# Recognizing and Managing Antiretroviral Treatment Failure

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## Panel's Recommendations

- 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).**
- Perform ARV drug-resistance testing when virologic failure occurs, while the child is still taking the failing regimen **(AI*)** (see Drug-Resistance Testing in the Adult and Adolescent Antiretroviral Guidelines for more information).
- New ARV regimens should be chosen based on treatment history and drug-resistance testing, including both past and current resistance test results **(AI*).**
  - The new regimen should include preferably two or three fully active ARV medications; the assessment of anticipated ARV activity should be based on treatment history and past resistance test results **(AI*).**
  - When using a new regimen with only two fully active ARV medications, at least one should have a high barrier to resistance (i.e., second-generation integrase strand transfer inhibitor [INSTI] or boosted protease inhibitor [PI]) **(AI*).** See the Therapeutic Options to Achieve Complete Virologic Suppression After Virologic Failure section below for recommended regimens, as some ARVs, such as zidovudine, **are not recommended** in this scenario.
  - If two fully active ARV medications are not available, at least one fully active medication with high barrier to resistance (i.e., second-generation INSTI, boosted PI) should be used plus two partially active nucleos(t)ide reverse transcriptase inhibitors, (i.e., tenofovir disoproxil fumarate or tenofovir alafenamide with lamivudine (3TC) or emtricitabine; abacavir and 3TC). In this case, frequent viral load monitoring is recommended for early detection of virologic failure **(BI).**
- 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*).**
- When complete virologic suppression cannot be achieved, the goals of therapy are to preserve or restore immunologic function (as measured by CD4 T lymphocyte cell values), prevent clinical disease progression, and prevent the development of additional drug resistance that could further limit future ARV drug options **(AII).**
- 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*

***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*

*[†] 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 that the U.S. Food and Drug Administration (FDA) approved for use in infants aged <30 days. However, to avoid the use of RAL in the first 30 days of life, the Panel on Antiretroviral Therapy and Medical Management of Children Living With HIV (the Panel) recommends using dolutegravir (DTG), a second-generation INSTI, for infants weighing >2 kg and aged ≥37 weeks' gestation. For very young infants started on an ARV regimen with RAL or the NNRTI nevirapine (NVP), a change to DTG is recommended for effective and durable viral suppression. Refer to the What to Start: Antiretroviral Treatment Regimens Recommended for Initial Therapy in Infants and Children With HIV and Dolutegravir sections for dosing instructions.

The clinical implications of low-level viremia—HIV RNA levels that are between the lower level of detection and <200 copies/mL in people on ART—remain unclear. Adults with HIV who have detectable viral loads and a quantified result of <200 copies/mL after 6 months of ART generally achieve virologic suppression without changing regimens.[4,5] However, additional studies in adults have found that low-level viremia may be associated with an increased risk of later virologic failure.[6-10] Children with low-level viremia should have their viral load monitored more frequently (at least every 3 months) to assess for virologic failure or the need for ART optimization.[11]

"Blips"—defined as isolated episodes of a detectable but low level of plasma viral load 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.[12-14] Children who have a detectable viral load should have their viral load monitored closely to ensure it has returned to undetectable levels. As noted above, persistent viremia >200 copies/mL indicates virologic failure.

## Poor Immunologic Response Despite Virologic Suppression

Poor immunologic response despite virologic suppression is uncommon in children.[15] Children with baseline severe immunosuppression often take longer than 1 year to achieve CD4 T lymphocyte (CD4) cell count 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). Children who have very low baseline CD4 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.[16-18] 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 children and adolescents had a poor immunologic response (defined as advanced/severe immunosuppression for age) 1 year after viral suppression (defined as <400 copies/mL).[19] 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. Poor immunologic response dropped to 7% at 2 years and 3% at 3 years in those with continued viral suppression. 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).[20]

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). When laboratory results are confirmed, evaluate children 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.[21]

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 **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 children 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, children 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.[22,23] 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.[24] 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.[15] 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.[25,26]

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

| Differential Diagnosis of Poor Immunologic Response Despite Virologic Suppression |
|---|
| **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) (see Table 5. CD4 Cell Counts and Percentages in Healthy Children: Distribution by Age) |
| • 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) |

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

- 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.

Resistance testing should take place while a child is on ART. After discontinuing ART, 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). If the child was on long-acting ART, resistance testing should be performed regardless of the timing of the last dose.

### 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 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 child or adolescent 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 children and adolescents 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).

