# Recognizing and Managing Antiretroviral Treatment Failure

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| Panel's Recommendations |
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| • The causes of antiretroviral (ARV) treatment failure—which include poor adherence, drug resistance, poor absorption of medications, inadequate dosing, and drug–drug interactions—should be assessed and addressed (AII).<br>• Perform ARV drug-resistance testing when virologic failure occurs, while the patient is still taking the failing regimen (AI*) (see Drug-Resistance Testing in the Adult and Adolescent Antiretroviral Guidelines for more information).<br>• ARV regimens should be chosen based on treatment history and drug-resistance testing, including both past and current resistance test results (AI*).<br>• The new regimen should include at least two, but preferably three, fully active ARV medications; the assessment of anticipated ARV activity should be based on treatment history and past resistance test results (AII*).<br>• The goal of therapy following treatment failure is to achieve and maintain virologic suppression, which is defined as a plasma viral load that is below the limits of detection as measured by highly sensitive assays with lower limits of quantification of 20 copies/mL to 75 copies/mL (AI*).<br>• When complete virologic suppression cannot be achieved, the goals of therapy are to preserve or restore immunologic function (as measured by CD4 T lymphocyte values), prevent clinical disease progression, and prevent the development of additional drug resistance that could further limit future ARV drug options (AII).<br>• Children who require evaluation and management of treatment failure should be managed by or in collaboration with a pediatric HIV specialist (AIII). |
| *Rating of Recommendations: A = Strong; B = Moderate; C = Optional*<br><br>*Rating of Evidence: I = One or more randomized trials in children† with clinical outcomes and/or validated endpoints; I* = One or more randomized trials in adults with clinical outcomes and/or validated laboratory endpoints with accompanying data in children† from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies in children† with long-term outcomes; II* = One or more well-designed, nonrandomized trials or observational studies in adults with long-term clinical outcomes with accompanying data in children† from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion*<br><br>*† Studies that include children or children/adolescents, but not studies limited to postpubertal adolescents* |

## Categories of Treatment Failure

Treatment failure can be categorized as virologic failure, immunologic failure, clinical failure, or some combination of the three. Immunologic failure refers to a suboptimal immunologic response to therapy or an immunologic decline while on therapy, but no standardized definition exists. Clinical failure is defined as the occurrence of new opportunistic infections (OIs) (excluding immune reconstitution inflammatory syndrome [IRIS]) and/or other clinical evidence of HIV disease progression during therapy. Almost all antiretroviral (ARV) management decisions for treatment failure are based on addressing virologic failure.

## *Virologic Failure*

Virologic failure refers to either an incomplete initial response to therapy or a viral rebound after virologic suppression is achieved. *Virologic suppression* is defined as having a plasma viral load below the lower level of detection, as measured by highly sensitive assays with lower limits of quantitation of <20 copies/mL to <75 copies/mL. *Virologic failure* is defined as the inability to achieve or maintain plasma viral load <200 copies/mL after 6 months of therapy. Laboratory results must be confirmed with repeat testing before a final assessment of virologic failure is made.

Infants with high plasma viral loads at the initiation of antiretroviral therapy (ART) occasionally take longer than 6 months to achieve virologic suppression. Because of this, some experts continue the treatment regimen for infants if their viral load is declining but is still ≥200 copies/mL at 6 months. These infants should be monitored closely until they achieve virologic suppression.[1] However, ongoing nonsuppression—especially with non-nucleoside reverse transcriptase inhibitor (NNRTI)– or raltegravir (RAL)-based regimens—increases the risk of drug resistance.[2,3] RAL, a first-generation integrase strand transfer inhibitor (INSTI), has a low barrier to resistance and requires twice-daily dosing in children and adolescents; it is the only INSTI approved for use in infants <30 days of age. For very young infants started on an antiretroviral therapy (ART) regimen with RAL or the NNRTI nevirapine (NVP), a change to dolutegravir (DTG), a second-generation INSTI, is recommended after 30 days of age for effective and durable viral suppression (see What to Start: Antiretroviral Treatment Regimens Recommended for Initial Therapy in Infants and Children with HIV).

