Recognizing and Managing Antiretroviral Treatment Failure  (Last updated April 16, 2019; last reviewed April 16, 2019)

**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 there is no standardized definition. Clinical failure is defined as the occurrence of new opportunistic infections (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 plasma viral load below the lower level of detection (LLD), as measured by highly sensitive assays with lower limits of quantitation of 20 copies/mL to 75 copies/mL. **Virologic failure** is defined as repeated instances of a 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 initiation of therapy occasionally take longer than 6 months to achieve virologic suppression. Because of this, some experts 1) continue the treatment regimen for infants receiving lopinavir/ritonavir (LPV/r)-based therapy if viral load is declining but is still ≥200 copies/mL at 6 months and 2) monitor closely for continued decline to virologic suppression. However, ongoing nonsuppression—especially with non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens—increases the risk...
of drug resistance.\textsuperscript{2,3}

There is controversy regarding the clinical implications of HIV RNA levels between the LLD and <200 copies/mL in patients on antiretroviral therapy (ART). 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.\textsuperscript{4,6} However, some studies in adults have found that multiple viral load measurements of 50 copies/mL to <200 copies/mL may be associated with an increased risk of later virologic failure.\textsuperscript{7-9} “Blips”—defined as isolated episodes of detectable low level of plasma viral load (i.e., <500 copies/mL) followed by a return to viral suppression—are common and not generally reflective of short-term virologic failure; they may indicate an increased risk of virologic failure after 12 months to 24 months.\textsuperscript{10-12} However, repeated or persistent plasma viral load detection ≥200 copies/mL (especially if >500 copies/mL) after having achieved virologic suppression usually represents virologic failure.\textsuperscript{6,12-14}

**Poor Immunologic Response Despite Virologic Suppression**

Poor immunologic response despite virologic suppression is uncommon in children.\textsuperscript{15} Patients with baseline severe immunosuppression often take more than 1 year to achieve immune recovery (i.e., a CD4 T lymphocyte [CD4] cell count >500 cells/mm\textsuperscript{3}), even if virologic suppression occurs more promptly. During this early treatment period of persistent immunosuppression, additional clinical disease progression can occur.

In cases of poor immunologic response despite virologic suppression, clinicians should first exclude laboratory error in CD4 or viral load measurements and ensure that CD4 values have been interpreted correctly in relation to the natural decline in CD4 cell count over 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 or 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 17).

Patients who have very low baseline CD4 values before initiating ART are at higher risk of an impaired CD4 response to ART and, based on adult studies, may be at higher risk of death and AIDS-defining illnesses, despite virologic suppression.\textsuperscript{16-18} In a study of 933 children aged ≥5 years who received ART that resulted in virologic suppression, 348 children (37%) had CD4 cell counts <500 cells/mm\textsuperscript{3} at ART initiation, including 92 (9.9%) who had CD4 cell counts <200 cells/mm\textsuperscript{3}. After 1 year of virologic suppression, only seven children (1% of the cohort) failed to reach a CD4 cell count ≥200 cells/mm\textsuperscript{3} and 86% had CD4 cell counts >500 cells/mm\textsuperscript{3}. AIDS-defining events were uncommon overall (occurring in 1% of participants), but they occurred both in children who did achieve improved CD4 cell counts and those who did not.\textsuperscript{15}

Several drugs (e.g., corticosteroids, chemotherapeutic agents) and other conditions (e.g., hepatitis C virus, tuberculosis [TB], malnutrition, Sjogren’s syndrome, sarcoidosis, syphilis, acute viral infections) are independently associated with low CD4 values.

In summary, poor immunologic response to treatment can occur. Management consists of confirming that CD4 and virologic tests are accurate, avoiding drugs 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 does not recommend modifying an ART 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 of these cases represent ART failure. IRIS is one of the most important reasons that new or recurrent opportunistic conditions occur, even in cases where virologic suppression and immunologic restoration/preservation are achieved within the first months of initiating ART. IRIS does not mean that ART has failed and does not generally require discontinuation of ART.\textsuperscript{19,20} Children who have suffered irreversible damage to their lungs, brain, or other organs—especially during prolonged
and profound pretreatment immunosuppression—may continue to have recurrent infections or symptoms in the damaged organs because the immunologic improvement may not reverse damage to the organs. Such cases do not represent ART failure and, in these instances, children would not benefit from a change in ARV regimen. Before a definitive conclusion of ART clinical failure is reached, a child should also be evaluated to rule out (and, if 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 opportunistic conditions (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. Although such cases are rare, they may represent ART clinical failure and suggest that 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 this strategy are mixed.

