history of treatment failure or drug resistance in 3 classes of ARVs were randomized 2:1 to receive optimized background therapy with or without the addition of T20, those who received T20 had improved viral suppression and CD4 recovery at 24 weeks. Virtually all participants who received T20 (98%) had adverse injection site reactions, leading to treatment withdrawal in 2.8% [Lalezari, et al. 2003].

Lenacapavir (LEN): LEN is a long-acting, injectable capsid inhibitor administered subcutaneously every 6 months after oral lead-in doses. The capsid protein protects the viral RNA, and inhibition of its function can affect early (uncoating, reverse transcription), mid (nuclear entry), and late (assembly) stages in the HIV lifecycle [Carnes, et al. 2018]. Analysis of week 52 results from the phase 2/3 CAPELLA study of highly treatment-experienced participants with HIV found that 83% maintained a viral load of <50 copies/mL and 86% maintained a viral load of <200 copies/mL (randomized cohort) when LEN was used with optimized background ART [Ogbuagu, et al. 2022]. At enrollment, 47% of participants had resistance to all 4 classes of ARVs, 54% to INSTIs, 42% to all PIs, and one-third to IBA and FTR [Segal-Maurer, et al. 2022]. Further, 67% of participants maintained viral suppression despite having no fully active agent in their optimized background regimen, 79% maintained viral suppression with 1 fully active agent, and 94% maintained it with 2 fully active agents. Among 8 participants with resistance mutations at virologic failure, 1 died at week 11, 3 had no fully active background agent, and 4 had inadequate adherence with the background therapy. The most common adverse effects associated with LEN were diarrhea, nausea, and injection site reactions, and 1% of participants discontinued treatment because of toxic effects. LEN is a moderate cytochrome P450 3A inhibitor and may interact with coadministered ART and other medications (see package insert). After subcutaneous dosing, LEN can persist in the blood for more than 12 months at diminishing

concentrations; therefore, if LEN is discontinued, a fully suppressive ART regimen should be initiated within 28 weeks after the final injection [FDA 2022]. As LEN will be a single component of a mixed oral/injectable regimen, it is critically important that adherence to the other agents in the combination be strict because the risk of monotherapy with the potential for development of resistance is high.

ART Changes for Adverse Effects, Drug-Drug Interactions, or Pregnancy

☑ RECOMMENDATIONS

Changes to Address Adverse Effects

- When changing a patient's ART regimen to address adverse effects, the clinician should (A2):
  - Review all prior genotype and phenotype resistance test results and ART history for evidence of virologic failure to inform the choice of a fully active regimen when switching from a suppressive regimen.
  - Account for the adverse effect profiles of ARVs, including cross-class toxicities.
  - Account for potential drug-drug interactions with chronically used concomitant medications, including nonprescription and over-the-counter medications, especially when switching from or to a regimen that may induce or inhibit shared metabolic pathways.
  - Minimize the potential for negative effects of a new ART regimen on any underlying chronic medical conditions, such as cardiovascular disease or risk, impaired renal function, or chronic anemia.
- If a patient has chronic HBV infection, the clinician should include TAF/TDF in conjunction with 3TC/FTC or another agent with activity against HBV (e.g., ETV) in the patient's ART regimen. (A2)

Changes to Address Drug-Drug Interactions

- When changing a patient's ART regimen to address drug-drug interactions, the clinician should (A2):
  - Acquire a current list of all medications that a patient is taking or any medications planned for treatment of a comorbid condition before constructing an ART regimen.
  - Account for the drug-clearance mechanisms and pharmacokinetic drug-drug interactions of ARVs to select optimal regimens.
  - Pay particular attention to the effect of starting or stopping specific ARVs, such as COBI or RTV, on concurrent medications that may require dose adjustment.

Changes Due to Pregnancy

- When changing an ART regimen for a patient who is pregnant or planning pregnancy, the clinician should follow the recommendations of the DHHS: Recommendations for the Use of Antiretroviral Drugs During Pregnancy and Interventions to Reduce Perinatal HIV Transmission in the United States. (A3)

Abbreviations: 3TC, lamivudine; ART, antiretroviral therapy; ARV, antiretroviral medication; COBI, cobicistat; DHHS, U.S. Department of Health and Human Services; FTC, emtricitabine; HBV, hepatitis B virus; RTV, ritonavir; TAF, tenofovir alafenamide fumarate; TDF, tenofovir disoproxil fumarate.

It is imperative that clinicians review the appropriateness of their patient's ART regimen at every visit in the context of updated laboratory testing results, medication reconciliation, and development of new diagnoses. In addition, clinicians should remain informed about the prescribed ART regimen's adverse effects and drug-drug interaction profiles.

Changes to Address Adverse Effects

Table 6, below, lists common adverse effects associated with ARVs.

Table 6: Common Adverse Effects Associated With Antiretroviral Medications

Drug	Adverse Effect(s)
Nucleoside/Nucleotide Reverse Transcriptase Inhibitors	
Abacavir [a]	Cardiovascular disease, hypersensitivity
Didanosine	Mitochondrial toxicity, lipodystrophy, lactic acidosis
Stavudine	Mitochondrial toxicity, lipodystrophy, lactic acidosis
Tenofovir alafenamide	Weight gain, lipids [Mallon, et al. 2021]
Tenofovir disoproxil fumarate	Proximal renal tubule injury, decrease in bone mineral density
Zidovudine	Mitochondrial toxicity, lipodystrophy, lactic acidosis
Non-Nucleoside Reverse Transcriptase Inhibitors	
Doravirine	CNS effects
Efavirenz	Hepatotoxicity, vitamin D deficiency, CNS effects, skin reactions, depression, morning somnolence
Nevirapine	Hepatotoxicity, hypersensitivity
Rilpivirine	CNS effects, skin reactions, effects on the measure of eGFR
Protease Inhibitors [Tsiodras, et al. 2000]	
Class effect [b]	Increased cholesterol [c], increased triglycerides [c], increased glucose, lipodystrophy
Atazanavir	Nephrolithiasis, renal insufficiency, hyperbilirubinemia
Darunavir	Cardiovascular disease, skin reactions
Lopinavir/ritonavir	Cardiovascular disease [Ryom, et al. 2018]
Integrase Strand Transfer Inhibitors	
Class effect [b]	Weight gain [Sax(b), et al. 2020]
Bictegravir	Effects on the measure of eGFR
Dolutegravir	CNS effects [Yombi 2018; Hoffmann, et al. 2017], effects on the measure of eGFR
Elvitegravir/cobicistat	Increased lipids, effects on the measure of eGFR