The clinical implications of HIV RNA levels that are between the lower level of detection and <200 copies/mL in patients on ART remain unclear. Adults with HIV who have detectable viral loads and a quantified result <200 copies/mL after 6 months of ART generally achieve virologic suppression without changing regimens.[4,5] However, some studies in adults have found that multiple viral load measurements of 50 copies/mL to <200 copies/mL (sometimes characterized as low-level viremia) may be associated with an increased risk of later virologic failure.[6-9] In contrast, a recent study that followed a cohort of 57 adult patients with low-level viremia (21–200 copies/mL) reported that none of the patients had resistance to their regimens, and all had adequate plasma ARV concentrations. At 96 weeks of follow-up, 67% remained with low-level viremia, 26% had viral loads <20 copies/mL, and only 7% had virologic failure; none was attributed to viral resistance.[10]

"Blips"—defined as isolated episodes of a detectable but low level of plasma viral load (i.e., <500 copies/mL) that are followed by a return to viral suppression—are common and not generally reflective of short-term virologic failure, although they may indicate an increased risk of virologic failure after 12 to 24 months.[11-13] However, repeated or persistent plasma viral loads that are ≥200 copies/mL (especially viral loads that are >500 copies/mL) in patients who have previously achieved virologic suppression usually indicate virologic failure.[5,13-15]

## *Poor Immunologic Response Despite Virologic Suppression*

Poor immunologic response despite virologic suppression is uncommon in children.[16] Patients with baseline severe immunosuppression often take longer than 1 year to achieve immune recovery, even if virologic suppression occurs more promptly (see Appendix C. Centers for Disease Control and Prevention Pediatric HIV CD4 Cell Count/Percentage and HIV-Related Diseases Categorization). Patients who have very low baseline CD4 T lymphocyte (CD4) cell counts before initiating ART are at higher risk of an impaired CD4 response to ART and, based on data from adult studies, may be at higher risk of death and AIDS-defining illnesses despite virologic suppression.[17-19] During the early

treatment period, before immune recovery or in cases of persistent immunosuppression, clinical disease progression can occur. In an international study, 68% of children and adolescents had advanced/severe immunosuppression for age at initiation of ART, and 12% of pediatric and adolescent patients had a poor immunologic response (defined as advanced/severe immunosuppression for age) 1 year after viral suppression (defined as <400 copies/mL).[20] Among those with a poor immunologic response at 1 year after viral suppression, a fourfold increased risk of an AIDS diagnosis or death was observed compared with immune responders (rate ratio 4.04; 95% confidence interval [CI], 1.83–8.92). Poor immunologic response dropped to 7% at 2 years and 3% at 3 years in those with continued viral suppression.[20] Studies in adults with HIV note that CD4 count recovery at 1 year and 2 years after initiation of initial therapy is independent of the drug class used (i.e., boosted protease inhibitor [PI], INSTI, or NNRTI).[21]

In cases of poor immunologic response despite virologic suppression, clinicians should first exclude laboratory error in CD4 values or viral load measurements and ensure that CD4 values have been interpreted correctly in relation to the natural decline in CD4 count that occurs during the first 5 to 6 years of life. Another laboratory consideration is that some viral load assays may not amplify all HIV groups and subtypes (e.g., HIV-1 non-M groups, HIV-2), resulting in falsely low or negative viral load results (see Diagnosis of HIV Infection in Infants and Children and Clinical and Laboratory Monitoring of Pediatric HIV Infection). Once laboratory results are confirmed, clinicians should evaluate patients for adverse events, medical conditions, and other factors that can cause CD4 values to decrease (see Table 19 below). Several drugs (e.g., corticosteroids, chemotherapeutic agents) and conditions (e.g., hepatitis C virus, tuberculosis [TB], malnutrition, Sjogren's syndrome, sarcoidosis, syphilis, cirrhosis, acute viral infections) are independently associated with low CD4 values.[22]

In summary, poor immunologic response to treatment can occur. Management consists of confirming that CD4 values and viral load measurements are accurate, avoiding the use of drugs that are associated with low CD4 values, and treating other conditions that could impair CD4 recovery. The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) **does not recommend** modifying an ARV regimen based on lack of immunologic response if virologic suppression is confirmed.