New data are emerging supporting the use of long-acting injectable cabotegravir plus rilpivirine (LA CAB/RPV) in people aged ≥18 years with virologic failure secondary to nonadherence. The LATITUDE trial[27] enrolled people with nonadherence, defined as either a sustained viral load >200 copies/mL with an active ART prescription or lost to follow-up with poor ART adherence for at least 6 consecutive months in the 18 months prior to enrollment. Exclusion criteria included people younger than 18 years, with hepatitis B coinfection, and with resistance to either or both INSTIs and rilpivirine (RPV). After 24 weeks of an oral standard three-drug ARV regimen, participants were randomized to either continue standard oral therapy or switch to monthly LA CAB/RPV. The primary outcome measurement was regimen failure, defined as either discontinuation of therapy or two consecutive HIV viral loads >200 copies/mL. At 48 weeks, the long-acting injectable regimen was superior to the oral standard of care in reducing the risk of regimen failure. Active trials continue to study the use of LA CAB/RPV for virologic failure due to nonadherence; further information on this important topic is forthcoming.

## 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 child'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. However, there is evidence demonstrating that substituting out a failing NNRTI with either DTG or a boosted PI and continuing the nucleoside reverse transcriptase inhibitors (NRTI) backbone (even if not fully active) can result in sustained virologic suppression.[33] Both DTG and boosted darunavir (DRV) have a high barrier to developing drug resistance, which may contribute to the ability to sustain viral suppression without two active ARV agents. See the description of the Nucleosides And Darunavir/Dolutegravir in Africa (NADIA) and Once-daily DTG-based ART in Young People vs. Standard Therapy (ODYSSEY) trials under Therapeutic Options to Achieve Complete Virologic Suppression After Virologic Failure.

When reviewing results of current and past 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 so, 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 child 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 child'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.[34]

## 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.[35,36] 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 people who have experienced treatment failure on RAL-based therapy (see the Dolutegravir and Bictegravir sections for the latest age and weight indications).[37] 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.[38]

Data from pediatric and adult studies support the efficacy of a regimen that contains a second-generation INSTI (i.e., DTG) plus two NRTIs for those who experience treatment failure on an initial NNRTI-based regimen. Both the ODYSSEY[39] and NADIA[40] 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 ≥14 kg, with a median age of 12.2 years, were randomized to DTG-based ART versus the standard of 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 ≥500 copies/mL. Participants were randomized 1:1 to either DTG and two NRTIs or second-line standard of 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 (LPV), 24% boosted atazanvir (ATV), and 1% boosted DRV. NRTI backbone therapies included abacavir (ABC) and lamivudine (3TC), tenofovir disoproxil fumarate (TDF) and 3TC or TDF and emtricitabine (FTC), and zidovudine (ZDV) and 3TC. Across both cohorts, the risk of treatment failure was approximately 40% lower 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. In this study, full activity of the NRTIs based on genotyping was not required. 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.

Using evidence from both the ODYSSEY and NADIA trials, if a child is on a failing regimen of one NNRTI plus two NRTIs, either DTG or a boosted PI could be substituted for the NNRTI, even with partially active NRTIs. Importantly, in this scenario, the NRTI backbone should either have TDF or tenofovir alafenamide (TAF) plus 3TC or FTC, or ABC and 3TC. A secondary analysis of the ODYSSEY trial demonstrated that children who switched from another regimen to DTG and either TDF- or ABC-based NRTI regimens had similar rates of virologic failure ($P = 0.70$). However, children who switched to DTG plus a ZDV-based NRTI backbone had higher rates of virologic failure than the DTG and ABC-based NRTI group ($P = 0.048$). Further, although not statistically significant, the children with high-level ABC resistance had lower rates of virologic failure than children on DTG with ZDV with no or intermediate resistance.[33] Therefore, continuing or switching to ZDV, even with fully retained activity, would not be recommended because of the potential side effects of the medication, the need for twice-daily dosing, and the increased risk of virologic failure with the development of INSTI resistance.

Advancing the evidence from both the NADIA and ODYSSEY trials was a recent trial[41] of 919 children in Africa experiencing virologic failure while on initial NNRTI-based regimens were randomized to second-line therapy with TAF/FTC or the standard of care (ABC/3TC or ZDV/3TC) and either DTG, DRV/r, ritonavir-boosted LPV, or ritonavir-boosted ATV. After 96 weeks, TAF/FTC was non-inferior (and superior) to standard of care with 89.4% vs. 83.3% reaching virologic suppression (defined as less than 400 copies/mL). Similarly, DTG was non-inferior to ritonavir-boosted DRV, LPV, and ATV, with viral suppression of 92.0% vs. 88.3%, 84.3%, and 80.7%, respectively, and was superior to ritonavir-boosted LPV and ritonavir-boosted ATV.