Abbreviations: CNS, central nervous system; eGFR, estimated glomerular filtration rate.

Notes:

a. Screen to document that the patient is negative for HLA-B*5701 before use
b. Adverse effects apply to all drugs in this class
c. Especially with ritonavir and cobicistat pharmaco-enhancement

The presence of chronic comorbid conditions, such as diabetes, cardiovascular disease, osteoporosis, chronic kidney disease, and dyslipidemia, should influence ART choices. Patients with preexisting kidney disease or osteoporosis may experience worsening of both over time with TDF, given its association with renal insufficiency and bone mineral density loss. A newer formulation, TAF, has demonstrated less effect on bone density and renal function parameters than TDF, although it is also associated with increased total cholesterol and the potential for weight gain [Squillace, et al. 2020]. Although no consensus exists, some studies have shown an increased risk of cardiovascular events with ABC [Jaschinski, et

al. 2022; Dorjee, et al. 2018; Sabin, et al. 2018]. In addition, some drugs, and especially PIs, may cause unfavorable lipid changes.

A multicenter, open-label study of 1,443 adults with a glomerular filtration rate (GFR) >50 mL/min on stable TDF-containing ART regimens who were randomized 2:1 to switch to TAF or remain on TDF demonstrated equivalent maintenance of viral suppression with improved bone mineral density at the hip and spine and improved GFR in the TAF arm at 48 weeks [Mills, et al. 2016]. These findings were similar to those reported in a double-blind, multicenter, placebo-controlled, noninferiority trial of 630 virally suppressed adults taking TDF/FTC/rilpivirine (RPV) who were randomized 1:1 to switch to TAF/FTC/RPV or remain on current therapy [Orkin, et al. 2017]; viral suppression was found to be noninferior and similar adverse effects were found between the arms at 48 weeks.

Weight gain after ART initiation, especially with integrase strand transfer inhibitor (INSTI)-based regimens, with protease inhibitor (PI)-based regimens being intermediate and non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens being less likely to have this association, has been a focus of great attention in recent reports [Sax(b), et al. 2020]. The inclusion of TAF as a component of an INSTI-based regimen has been shown to have a stronger link with weight gain [Venter, et al. 2019]. The mechanism(s) underlying this association are under investigation. To date, no data demonstrate that switching the ART regimen would reverse this finding. The potential for weight gain and monitoring of weight gain should be discussed with patients initiating INSTIs. Weight gain is variable and may be managed in some people without ART modification. However, after discussion of these findings with their patients, clinicians may decide to switch ART because of this adverse effect.

The PROBE 2 trial examined switching to a 2-drug regimen of RPV plus darunavir/COBI from a fully suppressive 3-drug regimen of 2 nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) plus an NNRTI, an INSTI, or an RTV-boosted PI to avoid potential NRTI toxicities. Participants had no baseline NNRTI or PI resistance-associated mutations (RAMs) and did not have chronic HBV infection [Maggiolo, et al. 2021]. Half of participants were randomized to switch immediately (early) and half at week 48 (late), allowing a comparison with standard of care (n = 80 in each arm). At week 48, viral suppression <50 copies/mL was maintained in 87.5% of participants in the early switch arm (12.5% missing data) and 94.8% in the late-switch arm (2.6% missing data; noninferiority), and no virologic failures occurred in the early switch group. Although simplification achieved favorable virologic outcomes, lipids increased in the participants switched from TDF-containing regimens, but no increases in body weight were noted.

Many adverse effects may be shared across a class of drugs because of shared mechanisms of action and metabolic pathways; therefore, switches due to adverse effects may require a change to a different therapeutic class. A study of 415 adults >50 years old with a Framingham cardiovascular risk of ≥10% who were virally suppressed on a PI-containing regimen and randomized to early versus deferred switch to a dolutegravir (DTG)-containing regimen demonstrated improvement in the lipid profile in both arms after the switch [Gatell, et al. 2019]. Unfortunately, the study was not powered to show an effect on cardiovascular disease. Switching ART alone may not be sufficient to reduce cardiovascular disease risk, and the addition of lipid-lowering therapy may be indicated with or without switching [Palella, et al. 2014]. Insufficient data are available on the effect on weight gain when switching INSTIs to other ARV classes; clinical trials are underway that may provide evidence for guidance on this issue.

If a switch of ART regimen is indicated because of diminished renal function, prescribers should be aware that certain ARVs may alter the assessment of creatinine clearance. COBI, DTG, bictegravir (BIC), and, to a lesser extent, RPV have been associated with decreased creatinine secretion, leading to a slight rise in serum creatinine levels without a concomitant decline in GFR. A consensus statement from Australia recommends that serum creatinine levels be checked 1 month after initiation of these agents to establish a new baseline measurement [Holt, et al. 2014]. However, no data suggest this approach alters clinical management. Small studies show that estimation of GFR with cystatin C measurements may be more accurate in patients taking agents that affect creatinine secretion; this assay may be used if a more refined assessment of GFR is needed [Galizzi, et al. 2018; Yukawa, et al. 2018].