## *Poor Clinical Response Despite Adequate Virologic and Immunologic Responses*

Clinicians must carefully evaluate patients who experience clinical disease progression despite favorable immunologic and virologic responses to ART; not all cases represent ART failure. At times, after initiation of ART, patients will suffer a clinical deterioration due to paradoxical worsening of a known OI or unmasking of a previously undiagnosed OI due to a profound immune response (i.e., IRIS) related to successful viral suppression. These circumstances, including IRIS, do not represent ART treatment failure and do not generally require discontinuation or change in ART.[23,24] Children who have suffered irreversible damage to their lungs, brain, or other organs—especially during prolonged and profound pre-treatment immunosuppression—may continue to have recurrent infections or symptoms in the damaged organs, because the immunologic improvement may not reverse damage to the organs.[25] Such cases do not represent ART failure, and these children would not benefit from a change in ARV regimen. Before a definitive conclusion of ART clinical failure is reached, a child should be evaluated to rule out (and, when indicated, treat) other causes or conditions that can occur with or without HIV-related immunosuppression, such as pulmonary TB, malnutrition, and malignancy.

Occasionally, however, children will develop new HIV-related OIs (e.g., *Pneumocystis jirovecii* pneumonia or esophageal candidiasis that occurs more than 6 months after achieving markedly improved CD4 values and virologic suppression) that are not related to IRIS, pre-existing organ damage, or another cause.[16] Although such cases are rare, they may represent ART clinical failure, and improvement in CD4 values may not necessarily normalize immunologic function. In children who have signs of new or progressive abnormal neurodevelopment, some experts change the ARV regimen, aiming to include agents that are known to achieve higher concentrations in the central nervous system. However, the data regarding the effectiveness of this strategy are inconclusive.[26,27]

**Table 19. Discordance Among Virologic, Immunologic, and Clinical Responses**

| Differential Diagnosis of Poor Immunologic Response Despite Virologic Suppression |
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| Poor Immunologic Response Despite Virologic Suppression and Good Clinical Response |
| • Laboratory error (in CD4 value or viral load measurement) |
| • Misinterpretation of normal, age-related CD4 count decline (i.e., the immunologic response is not actually poor) |
| • Low pre-treatment CD4 count or percentage |
| • AEs that are associated with the use of certain drugs (e.g., ZDV, TMP-SMX, systemic corticosteroids) |
| • Use of systemic corticosteroids or chemotherapeutic agents |
| • Conditions that can cause low CD4 values (e.g., HCV, acute viral infections, TB, malnutrition, Sjogren's syndrome, sarcoidosis, syphilis) |
| Poor Immunologic and Clinical Responses Despite Virologic Suppression |
| • Laboratory error (in CD4 value or viral load measurement) |
| • Falsely low viral load result for an HIV strain/type that is not detected by viral load assay (i.e., HIV-1 non-M groups, HIV-1 non-B subtypes, HIV-2 [although this is unusual with newer viral load assays]) |
| • Persistent immunodeficiency that occurs soon after initiating ART, but before ART-related reconstitution |
| • Primary protein-calorie malnutrition |
| • Untreated TB |
| • Malignancy |
| **Differential Diagnosis of Poor Clinical Response Despite Adequate Virologic and Immunologic Responses** |
| • IRIS |
| • A previously unrecognized, pre-existing infection or condition (e.g., TB, malignancy) |
| • Malnutrition |
| • Clinical manifestations of previous organ damage: brain (e.g., strokes, vasculopathy, worsening neurodevelopmental delay), lungs (e.g., bronchiectasis), cardiac (e.g., cardiomyopathy), renal (e.g., HIV-related kidney disease) |
| • A new clinical event due to a non-HIV illness or condition |
| • A new, or otherwise unexplained, HIV-related clinical event (e.g., treatment failure) |

Key: AE = adverse effect; ART = antiretroviral therapy; CD4 = CD4 T lymphocyte; HCV = hepatitis C virus; IRIS = immune reconstitution inflammatory syndrome; TB = tuberculosis; TMP-SMX = trimethoprim-sulfamethoxazole; ZDV = zidovudine

## Management of Virologic Failure

The approach to managing and subsequently treating virologic failure will differ depending on the etiology of the problem. When assessing a child with suspected virologic failure, clinicians should evaluate therapy adherence and medication intolerance, confirm that the prescribed dosing is correct (and understood by the child and/or caregiver) for all medications in the regimen, consider possible pharmacokinetic interactions that might lead to low drug levels, and test for possible drug resistance (see Management of Medication Toxicity or Intolerance, Appendix A. Pediatric Antiretroviral Drug Information, and Drug-Resistance Testing in the Adult and Adolescent Antiretroviral Guidelines). Although many factors can contribute to virologic failure, the main barrier to sustained virologic suppression in adults and children is incomplete adherence to medication regimens, with the subsequent emergence of viral mutations that confer partial or complete resistance to one or more components of the ARV regimen. See Adherence to Antiretroviral Therapy in Children and Adolescents with HIV for guidance on assessing adherence and strategies for improving adherence.