### Table 17. 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:**
- Lab error (in CD4 or viral load measurement)
- Misinterpretation of normal, age-related CD4 decline (i.e., the immunologic response is not actually poor)
- Low pretreatment CD4 cell count or percentage
- Adverse effects of using ZDV
- Use of systemic corticosteroids or chemotherapeutic agents
- Conditions that can cause low CD4 values, such as HCV, acute viral infections, TB, malnutrition, Sjogren's syndrome, sarcoidosis, and syphilis

**Poor Immunologic and Clinical Responses Despite Virologic Suppression:**
- Lab error
- Falsely low viral load result for an HIV strain/type that is not detected by viral load assay (HIV-1 non-M groups, non-B subtypes; HIV-2)
- Persistent immunodeficiency soon after initiation of 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), lungs (e.g., bronchiectasis), cardiac (cardiomyopathy), renal (HIV-related kidney disease)
- A new clinical event due to a non-HIV illness or condition
- A new, otherwise unexplained HIV-related clinical event (treatment failure)

**Key to Acronyms:** ART = antiretroviral therapy; CD4 = CD4 T lymphocyte; HCV = hepatitis C virus; IRIS = immune reconstitution inflammatory syndrome; TB = tuberculosis; ZDV = zidovudine

### Management of Virologic Failure

The approach to managing and subsequently treating virologic failure will differ depending on the etiology of the problem. Assessment of a child with suspected virologic failure should include an evaluation of therapy adherence and medication intolerance, confirmation that prescribed dosing is correct (and understood by the child and/or caregiver) for all medications in the regimen, consideration of pharmacokinetic (PK) explanations of low drug levels or elevated and potentially toxic levels, and evaluation of suspected drug resistance (see [Drug-Resistance Testing](https://aidsinfo.nih.gov/guidelines) in the [Adult and Adolescent Antiretroviral Guidelines](https://aidsinfo.nih.gov/guidelines)). While 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 subsequent emergence of viral mutations that confer partial or complete resistance to one or more components of the ART regimen. Please see Adherence to Antiretroviral Therapy in Children and Adolescents Living with HIV for guidance on assessing adherence and strategies to improve 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 exclude 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 discontinuation of therapy, plasma viral strains may quickly revert to wild type and reemerge as the predominant viral population, in which case resistance testing would fail to reveal drug-resistant virus (see Drug-Resistance Testing in the Adult and Adolescent Antiretroviral Guidelines). Resistance can be identified in this situation 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 treatment failure.

Virologic Treatment Failure with Antiretroviral Drug Resistance Identified
After deciding that a change in therapy is needed, 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 patient’s past and recent drug resistance test results, the patient’s prior exposure to ARV drugs, whether the patient is likely to adhere to the regimen, and whether the patient finds a particular regimen acceptable. This process often requires using agents from one or more drug classes that are new to the patient. Substitution or addition of a single drug to a failing regimen is not recommended, because it is unlikely to lead to durable virologic suppression and will likely result in additional drug resistance. A drug may be new to the patient but have diminished antiviral potency due to the presence of drug-resistance mutations that confer cross-resistance within a drug class.

The process of switching a patient to a new regimen must include an extensive discussion of treatment adherence and potential toxicity with the patient and the patient’s caregivers. This discussion should be appropriate for the patient’s age and stage of development. Clinicians must recognize that conflicting requirements of some medications with respect to food and concomitant medication restrictions may complicate the administration of a regimen. Timing of medication administration is particularly important, as this 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.

**Therapeutic Options to Achieve Complete Virologic Suppression After Virologic Failure**
Determination of a new regimen with the best chance for complete virologic suppression in children who have already experienced treatment failure should be made by (or in collaboration with) a pediatric HIV specialist. ARV regimens should be chosen based on a patient’s treatment history and drug-resistance test results to optimize ARV drug potency in the new regimen. A general strategy for regimen change is shown in Table
18; however, as additional agents are licensed and studied for use in children, newer strategies that are better tailored to the needs of each patient may be constructed.