Changes for Drug-Drug Interactions

Pharmacokinetics: A thorough search for drug-drug interactions should be performed whenever an ART regimen is initiated or changed or new medications are added to treat concomitant conditions (see the NYSDOH AI resource ART Drug-Drug Interactions). Drug classes that commonly cause pharmacokinetic interactions with ARVs include:

- Statins and other lipid-lowering and cardiovascular medications
- Inhaled and intra-articular corticosteroids
- Select psychotropics

- Narcotics and other sedatives
- Anticoagulants (factor Xa inhibitors) and antiplatelet agents (clopidogrel)
- Alpha-adrenergic blocking drugs to manage benign prostatic hyperplasia
- Phosphodiesterase inhibitors used for erectile dysfunction or pulmonary hypertension
- Antacids, proton pump inhibitors, and H_2 blockers
- Anticonvulsants
- Rifampin/rifabutin
- Recreational drugs (ketamine; benzodiazepines; crystal meth; 3,4-methylenedioxy-methamphetamine [MDMA]; mephedrone)
- PIs and NNRTIs, when combined

Most of these interactions are associated with ART regimens containing RTV or COBI. These agents are pharmacokinetic inhibitors of cytochrome P450 3A (CYP3A), a major enzyme system involved in most drug metabolism [Lynch and Price 2007]. The INSTIs BIC and raltegravir do not cause and are not affected by CYP3A interactions. CYP3A partly metabolizes DTG, and a coadministered inducer may reduce its levels. The NNRTIs doravirine (DOR) and RPV and the CCR5 antagonist maraviroc are substrates for CYP3A, and their levels may be affected by the concomitant use of an inducer or inhibitor. Etravirine (ETR), a second-generation NNRTI that may be useful for patients with NNRTI drug resistance, is an inducer of CYP3A and UGT1A1 and may reduce the levels of coadministered DTG [Rathbun and Liedtke 2010]. Use of DOR or RPV in place of ETR, if active, may avoid this interaction (see the discussion of cross-resistance within ARV classes in this guideline). Therefore, when changing an ART regimen, it is important to assess drug-drug interactions not only between ARVs and concomitantly used medications but also within the ART regimen itself. Additional resources to assess ART drug interactions include the University of Liverpool HIV Interaction Checker and the DHHS HIV guidelines.

Antacids are one common drug class responsible for interactions that could lead to subtherapeutic ARV concentrations. The NNRTI RPV and the PI atazanavir require an acidic gastric environment for optimal absorption, and concomitant use of antacids can lead to virologic failure. In addition, a history of bariatric surgery would likely influence ART choices, given the need to crush pills for up to 3 months post-surgery and the possibility of poor absorption of extended-release medications [Cimino, et al. 2018]. Divalent cations, commonly found in multivitamins, can bind to and reduce the absorption of certain INSTIs. Phosphate-binding resins (e.g., sevelamer) used in end-stage renal disease may interfere with the absorption of many medications, including ARVs, which should be taken at least 1 hour before or 3 hours after the resin.

Complementary and herbal therapies, health supplements, minerals, and vitamins can also cause drug-drug interactions that may affect concentrations of ARVs [Bordes, et al. 2020]. A thorough accounting of all coadministered drugs, including over-the-counter and herbal remedies, should be conducted before prescribing ART and periodically during therapy or in the event of unexplained virologic failure. It is also appropriate to assess drug-food interactions, as some ARVs have food restrictions. Food can affect the rate and extent of ART absorption or alter the acid milieu of the gastrointestinal tract, which may affect effectiveness [Jones 2019; University of Liverpool 2016].

Prolonged viremia attributable to adverse pharmacokinetic drug-drug interactions can lead to the development of RAMs and potential cross-resistance among ARVs within the same class. Genotypic resistance testing should be considered to assess the effect of emergent RAMs on continued or reconfigured ART regimens.

In addition, if ART is changed and the new regimen includes or removes a pharmacokinetic inhibitor (e.g., RTV or COBI) or inducer (e.g., efavirenz), an assessment must be made of chronic coadministered medications whose metabolism may be affected. The addition or removal of pharmacokinetic “boosters” or “inducers” can cause adverse effects associated with elevated exposure or withdrawal of concomitant medication. However, because the only change made is the ART regimen, adverse effects may be falsely attributed to the new treatment regimen rather than the need for dose adjustment or modification of the coadministered medication.

→ KEY POINT

- Addition or removal of pharmacokinetic “boosters” or “inducers” can cause adverse effects associated with elevated exposure or withdrawal of concomitant medication. These adverse effects may be falsely attributed to a new ART regimen rather than the need for dose adjustment or modification of the coadministered medication.

Changes for Pregnancy

Patients of childbearing potential should be assessed for pregnancy status or plans to become pregnant. See the DHHS Recommendations for the Use of Antiretroviral Drugs During Pregnancy and Interventions to Reduce Perinatal HIV Transmission in the United States.

Preliminary data suggested an increased rate of neural tube defects (NTDs) in a clinical trial in Botswana among infants born to mothers using DTG at the time of conception. The latest available data, through April 2020, show that the rate of infant NTDs with maternal DTG-based ART use at conception (0.19%) is not significantly greater than for infants exposed to non-DTG-based ART at conception (0.11%). In addition, studies conducted in populations in the United States where folate supplementation is common did not demonstrate an excess in NTDs with use of DTG at conception [DHHS 2022; APR 2020; Zash, et al. 2018]. The current DHHS guideline recommends DTG as a preferred ARV at all stages of pregnancy.