### *Virologic Failure with No Antiretroviral Drug Resistance Identified*

Persistent viremia in the absence of detectable viral resistance to current medications is usually a result of nonadherence, but it is important to consider other factors, such as poor drug absorption, incorrect dosing, and drug interactions. If adequate drug exposure can be ensured, then adherence to the current regimen should result in virologic suppression. Resistance testing should take place while a child is on therapy. After discontinuing therapy, plasma viral strains may quickly revert to wild type and reemerge as the predominant viral population, in which case, resistance testing can fail to identify the drug-resistant virus (see Drug-Resistance Testing in the Adult and Adolescent Antiretroviral Guidelines). In this situation, resistance can be identified by restarting the prior medications while emphasizing adherence and repeating resistance testing in 4 weeks if plasma virus remains detectable. If the HIV plasma viral load becomes undetectable, then nonadherence was likely the original cause of virologic failure.

If a new, more convenient regimen could address the main barrier to adherence, it is reasonable for a clinician to switch a patient to this new regimen (e.g., a single fixed-dose combination [FDC] tablet taken once daily) while closely monitoring adherence and viral load (see Appendix A, Table 1. Antiretrovirals Available in Fixed-Dose Combination Tablets or as a Co-packaged Formulation, by Drug Class and Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets and Co-packaged Formulations: Minimum Body Weights and Considerations for Use in Children and Adolescents in Appendix A. Pediatric Antiretroviral Drug Information). Similarly, if an ART side effect or tolerability is found to be impacting adherence, switching to a new regimen with close monitoring should be considered. INSTI-based, once-daily regimens in FDCs address both convenience and tolerability in most cases. However, in cases where clinicians determine that patients have poor adherence to the current regimen and that adherence is unlikely to improve with a new regimen, clinicians should address barriers to adherence before initiating a new regimen (see Adherence to Antiretroviral Therapy in Children and Adolescents with HIV).

### *Virologic Treatment Failure with Antiretroviral Drug Resistance Identified*

After deciding that a change in therapy is necessary, a clinician should attempt to identify at least two, but preferably three, fully active ARV agents from at least two different drug classes to use in a patient's new regimen. The clinician should consider all of the child's past and recent drug-resistance test results, the child's prior exposure to ARV drugs, whether the child and caregiver is likely to

adhere to the regimen, and whether the child and caregiver find a particular regimen acceptable.[28-32] This process often requires using agents from one or more drug classes that are new to the child. However, clinicians should be aware that drug-resistance mutations can confer cross-resistance within a drug class, so a drug that is new to the child may still have diminished antiviral potency. Substituting or adding a single drug to a failing regimen **is not recommended,** because this is unlikely to lead to durable virologic suppression and will likely result in additional drug resistance. When reviewing results of drug-resistance assays, clinicians should review the Stanford University HIV Drug Resistance Database to determine if a change in the ARV regimen is required and, if a change is required, which ARV agents can be retained. A pediatric HIV specialist should be consulted when determining which new regimen will have the best chance of achieving complete virologic suppression in children who have experienced treatment failure.

The process of switching a patient to a new regimen must include a discussion of treatment adherence and potential toxicity with the child and the child's caregivers. This discussion should be appropriate for the childs's age and stage of development. Clinicians should be aware that some medications have conflicting food requirements and concomitant medication restrictions that may complicate the administration of a regimen. Timing of medication administration is particularly important because it helps ensure adequate ARV drug exposures throughout the day. Palatability, pill size, number of pills, and dosing frequency all need to be considered when choosing a new regimen.[33]

## Therapeutic Options to Achieve Complete Virologic Suppression After Virologic Failure

ARV regimens should be chosen based on a child's treatment history and drug-resistance test results to optimize ARV drug potency in the new regimen (see Adherence to Antiretroviral Therapy in Children and Adolescents with HIV). A general strategy for regimen changes is shown in Table 20 below; however, as additional agents are licensed and studied for use in children, newer regimens that are better tailored to the needs of each child may be constructed.