If a child experiences failure of initial therapy on an NNRTI-based regimen, changing to a PI-based regimen is generally effective. Studies of adults have found no evidence that a regimen that contains a boosted PI and raltegravir produces better outcomes than a regimen that contains a boosted PI and two nucleoside reverse transcriptase inhibitors (NRTIs). Therefore, most children who experience treatment failure on an initial NNRTI-based regimen should be changed to a regimen of a boosted PI plus two NRTIs. Limited data support the use of two NRTIs plus an integrase strand transfer inhibitor (INSTI) following the failure of an NNRTI-based regimen. A trial in adults who had experienced failure of an initial NNRTI-based regimen reported that dolutegravir had better efficacy and a better safety profile than LPV/r when these drugs were used in a second-line regimen that included at least one active NRTI.

There is concern about using this approach in children (especially when using INSTIs with a lower barrier to resistance, such as raltegravir), because children who experience treatment failure on NNRTI-based regimens often have substantial NRTI resistance. Resistance to the NNRTI nevirapine results in cross-resistance to the NNRTI efavirenz, and vice versa. The NNRTIs etravirine and rilpivirine can retain activity against nevirapine-resistant virus or efavirenz-resistant virus in the absence of certain key NNRTI mutations (see below), but etravirine has generally been tested only in regimens that also contain a boosted PI.

If a child experiences initial therapy failure on a PI-based regimen, there are often limited resistance mutations detected; in these cases, an alternative PI that is better tolerated and potent can be used. For example, LPV/r-based regimens have been shown to have durable ARV activity in some PI-experienced children. Darunavir/ritonavir-based therapy has also been used. Based on more limited data, a change to an INSTI-based regimen can be effective, though the barrier to resistance may be less than for a PI-based regimen.

The availability of newer drugs in existing 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 18). As previously discussed, INSTI-based regimens are increasingly used for children who have experienced treatment failure on NNRTI-based regimens or PI-based regimens. Raltegravir is the INSTI that has been studied and used most in children, but dolutegravir (see the dolutegravir section for latest age/weight indications) is increasingly appealing for its once-daily administration, small pill size, and higher barrier to development of drug resistance; it also has activity in patients who have experienced treatment failure on raltegravir-based therapy. However, because of recent concerns about the potential for neural tube defects in infants born to women who conceived while taking regimens that contained dolutegravir, this drug should be prescribed with caution in female adolescents (see dolutegravir section). Specific recommendations about the initiation and use of dolutegravir in women of childbearing potential and in pregnant women are available in the Adult and Adolescent Antiretroviral Guidelines (see Adolescents and Young Adults with HIV and Management of the Treatment-Experienced Patient) and in the Perinatal Guidelines (see Teratogenicity and Recommendations for Use of Antiretroviral Drugs During Pregnancy).

Maraviroc, a CCR5 antagonist, provides a new drug class, but many treatment-experienced children already harbor CXCR4-tropic virus, which precludes its use. Regimens that include an INSTI and a potent, boosted PI plus or minus etravirine have been effective during small studies of extensively ARV-experienced patients with multiclass drug resistance. 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 formulation, pediatric and adult dosing, and toxicity, as well as discussions of 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 ARV 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 a fixed-dose combination tablet). Limited data in adults suggest that continuing lamivudine can contribute to suppression of HIV replication,
despite the presence of lamivudine resistance mutations. Continuation of lamivudine can also maintain a lamivudine mutation (184V) that can partially reverse the effects of other mutations that confer resistance to zidovudine, stavudine, and tenofovir disoproxil fumarate.49-51

The use of new drugs that have been evaluated in adults but have not been fully evaluated in children may be justified; ideally, this would be done in the framework of a clinical trial. Expanded access programs or clinical trials may be available (see ClinicalTrials.gov). New drugs should be used in combination with at least one, and ideally two, additional active agents.

Enfuvirtide has been approved by the Food and Drug Administration (FDA) for use in treatment-experienced children aged ≥6 years, but it must be administered by subcutaneous injection twice daily.52,53 PK studies of regimens that included two boosted PIs (LPV/r with saquinavir) suggest that PK targets for both PIs can be achieved or exceeded when these drugs are used in combination in children.54-56 Regimens containing more than three drugs (up to three PIs and/or two NNRTIs) have shown efficacy in a pediatric case series, but they are complex, often poorly tolerated, and subject to unfavorable drug-drug interactions.57 Availability of newer PIs (e.g., darunavir for children aged ≥3 years) and new classes of ARV drugs (e.g., integrase and CCR5 inhibitors) have lessened the need for enfuvirtide, dual-PI regimens, and regimens of four or more drugs. The FDA has recently granted approval for a humanized monoclonal antibody, ibalizumab, that must be infused every 2 weeks in adolescents (those aged >18 years) and adults with multidrug resistance.58

Studies of NRTI-sparing regimens in adults with virologic failure and multidrug resistance have demonstrated no clear benefit of including NRTIs in the new regimen.59,60 One of these studies reported higher mortality in adults who were randomized to receive a regimen that included NRTIs compared to adults who were randomized to receive an NRTI-sparing regimen.60 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.