People with HIV who are pregnant or planning a pregnancy may require ART modification due to pharmacokinetic factors [Gilbert, et al. 2015]. The efficacy of 2-drug ART in pregnancy has not been established; if a patient who is stable on 2-drug ART becomes pregnant, it may be appropriate to consider a switch to a preferred 3-drug regimen or the addition of a third ARV during pregnancy. In addition, patients with viral suppression on a COBI-containing ART regimen should consider switching to an alternative regimen or be monitored closely for virologic breakthrough during pregnancy.

ART Changes for Regimen Simplification

☑ RECOMMENDATIONS

ART Changes for Regimen Simplification

- Clinicians should not prescribe single-agent antiretroviral therapy (ART). (A1)
- When changing an ART regimen for simplification, i.e., to improve adherence, reduce cost, improve quality of life, or respond to a patient's request, clinicians should construct a new regimen based on an assessment of:
  - Prior resistance testing results (A1)
  - History of ART failure (A2)
  - Tolerability (A2)
  - Evidence of clinical effectiveness (A2)

Avoid Monotherapy

The evolution of ART has been steady and at times brisk, resulting in new classes of medications to address emergent drug resistance, dosing convenience, coformulation capacity, reduced drug-drug interactions, and reduced toxic effects. Patients who have had persistent virologic suppression on older ART regimens that contained agents associated with long-term, organ-specific, or metabolic adverse effects; had food or fluid intake restrictions; or had dosing frequency and pill burden challenges may seek to have their regimens reviewed for opportunities to simplify or reduce the potential toxic effects of their current medications. Such switches may lead to improved adherence, enhanced quality of life, persistence in treatment, and reduced long-term adverse effects.

Recommendations for regimen change should be based on shared decision-making and not be driven by any hype around the newest regimen. It is appropriate for clinicians to discuss new treatment options with their patients as they become available so that they may benefit from an unbiased evaluation. At times, the issue of ART regimen switches is raised because of insurance coverage restrictions or out-of-pocket expenses for the patient. As with consideration of any ART switch, decisions in such cases must be guided by the principles of enhancing efficacy, safety, and durability of the therapeutic response.

All ART changes must be made with careful planning because regimen failure after the switch is always possible. The goal of the regimen change should be clearly defined and the new regimen assessed for potential adverse effects due to unrecognized preexisting drug resistance, effect on chronic comorbid conditions (e.g., hepatitis B virus [HBV] infection, cardiovascular disease, obesity), and exposure to other chronic concurrent medications, especially when switching to or

from an antiretroviral medication that is an inducer, inhibitor, or substrate of cytochrome P450 3A or P-glycoprotein (see the NYSDOH AI resource ART Drug-Drug Interactions).

Switching to a 3-Drug Single-Tablet Regimen

Studies in which a switch from a multi-tablet ART regimen to a 3-drug single-tablet regimen was made for simplification in participants with effective viral suppression are discussed below. Many of these trials were developed and conducted by pharmaceutical companies. Results must be interpreted with care because they may be biased as a result of numerous factors, including open-label study design, recruitment of participants who are dissatisfied with their ART regimen or looking for new options, and recruitment of participants with a proven record of adherence (i.e., virally suppressed at trial entry).

Integrase strand transfer inhibitor (INSTI)-based switches: Including switches to tenofovir alafenamide/emtricitabine/bictegravir (TAF/FTC/BIC) and INSTI-to-INSTI within-class switches:

- **Switch for safety and tolerability:** Gilead Study 380-1844, a double-blind study designed to explore options to avoid abacavir (ABC)-associated cardiovascular concerns or dolutegravir (DTG)-associated neuropsychiatric concerns, randomly assigned 563 adults who were virally suppressed on a regimen of abacavir/lamivudine/dolutegravir (ABC/3TC/DTG) 1:1 to remain on their current therapy or switch to TAF/FTC/BIC [Molina, et al. 2018]. The study found TAF/FTC/BIC to be noninferior to remaining on ABC/3TC/DTG based on viral load suppression at week 48. No resistance emerged in either arm. No difference was found in adverse effects except for more gastrointestinal-related complaints among participants in the DTG arm.
- **Switch from a boosted protease inhibitor (PI)-based regimen to TAF/FTC/BIC:** Gilead Study 380-1878 was an open-label phase 3 study that enrolled 577 virologically suppressed adults taking a nucleoside/nucleotide reverse transcriptase inhibitor (NRTI; tenofovir disoproxil fumarate [TDF]- or ABC-based) plus a boosted PI (ritonavir [RTV] or cobicistat [COBI] with darunavir [DRV] or atazanavir [ATV]) who were randomized to remain on their baseline therapy or switch to TAF/FTC/BIC [Daar, et al. 2018]. At 48 weeks, the switch was noninferior with regard to viral suppression (HIV RNA <50 copies/mL), and the regimens in both arms were well tolerated. More treatment-related adverse effects occurred in the TAF/FTC/BIC group, especially headache, with most being mild or moderate in intensity. Discontinuation due to adverse effects was 1% or less in both arms. At week 96, viral suppression on a TAF/FTC/BIC regimen was maintained after the switch despite blips or baseline resistance mutations [Andreatta, et al. 2021].
- **Switch to an INSTI-based single-tablet regimen (ABC/3TC/DTG):** In the open-label STRIIVING study, 553 virally suppressed adults who were HLA-B*5701 negative with no history of treatment failure on non-nucleoside reverse transcriptase inhibitor (NNRTI)-, PI-, or INSTI-based regimens were randomized 1:1 to switch immediately to ABC/3TC/DTG or continue their current therapy for 24 weeks, after which all participants received ABC/3TC/DTG [Trottier, et al. 2017]. Switching was noninferior to remaining on current therapy with regard to viral suppression. Although more participants reported adverse effects in the switch arm at 48 weeks (75% vs. 60%), most were mild or moderate, and 4% discontinued treatment because of adverse effects.
- **Switch to a 3-drug NNRTI-based single-tablet regimen (TDF/3TC/doravirine [DOR]):** DRIVE-SHIFT was an open-label study of 670 adults with HIV viral suppression on an NNRTI-, INSTI-, or PI-based regimen randomized 2:1 to switch to TDF/3TC/DOR or remain on current therapy [Johnson, et al. 2019]. At 48 weeks, viral suppression data demonstrated that TDF/3TC/DOR was noninferior to continuing the baseline regimen. TDF/3TC/DOR was well tolerated, leading to treatment discontinuation in 2.5% of participants. Long-term viral suppression was sustained through week 144. [Kumar, et al. 2021].
- **Switch to a 3-drug NNRTI-based single-tablet regimen (TAF/FTC/rilpivirine [RPV]):** Two randomized, double-blind, active-controlled, noninferiority trials in adults with HIV taking TDF/FTC/RPV (Study 1216; N = 630) or TDF/FTC/efavirenz (Study 1160; N = 875) reported noninferior viral suppression at 96 weeks following 1:1 randomization in each to switch to TAF/FTC/RPV or remain on current therapy [Hagins, et al. 2018; DeJesus, et al. 2017]. Improvement in renal and bone parameters was noted among the participants who switched to TAF/FTC/RPV [Hagins, et al. 2018; DeJesus, et al. 2017].
- **Switch to a boosted PI-based single-tablet regimen (TAF/FTC/DRV/COBI):** The EMERALD study, which included 1,141 virally suppressed adults who may have experienced previous non-DRV treatment failure, randomized participants 2:1 to switch to TAF/FTC/DRV/COBI or to remain on their current regimen for 48 weeks, with a late-switch additional extension phase (N = 1,080) through week 96. TAF/FTC/DRV/COBI effectively maintained viral suppression (no comparator for the extension phase). Furthermore, the study demonstrated the high genetic barrier of the regimen in that no primary PI, TFV, or FTC mutations emerged during treatment and no participants withdrew because of lack of