It is important to review individual drug profiles for information about drug interactions and dose adjustments when devising a regimen for children with multiclass drug resistance. Appendix A. Pediatric Antiretroviral Drug Information provides detailed information on drug formulations, pediatric and adult doses, and toxicity, as well as discussions of the available data on the use of ARV drugs in children. Previously prescribed drugs that were discontinued because of poor tolerance or poor adherence may sometimes be reintroduced if drug resistance did not develop and if prior difficulties with tolerance and adherence can be overcome (e.g., by switching to a new formulation, such as an FDC tablet).

The availability of newer drugs within existing drug classes and the introduction of new classes of drugs increase the likelihood of finding three active drugs, even for children with extensive drug resistance (see Table 20 below). INSTI-based regimens are increasingly used for children who have experienced treatment failure on NNRTI-based regimens or PI-based regimens.[34,35] Second-generation INSTIs DTG and bictegravir have the advantage of once-daily dosing, small pill size or dispersible formulations, and higher barrier to the development of drug resistance; they also often retain ARV activity in patients who have experienced treatment failure on RAL-based therapy (see the Dolutegravir and Bictegravir sections for the latest age and weight indications).[36] Caution should be exercised when considering regimens that include first-generation INSTIs with a lower barrier to

resistance (e.g., RAL, elvitegravir) in children who are highly treatment experienced as they are less likely to achieve viral suppression.[37]

Data from pediatric and adult studies support the efficacy of a regimen that contains a second-generation INSTI (DTG) plus two nucleoside reverse transcriptase inhibitors (NRTIs) for those who experience treatment failure on an initial NNRTI-based regimen. Both the Once-daily DTG-based ART in Young People vs. Standard Therapy (ODYSSEY)[38] and Nucleosides And Darunavir/Dolutegravir in Africa (NADIA)[39] trials indicate that DTG is non-inferior to a boosted-PI regimen when transitioning from a failing NNRTI-based regimen.

In ODYSSEY, 707 children weighing at least 14 kg, with a median age of 12.2 years, were randomized to DTG-based ART versus standard care for either first-line or second-line treatment. Fifty-six percent (n = 396) of participants were in the second-line therapy group (ODYSSEY B cohort), with an enrollment HIV-1 RNA viral load of at least 500 copies/mL. Participants were randomized 1:1 to either DTG and two NRTIs or second-line standard care (a third new agent and two NRTIs with at least one NRTI with preserved activity); 98% of those in the standard-care group received a boosted PI–based regimen. Boosted-PI regimens were 72% boosted lopinavir, 24% boosted atazanvir, and 1% boosted darunavir. NRTI backbone therapies included abacavir and lamivudine (3TC) in 65% of participants, tenofovir disoproxil fumarate (TDF) and 3TC or TDF and emtricitabine (FTC) in 23% of participants, and zidovudine (ZDV) and 3TC in 11% of participants, and 1% of participants received a different combination. The NRTIs were balanced across the groups. Across both cohorts, the risk of treatment failure was approximately 40% lower (hazard ratio 0.60; 95% CI, 0.42–0.86) in the DTG-based treatment group than in the standard-care group. Within the ODYSSEY B cohort at 96 weeks, 32 of 196 participants (16%) in the DTG group had treatment failures, and 41 of 200 participants (20%) in the standard-care group had treatment failures. Twenty-nine of the 32 participants in the DTG group with treatment failure had a post-treatment resistance test available, with 23 of 29 having at least one major mutation after treatment. In the standard-care cohort, 36 of 40 participants with virologic failure had a major mutation after treatment. In the DTG group, four participants had an INSTI-related mutation, and three of the four were receiving ZDV and 3TC. In the standard-care group, two participants had a new PI-related mutation.