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 AIDSinfo Clinical Trial Search and by consulting a pediatric HIV specialist. Children should be enrolled in clinical trials of new drugs whenever possible.

Pediatric dosing for off-label use of ARV drugs is problematic, because absorption, hepatic metabolism, and excretion change with age.61 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.62

Off-label use of ARV agents be necessary for children with HIV who have limited ARV 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 use, and referral to suitable clinical trials is recommended.

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

It may be impossible to provide an effective and sustainable therapeutic regimen because no combination of currently available agents is active against extensively drug-resistant virus in a patient or because 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 costs. 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, 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. 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 statuses, and the potential to successfully initiate a fully suppressive ART regimen should be reassessed at every opportunity.

The use of NRTI-only holding regimens or a complete interruption of therapy are not recommended. One trial (IMPAACT P1094) randomized children harboring the M184V resistance mutation with persistent nonadherence and virologic failure to continue their nonsuppressive, non-NNRTI-based regimen or to switch to a lamivudine (or emtricitabine) monotherapy holding regimen. Children who switched to monotherapy were significantly more likely to experience a 30% decline in absolute CD4 cell count (the primary outcome) over a 28-week period. The median age of the participants was 15 years, the median entry CD4 cell count was 472 cells/mm³, and the median number of interventions that had been used to address nonadherence was four. Only patients in the lamivudine/emtricitabine arm experienced the primary outcome. Although this was a small study (N = 33), it is the only study ever to randomize patients to either continue using nonsuppressive ART or to switch to lamivudine or emtricitabine monotherapy, and it is unlikely that it will be repeated.

Complete treatment interruption has also been associated with immunologic declines and poor clinical outcomes, and it is not recommended (see Considerations About Interruptions in Antiretroviral Therapy).

Table 18. Options for Regimens with at Least Two Fully Active Agents to Achieve Virologic Suppression in Patients with Virologic Failure and Evidence of Viral Resistance

<table>
<thead>
<tr>
<th>Prior Regimen</th>
<th>New Regimen Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two NRTIs plus NNRTI</td>
<td>Two NRTIs plus PI</td>
</tr>
<tr>
<td>Two NRTIs plus PI</td>
<td>Two NRTIs plus INSTI</td>
</tr>
<tr>
<td>Two NRTIs plus INSTI</td>
<td>Two NRTIs plus a different RTV-boosted PI</td>
</tr>
<tr>
<td>Failed Regimen(s) That Included NRTI(s), NNRTI(s), and PI(s)</td>
<td>INSTI plus two NRTIs (if NRTIs are fully active)</td>
</tr>
</tbody>
</table>

Clinicians should evaluate a patient’s treatment history and drug-resistance test results when choosing an ART regimen in order to optimize ARV drug effectiveness. This is particularly important in selecting the NRTI components of an NNRTI-based regimen, where drug resistance to the NNRTI 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 FTC and 3TC is present, these medications should be continued if the new regimen contains TDF, TAF, or ZDV as the presence of this mutation may increase susceptibility to these NRTIs. Please see individual drug profiles for information about age limitations (e.g., do not use DRV in children aged <3 years), drug interactions, and dose adjustments when devising a regimen for children with multiclass drug resistance. 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.

Because of recent concerns about the potential for neural tube defects in infants born to women who conceived while taking regimens that contained dolutegravir, this drug should be prescribed with caution in female adolescents. Specific recommendations about the initiation and use of dolutegravir in women of childbearing potential and in pregnant women are available in the Adult and Adolescent Antiretroviral Guidelines (see Adolescents and Young Adults with HIV and Management of the Treatment-Experienced Patient) and in the Perinatal Guidelines (see Teratogenicity and Recommendations for Use of Antiretroviral Drugs During Pregnancy).

Key to Acronyms: 3TC = lamivudine; ART = antiretroviral therapy; ARV = antiretroviral; DRV = darunavir; DTG = dolutegravir; ETR = etravirine; FTC = emtricitabine; INSTI = integrase strand transfer inhibitor; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; RPV = rilpivirine; RTV = ritonavir; T-20 = enfuvirtide; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; ZDV = zidovudine
References