efficacy; 2% withdrew for adverse effects, renal and bone parameters were improved from baseline, and a small increase in total cholesterol to high-density lipoprotein cholesterol ratio was observed [Eron, et al. 2019].

Switching to a 2-Drug Single-Tablet Regimen

Studies in which a switch from a 3- or 4-drug ART regimen to a 2-drug single-tablet regimen was made for simplification in participants with effective viral suppression are discussed below.

Note: Currently available 2-drug single-tablet regimens are not effective for treatment of pregnant patients or those who have HIV/HBV coinfection.

- **Switch from a 3- or 4-drug regimen to 2-drug NNRTI/INSTI regimen (RPV/DTG):** SWORD 1 and 2 were identical multinational, open-label studies that included 1,024 virally suppressed adults taking standard 3- or 4-drug ART regimens who were randomized 1:1 to switch to RPV/DTG for 52 weeks, followed by a late switch (N = 477) through 100 weeks of follow-up. Viral suppression was noninferior in the early switch compared with the late-switch group, and the 2-drug regimen was well tolerated [Aboud(b), et al. 2019; Llibre, et al. 2018].
- **Switch from TAF-based 3- or 4-drug regimen to 2-drug NRTI/INSTI regimen (3TC/DTG):**
  - The TANGO study was an open-label, multicenter study of 741 virally suppressed adults taking a 3- or 4-drug TAF-containing ART regimen who were randomized 1:1 to switch to the 2-drug regimen of 3TC/DTG or continue current therapy for 48 weeks. The 2-drug regimen was noninferior in maintaining viral suppression, and breakthrough virus did not demonstrate emergent INSTI or 3TC resistance mutations. M184V/I mutations were found at baseline (by proviral DNA assay) in 4 of 322 participants randomized to the 3TC/DTG arm, all 4 of whom maintained viral suppression. In the 3TC/DTG arm, 3.5% withdrew because of adverse effects [van Wyk, et al. 2020]. Baseline proviral DNA genotypic testing samples were obtained from 89% of participants in the 3TC/DTG arm and 87% in the TAF-containing arm and subsequently analyzed to identify if archived resistance could affect outcome at week 48 [van Wyk, et al. 2020]. Major NRTI RAMs were identified in 8% (1% had M184V) of proviral DNA in the 3TC/DTG arm and 5% (<1% with M184V) in the TAF-containing arm, and major INSTI RAMs were identified in 3 participants (<1%) in the 3TC/DTG arm and 5 (1%) in the TAF-containing arm. All participants in both arms with major NRTI or INSTI RAMs maintained 100% viral suppression at week 48.
  - The ART-PRO study included 41 INSTI-naive, virally suppressed adults with (n = 21) and without (n = 20) a history of 3TC-resistant mutations but with a negative proviral DNA test result (Sanger and next-generation sequencing) at the time of enrollment. Investigators speculated that the preexisting mutations had decayed over the course of long-term viral suppression in participants who switched their suppressive 3- or 4-drug ART regimen to 3TC/DTG. The median time from identification of 3TC RAMs and DNA sequencing was 12.9 years. Following the switch, 4 of 21 participants with historical 3TC resistance and 6 of 20 without past 3TC resistance had transient viremia; all participants were resuppressed at 48 weeks, 3TC RAMs did not reemerge during the transient viremia, and no INSTI RAMs were detected [De Miguel, et al. 2020].
  - The SALSA study included 493 virally suppressed adults who were randomized 1:1 to stay on their 3-drug regimen (2 NRTIs + an NNRTI, PI, or INSTI) or switch to 3TC/DTG. All participants had no documented NRTI or INSTI RAMs and no history of treatment failure [Llibre, et al. 2022]. Proviral DNA genotypic resistance test results obtained before randomization were available from 377 participants (192 from the 3TC/DTG arm and 185 from the 3-drug arm) and were reviewed for the presence of baseline RAMs on post hoc analysis. Major NRTI RAMs were found in 8% of the 3TC/DTG arm (including 3% with 3TC RAM M184V) and 9% of the 3-drug arm (including 2% with M184V). Major INSTI RAMs were found in 1 participant (<1%) in the 3TC/DTG arm and 4 (2%) in the 3-drug arm. Suppression of HIV RNA to <40 copies/mL was maintained in 80% (4 of 5) of participants with M184V in the 3TC/DTG arm and 50% (2 of 4) in the 3-drug arm, and 100% (1 of 1) and 100% (4 of 4) of participants with major INSTI RAMs in the 3TC/DTG and 3-drug arms, respectively. This study supports the effectiveness of the 2-drug regimen of 3TC/DTG when a patient has low-level preexisting RAMs, but because of the small numbers involved, these data do not change the recommendation to avoid use if such resistance is known.