In the NADIA trial, adults experiencing virologic failure on a NNRTI plus 3TC or FTC and TDF regimen were randomized to DTG or darunavir/ritonavir (DRV/r) plus 3TC and secondarily randomized to either TDF or ZDV. At both 48 and 96 weeks, >85% of participants met the primary endpoint of viral suppression, defined as <400 copies/mL in all arms of the study, and the DTG regimen was non-inferior to the DRV/r regimen. At 96 weeks, 9 of 235 (4%) participants on the DTG regimen developed DTG resistance, with the majority (6 of 9) also assigned to ZDV. No PI resistance was developed in the DRV/r group.

If a child experiences virologic failure on an initial PI-based regimen, there are often limited resistance mutations detected, indicating that poor adherence/tolerance of the regimen may be the cause of poor viral control.[40,41] In these cases, a more tolerable ARV regimen should be sought to improve adherence and achieve virologic suppression. Switching to an INSTI-based regimen can be effective in some PI-experienced children, and these are typically better tolerated than PI-based regimens.[34,35,42-44]

Some studies in adults have suggested that 3TC can still contribute to suppression of HIV replication in patients with 3TC resistance mutations. Continuation of 3TC also can maintain a 3TC mutation

(184V) that can partially reverse the effects of other mutations that confer resistance to ZDV and TDF.[45-47]

Studies have compared the use of NRTI-sparing and NRTI-containing regimens in adults with multidrug resistance who experienced virologic failure on a previous regimen. These studies have demonstrated no clear benefit of including NRTIs in the new regimen.[48,49] One of these studies reported no difference in rate of virologic suppression but a trend toward a higher mortality in adults who were randomized to receive a regimen that included NRTIs than in adults who were randomized to receive an NRTI-sparing regimen.[49] There are no studies of NRTI-sparing regimens in children with virologic failure and multidrug resistance, but an NRTI-sparing regimen may be a reasonable option for children with extensive NRTI resistance.

### *Additional Therapeutic Options to Achieve Virologic Suppression When Multidrug-Resistant Virus Is Present*

The NNRTIs etravirine (ETR) and rilpivirine can retain activity against NVP-resistant virus or EFV-resistant virus in the absence of certain key NNRTI mutations, but ETR has generally been tested only in regimens that also contain a boosted PI.[28,50] For this reason, the Panel recommends using ETR as part of a regimen that includes a boosted PI (see the Etravirine section). Doravirine is a once-daily NNRTI that retains activity against EFV/NVP-resistant virus and is approved by the U.S. Food and Drug Administration (FDA) for use in children and adolescents weighing ≥35 kg. Studies have been completed in adolescents aged 12 to <18 years demonstrating safety and tolerability[51,52] (see the Doravirine section).

Maraviroc, a CCR5 antagonist, provides a new drug class; however, many ART-experienced children and some ART-naive children already harbor a CXCR4-tropic virus, which precludes its use.[53,54] Regimens that include an INSTI and a potent boosted PI with or without ETR have been effective during small studies of extensively ART-experienced patients with multiclass drug resistance.[55-58]

When searching for at least two fully active agents in cases of extensive drug resistance, clinicians should consider the potential availability of new therapeutic agents that are not currently being studied in children or that may be approved for use in children in the future. Information about clinical trials can be found using the National Institute of Allergy and Infectious Diseases Clinical Trials database and by consulting a pediatric HIV specialist. Children should be enrolled in clinical trials of new drugs whenever possible. See ClinicalTrials.gov for more information.

Pediatric dosing for off-label use of ARV drugs is problematic, because absorption, hepatic metabolism, and excretion change with age.[59] In clinical trials of several ARV agents, direct extrapolation of a pediatric dose from an adult dose, based on a child's body weight or body surface area, was shown to result in an underestimation of the appropriate pediatric dose.[60]

Off-label use of ARV agents, however, may be necessary for children with HIV who have limited ARV drug options. In this circumstance, consulting a pediatric HIV specialist for advice about potential regimens, assistance with access to unpublished data from clinical trials or other limited off-label pediatric uses, and referral to suitable clinical trials are recommended.