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.[42,43] 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.[35,36,44-46]

Some studies in adults have suggested that 3TC can still contribute to suppression of HIV replication in people 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.[47-49]

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.[50,51] One of these studies reported no difference in the 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.[51] 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

Regimens that include an INSTI and a potent boosted PI with or without etravirine (ETR) have been effective during small pediatric studies of extensively ART-experienced children with multiclass drug resistance.[52-55] In the adult randomized control trial, D$^2$EFT, participants were switched from a failing NNRTI regimen to either DRV/r and DTG or DTG and two NRTIs (TDF plus either FTC or 3TC) versus standard of care DRV/r and two NRTIs. Viral suppression (defined as <50 copies/mL) at 48 weeks was achieved in 84% receiving DRV/r plus DTG, 78% receiving DTG plus two NRTIs, and 75% receiving DRV/r plus two NRTIs. DRV/r plus DTG was non-inferior to DRV/r and two NRTIs.[56]

The NNRTIs ETR and RPV 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.[28,57] 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 FDA for use in children and adolescents weighing ≥35 kg. Studies have been completed in adolescents aged 12 years to <18 years demonstrating safety and tolerability[58,59] (see the Doravirine section).

Maraviroc, a CCR5 antagonist, is an alternative drug class; however, many children with ART experience and some children with ART naivety already harbor a CXCR4-tropic virus, which precludes its use.[60,61]

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.[62] 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.[63]

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.[64,65] Because these represent drugs with new novel targets, they would be expected to be beneficial in people 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.[66] 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.[67]

Lenacapavir (LEN) is a capsid inhibitor that is 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 ARV regimen in 72 people with virologic failure who had multidrug-resistant HIV-1 (resistance to at least two antiretroviral medications from at least three main drug classes).[68] Although open to participants age ≥12 years, the youngest participant enrolled was 23 years old. The results showed that in Cohort 1 (n = 36) randomized 2:1 to either LEN or placebo, 21 of 24 (88%) participants 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 participants (17%) in the placebo group ($P < 0.001$); 81% of participants in the LEN group achieved durable viral suppression through 26 weeks of LEN plus an optimized background ARV regimen. None of the participants 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.[69] At 52 weeks,[70] 83% of participants in the LEN group achieved a viral load of <50 copies/mL and a mean CD4 count increase of 82 cells/$mm^3$. LEN resistance was more common when participants had no active drugs in their optimized background regimen (OBR) or when OBR was not at therapeutic levels, suggesting poor adherence.

Another newer ARV medication, islatravir, is currently being studied for both heavily treatment-experienced adults (when added to an optimized background ARV regimen) and for treatment-naive individuals. It is a nucleoside reverse transcriptase translocation inhibitor that is long-acting, making it attractive for daily, weekly, and monthly dosing. There were initial dose-related CD4 count reduction concerns, resulting in a temporary hold on development; however, clinical trials have resumed with dose adjustments. There are many ongoing trials, such as the FDC tablet doravirine/islatravir and combination therapy with islatravir and LEN.

## 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 child or when a child 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 child or adolescent is either working on adherence or awaiting access to new agents that are expected to achieve sustained virologic suppression.[71] 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). Children 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.[72]

Complete treatment interruption also has been associated with immunologic declines and poor clinical outcomes[73,74]; 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 Children 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**<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**<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 child 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 ARV regimen for an adolescent. When discussing ART options with adolescents and their caregivers, it is important to consider childbearing potential and 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 During Pregnancy and When 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 members of the Panel on Antiretroviral Therapy and Medical Management of Children Living With HIV would use BIC/FTC/TAF (Biktarvy) in children with prior treatment failure who have virus with the M184 mutation (see the Bictegravir section).

[d] NNRTIs could be an option in younger children 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

## Knowledge Gaps

- Research is needed to examine the role of long-acting injectable ART in youth aged <18 years with virologic failure secondary to nonadherence and/or other barriers to daily oral medications.
- Additional studies are needed to identify salvage therapy options in children who are heavily treatment-experienced.

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