Switching to 2-Drug Injectable Therapy

Phase 3 clinical trial results suggest that the injectable long-acting combination of the INSTI cabotegravir and the NNRTI rilpivirine (CAB/RPV LA) may be a suitable option for patients on suppressive ART who would prefer an alternative to daily oral therapy [Overton, et al. 2021; Orkin, et al. 2020; Swindells, et al. 2020]. For more information on this option, see the NYSDOH AI guideline Use of Injectable CAB/RPV LA as Replacement ART in Virally Suppressed Adults.

Resumption of ART After a Treatment Interruption

☑ RECOMMENDATIONS

Resumption of ART After a Treatment Interruption

- Although drug resistance may not be present in all cases, when reinitiating antiretroviral therapy (ART) after an interruption, clinicians should identify factors that may have contributed to potential selection of drug resistance, including:
  - Reason for a treatment interruption, i.e., strategic or unplanned (A3)
  - The patient's plasma HIV-1 RNA level (viral load) at the time of ART interruption (A2)
  - Duration of the interruption, particularly if agents with long clearance half-lives are being used (A2)
  - Pattern of adherence prior to discontinuation (A2)
  - Existence of any barriers to adherence before the treatment interruption, and whether they are still present (A2)
- If the factor(s) related to interruption confer a low likelihood of emerging resistance, the clinician should recommend resumption of an appropriate ART regimen (based on assessment above) as soon as possible. (A2)
- If a patient had a detectable viral load before a treatment interruption of <4 weeks, the clinician should obtain a plasma genotypic resistance test as soon as possible. (A2)

If a patient has a period of treatment interruption, several potential areas of concern must be assessed at the time of treatment reinitiation, including the circumstances or reason for the interruption, the level of the viral load at the time of the interruption, the length of time of the interruption, and the level of treatment adherence before the treatment interruption.

The simplest scenario is a treatment interruption due to unforeseen circumstances, such as loss of medication, travel without access to medication, or a gap in insurance coverage, in which the viral load was undetectable at the time of the interruption and all ART medications were used without missed doses and stopped simultaneously. In this scenario, the emergence of resistance to antiretroviral medications is unlikely, and the previously suppressive ART regimen can be restarted as soon as it is available [Jülg and Goebel 2006]. An exception to this scenario is with use of a combination with a prolonged clearance rate (such as injectable rilpivirine/cabotegravir or oral efavirenz) in which 1 or more drugs may persist at low levels, allowing selective pressure for resistance mutations to be present over an extended period [Landovitz, et al. 2020].

If the pre-interruption viral load was not suppressed and the patient had been on their ART regimen for over 6 months or had a prolonged period of intermittent adherence before completely stopping treatment, drug resistance may have emerged before the interruption in therapy. As previously discussed, if treatment interruption is less than 4 weeks, a standard genotype may be appropriate to demonstrate emergent resistance-associated mutations (RAMs).

After longer gaps, evidence of selected RAMs may be revealed on a proviral DNA genotype test, if available. Reinitiating treatment with a regimen that has a low genetic resistance barrier may not be successful. If the viral load was not suppressed before treatment interruption, reinitiating treatment with a regimen with a low genetic resistance barrier (e.g., 2 nucleoside/nucleotide reverse transcriptase inhibitors [NRTIs] + a first-generation non-nucleoside reverse transcriptase inhibitor [NNRTI] or first-generation integrase strand transfer inhibitor [INSTI]) may not be successful. Considering a regimen with a higher genetic resistance barrier (2 NRTIs + a second-generation INSTI or boosted protease inhibitor [PI]) or intensifying the regimen by adding a drug with a high genetic resistance barrier (a second-generation INSTI or boosted PI) would be appropriate. The regimen can be simplified once viral suppression is obtained and results of genotypic resistance testing are available.

All Recommendations

☑ ALL RECOMMENDATIONS: SECOND-LINE ART AFTER TREATMENT FAILURE OR FOR REGIMEN SIMPLIFICATION

Identifying and Managing Virologic Failure

- When a patient's plasma HIV-1 RNA level (viral load) is not suppressed to <200 copies/mL by 24 weeks after ART initiation or if it rebounds to ≥200 copies/mL after suppression has been achieved, the clinician should confirm the result with a repeat HIV RNA test within 4 weeks of the original test. (A3)
  - See the NYSDOH AI guideline Virologic and Immunologic Monitoring in HIV Care > Viral Load and CD4 Count Monitoring Intervals.
- When a patient's viral load test result indicates virologic failure (HIV RNA ≥200 copies/mL) or low-level viremia (HIV RNA 50 to 199 copies/mL) confirmed over a period of at least 1 month, the clinician should assess for and address the following factors that may reduce ART efficacy:
  - Adherence (A2)
  - Interactions between ART agents and concomitant medications, including over-the-counter medications and supplements (e.g., divalent cations, St. John's wort) (A*)
  - Adverse effects that lead to poor adherence or cessation of treatment (A2)
  - Reviews of all prior drug resistance testing results, previous treatment experience, and reason for treatment changes or discontinuation (A3)
- For all cases of virologic failure, clinicians should perform genotypic resistance testing, ideally while the patient is taking the failing regimen or no longer than 4 weeks after discontinuation. (A2)
  - If the viral load is ≥500 copies/mL, clinicians should obtain a plasma RNA genotype test. (A2)
  - If the breakthrough viral load is <500 copies/mL, clinicians should obtain an archived DNA genotype test if viral suppression is not achieved after any drug-drug interactions or problems with adherence have been addressed. (B3)
- In patients with persistent low-level viremia, clinicians should consult an experienced HIV care provider; low-level viremia can have multiple causes, and its clinical effect is unclear. (A3)