Two agents that inhibit the attachment of the glycoprotein 120 (gp120) region of the virus to the CD4 molecule are approved for adolescents >18 years with multidrug resistance. Oral fostemsavir (FTR) is a gp120 attachment inhibitor, and ibalizumab (given by infusion twice monthly) is a humanized

monoclonal antibody that targets the gp120 attachment area on the CD4 molecule.[61,62] Because these represent drugs with new novel targets, they would be expected to be beneficial in patients with multiclass drug resistance. In a Phase 3 study of adults with multidrug-resistant HIV-1 who are heavily treatment experienced, adding FTR to optimized background therapy resulted in improved and sustained viral suppression at 96 weeks in 163 of 272 (60%) of participants.[63] It should be noted that resistance can develop with incomplete adherence to these new agents, especially when added to a failing regimen. Although FTR is only approved for adults, research is ongoing to assess safety in the pediatric population.[64]

Lenacapavir (LEN) is a capsid inhibitor that is newly FDA approved for heavily treatment-experienced adults who have limited ARV options due to resistance, safety, or intolerance (see the Lenacapavir section). A randomized, placebo-controlled, double-blind, multicenter trial (CAPELLA) evaluated LEN in combination with an optimized background ART regimen in 72 patients with virologic failure who had multidrug-resistant HIV-1 (resistance to at least two antiretroviral medications from at least three main drug classes).[65] Although open to patients age ≥12 years, the youngest patient enrolled was 23 years. The results showed that in cohort one, 21 of 24 (88%) patients in the LEN group had a decrease of at least 0·5 $\log_{10}$ copies/mL in viral load by Day 15, as compared to 2 of 12 patients (17%) in the placebo group ($P < 0.001$); 81% of patients in the LEN group achieved durable viral suppression through 26 weeks of LEN plus an optimized background ART regimen. None of the patients developed serious adverse events related to LEN. Those receiving LEN had a greater reduction from baseline in viral load than those who received placebo. Eight participants of 72 enrolled developed LEN resistance.[66]

## Management Options When Two Fully Active Agents Cannot Be Identified or Administered

It may be impossible to provide an effective and sustainable therapeutic regimen when there is no combination of currently available agents that are active against an extensively drug-resistant virus in a patient or when a patient is unable to adhere to or tolerate ART.

The decision to continue a nonsuppressive regimen must be made on an individual basis after weighing potential benefits and risks. Specifically, providers must balance the inherent tension between the benefits of virologic suppression and the risks of continued viral replication with potential evolution of viral drug resistance in the setting of inadequate ARV drug exposure (e.g., nonadherence or a nonsuppressive, suboptimal regimen). Nonsuppressive regimens could decrease viral fitness and, thus, slow clinical and immunologic deterioration while a patient is either working on adherence or awaiting access to new agents that are expected to achieve sustained virologic suppression.[67] However, persistent viremia in the context of ARV drug pressure has the potential to generate additional resistance mutations that could further compromise agents in the same class that might otherwise have been active in subsequent regimens (e.g., continuing first-generation INSTIs or NNRTIs). Patients who continue to use nonsuppressive regimens should be followed more closely than those with stable virologic status, and the potential to successfully initiate a fully suppressive ARV regimen should be reassessed at every opportunity.

The use of NRTI-only holding regimens or a complete interruption of therapy **is not recommended.** One trial, the International Maternal Pediatric Adolescents AIDS Clinical Trials (IMPAACT P1094), randomized children with the M184V resistance mutation and documented nonadherence to continue their nonsuppressive, non NNRTI–based regimen or to switch to a 3TC (or FTC) monotherapy-

holding regimen. Children who switched to monotherapy were significantly more likely to experience a 30% decline in absolute CD4 count (the primary outcome) over a 28-week period.[68]

Complete treatment interruption also has been associated with immunologic declines and poor clinical outcomes[69,70]; therefore, it **is not recommended** (see Antiretroviral Treatment Interruption in Children with HIV).

### Table 20. Options for Regimens with at Least Two Fully Active Agents to Achieve Virologic Suppression in Patients with Virologic Failure and Evidence of Viral Resistance

To optimize antiretroviral (ARV) drug effectiveness, clinicians should evaluate a child's treatment history and drug-resistance test results when choosing a new ARV regimen. Doing so is particularly important when selecting the nucleoside reverse transcriptase inhibitor (NRTI) components of a non-nucleoside reverse transcriptase inhibitor (NNRTI)–based regimen, where drug resistance to the NNRTIs can occur rapidly if the virus is not sufficiently sensitive to the NRTIs. Regimens should contain at least two, but preferably three, fully active drugs for durable and potent virologic suppression. If the M184V/I mutation associated with emtricitabine and lamivudine is present, these medications should be continued if the new regimen contains tenofovir disoproxil fumarate, tenofovir alafenamide, or zidovudine. The presence of this mutation may increase susceptibility to these NRTIs.

Please see individual drug profiles for information about weight and age limitations (e.g., do not use darunavir in children aged <3 years), drug interactions, and dose adjustments when devising a regimen for children with multiclass drug resistance (see Appendix A. Pediatric Antiretroviral Drug Information). When modifying ARV regimens in children with chronic hepatitis B/HIV coinfection, the new regimen must contain agents active against hepatitis B. Collaboration with a pediatric HIV specialist is especially important when choosing regimens for children with multiclass drug resistance. Regimens in this table are provided as examples, but the list is not exhaustive.

| Prior Failed Regimen | New Regimen Options[a,b] |
|---|---|
| Two NRTIs Plus an NNRTI | **Preferred Regimen**<br>• Two NRTIs plus a second-generation INSTI (BIC or DTG)[c]<br>**Alternative Regimen(s)**<br>• Two NRTIs plus a boosted PI |
| Two NRTIs Plus a PI | **Preferred Regimen**<br>• Two NRTIs plus a second-generation INSTI (BIC or DTG)[c]<br>**Alternative Regimen(s)**<br>• DTG plus a different boosted PI and with or without NRTI(s) |
| Two NRTIs Plus an INSTI | • Two NRTIs plus a boosted PI<br>• Second-generation INSTI (DTG[c] or BIC[c] if not used in the prior regimen) with a boosted PI with or without NRTI(s). DTG may need to be given twice daily if a patient has certain documented INSTI mutations, or if there is concern about certain mutations (see the Dolutegravir section for dosing instructions).<br>• Two NRTIs plus an NNRTI[d] |

## Table 20. Options for Regimens with at Least Two Fully Active Agents to Achieve Virologic Suppression in Patients with Virologic Failure and Evidence of Viral Resistance

| Failed Regimen(s) That Included NRTI(s), NNRTI(s), and PI(s) | If NRTIs Are Fully Active<br>• Second-generation INSTI (DTG or BIC)[c] plus two NRTIs<br>If NRTIs Are Not Fully Active[b]<br>• Second-generation INSTI plus TAF/FTC or TDF/XTC if able to take TAF or TDF<br>• Second-generation INSTI plus two NRTIs with a boosted PI<br>• Second-generation INSTI with a boosted PI (based on resistance results). Consider ETR or RPV based on resistance results, age, and weight.<br>• Consider MVC if additional active drug(s) are needed.<br>• Consider off-label use of approved agents or enrollment in clinical trials for novel antiretroviral treatments. |
|---|---|

[a] The possibility of planned and unplanned pregnancy should be considered when selecting an ART regimen for an adolescent. When discussing ART options with adolescents of childbearing potential and their caregivers, it is important to consider the benefits and risks of all ARV drugs and to provide the information and counseling needed to support informed decision-making; refer to the Perinatal Guidelines (see Recommendations for Use of Antiretroviral Drugs During Pregnancy, Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs in Pregnant People and Nonpregnant People Who Are Trying to Conceive, and Appendix C. Antiretroviral Counseling Guide for Health Care Providers).

[b] When modifying ARV regimens in children with chronic hepatitis B/HIV coinfection, the new regimen must contain agents active against hepatitis B.

[c] RAL, a first-generation INSTI, has a low barrier to resistance and requires twice-daily dosing in children and adolescents; the second-generation INSTIs BIC and DTG have a higher barrier to resistance and only require once-daily dosing. Many Panel members would use BIC/FTC/TAF (Biktarvy) in patients with prior treatment failure who have virus with the M184 mutation (see the Bictegravir section).

[d] NNRTIs could be an option in younger patients with no exposure to NNRTIs and with taste aversion to boosted PIs, if NRTIs have preserved activity.

Key: ART = antiretroviral therapy; ARV = antiretroviral; BIC = bictegravir; DTG = dolutegravir; FTC = emtricitabine; ETR = etravirine; INSTI = integrase strand transfer inhibitor; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; RAL = raltegravir; RPV = rilpivirine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; XTC = 3TC (lamivudine) or FTC

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