ART Changes to Address Drug Resistance

- When choosing a new ART regimen for a patient with drug-resistant virus, clinicians should:
  - Choose a regimen that is likely to fully suppress viral replication, even if it may require multi-tablet dosing. (A1)
  - Document and evaluate the importance of all RAMs and identify the most tolerable regimen to suppress drug-resistant HIV effectively. (A3)
- Clinicians should address barriers to ART adherence that may have contributed to failure of a patient's first-line regimen. (A2)
- In constructing a new regimen to replace a failed ART regimen, the clinician should:
  - Review all prior genotype or phenotype resistance assay results that are retrievable and previous instances of virologic treatment failure to assist in identifying potentially active medications. (A2)
  - Select agents to which the patient is naive or active second-generation agents within a previously prescribed class to avoid potential within-class cross-resistance. (A2)
  - Select a regimen containing an agent with a high barrier to resistance, such as DRV, DTG, or BIC, if the M184V RAM is present and FTC/3TC will be used in conjunction with TAF/TDF. (A*)
  - Avoid monotherapy (i.e., an ART regimen with fewer than 2 fully active agents). (A1)
  - Choose the equivalent of 3 fully active ARVs; a 2-drug regimen may be prescribed when both are fully active and at least 1 is an agent with a high resistance barrier, i.e., a boosted PI or a second-generation INSTI. (A2)
  - Consult with an experienced HIV care provider when planning treatment regimens for patients with multiclass drug-resistant virus. (A3)
  - If a patient has chronic HBV infection, include TAF/TDF in conjunction with 3TC/FTC or another agent with activity against HBV (e.g., ETV) in the patient's ART regimen. (A2)
- Clinicians should closely monitor the patient's response to ART by obtaining an HIV RNA test within 4 weeks of a change in regimen and at least every 8 weeks thereafter until virologic suppression is achieved. (A3)
  - See the NYSDOH AI guideline Virologic and Immunologic Monitoring in HIV Care.

☑ ALL RECOMMENDATIONS: SECOND-LINE ART AFTER TREATMENT FAILURE OR FOR REGIMEN SIMPLIFICATION

Changes to Address Adverse Effects

- When changing a patient's ART regimen to address adverse effects, the clinician should (A2):
  - Review all prior genotype and phenotype resistance test results and ART history for evidence of virologic failure to inform the choice of a fully active regimen when switching from a suppressive regimen.
  - Account for the adverse effect profiles of ARVs, including cross-class toxicities.
  - Account for potential drug-drug interactions with chronically used concomitant medications, including nonprescription and over-the-counter medications, especially when switching from or to a regimen that may induce or inhibit shared metabolic pathways.
  - Minimize the potential for negative effects of a new ART regimen on any underlying chronic medical conditions, such as cardiovascular disease or risk, impaired renal function, or chronic anemia.
- If a patient has chronic HBV infection, the clinician should include TAF/TDF in conjunction with 3TC/FTC or another agent with activity against HBV (e.g., ETV) in the patient's ART regimen. (A2)

Changes to Address Drug-Drug Interactions

- When changing a patient's ART regimen to address drug-drug interactions, the clinician should (A2):
  - Acquire a current list of all medications that a patient is taking or any medications planned for treatment of a comorbid condition before constructing an ART regimen.
  - Account for the drug-clearance mechanisms and pharmacokinetic drug-drug interactions of ARVs to select optimal regimens.
  - Pay particular attention to the effect of starting or stopping specific ARVs, such as COBI or RTV, on concurrent medications that may require dose adjustment.

Changes Due to Pregnancy

- When changing an ART regimen for a patient who is pregnant or planning pregnancy, the clinician should follow the recommendations of the DHHS: Recommendations for the Use of Antiretroviral Drugs During Pregnancy and Interventions to Reduce Perinatal HIV Transmission in the United States. (A3)

ART Changes for Regimen Simplification

- Clinicians should not prescribe single-agent ART. (A1)
- When changing an ART regimen for simplification, i.e., to improve adherence, reduce cost, improve quality of life, or respond to a patient's request, clinicians should construct a new regimen based on an assessment of:
  - Prior resistance testing results (A1)
  - History of ART failure (A2)
  - Tolerability (A2)
  - Evidence of clinical effectiveness (A2)

Resumption of ART After a Treatment Interruption

- Although drug resistance may not be present in all cases, when reinitiating ART after an interruption, clinicians should identify factors that may have contributed to potential selection of drug resistance, including:
  - Reason for a treatment interruption, i.e., strategic or unplanned (A3)
  - The patient's plasma HIV-1 RNA level (viral load) at the time of ART interruption (A2)
  - Duration of the interruption, particularly if agents with long clearance half-lives are being used (A2)
  - Pattern of adherence prior to discontinuation (A2)
  - Existence of any barriers to adherence before the treatment interruption, and whether they are still present (A2)
- If the factor(s) related to interruption confer a low likelihood of emerging resistance, the clinician should recommend resumption of an appropriate ART regimen (based on assessment above) as soon as possible. (A2)
- If a patient had a detectable viral load before a treatment interruption of <4 weeks, the clinician should obtain a plasma genotypic resistance test as soon as possible. (A2)

Abbreviations: 3TC, lamivudine; ART, antiretroviral therapy; ARV, antiretroviral medication; COBI, cobicistat; DHHS, U.S. Department of Health and Human Services; DRV, darunavir; DTG, dolutegravir; ETV, entecavir; FTC, emtricitabine; HBV, hepatitis B virus; INSTI, integrase strand transfer inhibitor; PI, protease inhibitor; RAM, resistance-associated mutation; RTV, ritonavir; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

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Supplement: Guideline Development and Recommendation Ratings

Table S1: Guideline Development: New York State Department of Health AIDS Institute Clinical Guidelines Program	
Developer	New York State Department of Health AIDS Institute (NYSDOH AI) Clinical Guidelines Program
Funding Source	NYSDOH AI
Program Manager	Clinical Guidelines Program, Johns Hopkins University School of Medicine, Division of Infectious Diseases. See Program Leadership and Staff.
Mission	To produce and disseminate evidence-based, state-of-the-art clinical practice guidelines that establish uniform standards of care for practitioners who provide prevention or treatment of HIV, viral hepatitis, other sexually transmitted infections, and substance use disorders for adults throughout New York State in the wide array of settings in which those services are delivered.
Expert Committees	The NYSDOH AI Medical Director invites and appoints committees of clinical and public health experts from throughout NYS to ensure that the guidelines are practical, immediately applicable, and meet the needs of care providers and stakeholders in all major regions of NYS, all relevant clinical practice settings, key NYS agencies, and community service organizations. See Expert Committees.
Committee Structure	• Leadership: AI-appointed chair, vice chair(s), chair emeritus, clinical specialist(s), JHU Guidelines Program Director, AI Medical Director, AI Clinical Consultant, AVAC community advisor • Contributing members • Guideline writing groups: Lead author, coauthors if applicable, and all committee leaders
Conflicts of Interest Disclosure and Management	• Annual disclosure of financial relationships with commercial entities for the 12 months prior and upcoming is required of all individuals who work with the guidelines program, and includes disclosure for partners or spouses and primary professional affiliation. • The NYSDOH AI assesses all reported financial relationships to determine the potential for undue influence on guideline recommendations and, when indicated, denies participation in the program or formulates a plan to manage potential conflicts. Disclosures are listed for each committee member.
Evidence Collection and Review	• Literature search and review strategy is defined by the guideline lead author based on the defined scope of a new guideline or update. • A comprehensive literature search and review is conducted for a new guideline or an extensive update using PubMed, other pertinent databases of peer-reviewed literature, and relevant conference abstracts to establish the evidence base for guideline recommendations. • A targeted search and review to identify recently published evidence is conducted for guidelines published within the previous 3 years. • Title, abstract, and article reviews are performed by the lead author. The JHU editorial team collates evidence and creates and maintains an evidence table for each guideline.
Recommendation Development	• The lead author drafts recommendations to address the defined scope of the guideline based on available published data. • Writing group members review the draft recommendations and evidence and deliberate to revise, refine, and reach consensus on all recommendations. • When published data are not available, support for a recommendation may be based on the committee's expert opinion. • The writing group assigns a 2-part rating to each recommendation to indicate the strength of the recommendation and quality of the supporting evidence. The group reviews the evidence, deliberates, and may revise recommendations when required to reach consensus.

Table S1: Guideline Development: New York State Department of Health AIDS Institute Clinical Guidelines Program	
Review and Approval Process	• Following writing group approval, draft guidelines are reviewed by all contributors, program liaisons, and a volunteer reviewer from the AI Community Advisory Committee. • Recommendations must be approved by two-thirds of the full committee. If necessary to achieve consensus, the full committee is invited to deliberate, review the evidence, and revise recommendations when required. • Final approval by the committee chair and the NYSDOH AI Medical Director is required for publication.
External Reviewers	• External peer reviewers recognized for their experience and expertise review guidelines for accuracy, balance, clarity, and practicality and provide feedback. • Peer reviewers may include nationally known experts from outside of New York State.
Update Process	• JHU editorial staff ensure that each guideline is reviewed and determined to be current upon the 3-year anniversary of publication; guidelines that provide clinical recommendations in rapidly changing areas of practice may be reviewed annually. Published literature is surveilled to identify new evidence that may prompt changes to existing recommendations or development of new recommendations. • If changes in the standard of care, newly published studies, new drug approval, new drug-related warning, or a public health emergency indicate the need for immediate change to published guidelines, committee leadership will make recommendations and immediate updates. • All contributing committee members review and approve substantive changes to, additions to, or deletions of recommendations; JHU editorial staff track, summarize, and publish ongoing guideline changes.

Table S2: Recommendation Ratings and Definitions		
Strength	**Quality of Evidence**	
A: Strong B: Moderate C: Optional	1	Based on published results of at least 1 randomized clinical trial with clinical outcomes or validated laboratory endpoints.
	*	Based on either a self-evident conclusion; conclusive, published, in vitro data; or well-established practice that cannot be tested because ethics would preclude a clinical trial.
	2	Based on published results of at least 1 well-designed, nonrandomized clinical trial or observational cohort study with long-term clinical outcomes.
	2†	Extrapolated from published results of well-designed studies (including nonrandomized clinical trials) conducted in populations other than those specifically addressed by a recommendation. The source(s) of the extrapolated evidence and the rationale for the extrapolation are provided in the guideline text. One example would be results of studies conducted predominantly in a subpopulation (e.g., one gender) that the committee determines to be generalizable to the population under consideration in the guideline.
	3	Based on committee expert opinion, with rationale provided in the guideline text.