



Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Recognizing and Managing Antiretroviral Treatment Failure (Last updated April 27, 2017; last reviewed April 27, 2017)

Panel's Recommendations

- The causes of virologic 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 antiretroviral (ARV) drug-resistance testing when virologic failure occurs, while the patient is still taking the failing regimen, and before changing to a new regimen (**AI***).
- 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 at least 2, but preferably 3, fully active ARV medications with assessment of anticipated ARV activity based on past treatment history and resistance test results (**AII***).
- The goal of therapy following treatment failure is to achieve and maintain virologic suppression, as measured by a plasma viral load below the limits of detection using the most sensitive assay (**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 values), prevent clinical disease progression, and prevent development of additional drug resistance that could further limit future ARV options (**AII**).
- Children who require evaluation and management of treatment failure should be managed by or in collaboration with a pediatric HIV specialist (**AI***).

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 post-pubertal 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 there is no standardized definition. Clinical failure is defined as the occurrence of new opportunistic infections 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 occurs as an incomplete initial response to therapy or as a viral rebound after virologic suppression is achieved. Virologic suppression is defined as having plasma viral load below the lower level of detection (LLD) using highly sensitive assays with lower limits of quantitation (LLQ) of 20 to 75 copies/mL. Virologic failure is defined as a repeated 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 treatment failure is made. Because infants with high plasma viral loads at initiation of therapy occasionally take longer than 6 months to achieve virologic suppression, some experts continue the treatment regimen for infants receiving ritonavir-boosted (LPV/r)-based therapy if viral load is declining but is still ≥ 200 copies/mL at 6 months and monitor closely for continued decline to virologic suppression soon thereafter.¹ However, ongoing non-suppression—especially with non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens—increases the risk

of drug resistance.^{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 regimen change.⁴⁻⁶ However, some studies in adults have found that repeated viral loads of 50 to <200 copies/mL may be associated with an increased risk of later virologic failure.^{7,8} Blips—defined as isolated episodes of plasma viral load detectable at low levels (i.e., <500 copies/mL) followed by return to viral suppression—are common and not generally reflective of virologic failure.⁹⁻¹¹ 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.^{6,11-13}

Poor Immunologic Response Despite Virologic Suppression

Poor immunologic response despite virologic suppression is uncommon in children.¹⁴ Patients with baseline severe immunosuppression often take more than 1 year to achieve immune recovery (i.e., CD4 T lymphocyte [CD4] cell count >500 cells/mm³), even if virologic suppression occurs more promptly. During this early treatment period of persistent immunosuppression, additional clinical disease progression can occur.

The first considerations in cases of poor immunologic response despite virologic suppression are to exclude laboratory error in CD4 or viral load measurements and to 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](#) and [Clinical and Laboratory Monitoring](#)). Once laboratory results are confirmed, evaluation for adverse events, medical conditions, and other factors that can result in lower CD4 values is necessary (see [Table 15](#)).

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.¹⁵⁻¹⁷ In a study of 933 children aged ≥ 5 years who received ART that resulted in virologic suppression, 348 (37%) had CD4 cell counts <500 cells/mm³ at ART initiation, including 92 (9.9%) with CD4 cell counts <200 cells/mm³. After 1 year of virologic suppression, only 7 (1% of the cohort) failed to reach a CD4 cell count ≥ 200 cells/mm³ and 86% had CD4 cell counts >500 cells/mm³. AIDS-defining events were uncommon overall (1%) but occurred in children who did and did not achieve improved CD4 cell counts.¹⁴

Several drugs (e.g., corticosteroids, chemotherapeutic agents) and other conditions (e.g., hepatitis C virus, tuberculosis, malnutrition, Sjogren's syndrome, sarcoidosis, syphilis) 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 other agents and treating other conditions that could impair CD4 recovery. The Panel 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 cases represent ART failure. One of the most important reasons for new or recurrent opportunistic conditions—despite achieving virologic suppression and immunologic restoration/preservation within the first months of ART—is immune reconstitution inflammatory syndrome (IRIS), which does not represent ART failure and does not generally require discontinuation of ART.^{18,19} 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.²⁰ 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 tuberculosis, malnutrition, and malignancy. Occasionally, however, children will develop new HIV-related opportunistic conditions (e.g., *Pneumocystis jirovecii* pneumonia or esophageal candidiasis occurring more than 6 months after achieving markedly improved CD4 values and virologic suppression) not explained by IRIS, pre-existing organ damage, or another reason.¹⁴ Although such cases are rare, they may represent ART clinical failure and suggest that improvement in CD4 values may not necessarily represent normalization of 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 supporting the strategy are mixed.^{21,22}

Table 15. Discordance Among Virologic, Immunologic, and Clinical Responses

Differential Diagnosis of Poor Immunologic Response Despite Virologic Suppression
<p>Poor Immunologic Response Despite Virologic Suppression and Good Clinical Response:</p> <ul style="list-style-type: none"> • Lab error (in CD4 or viral load result) • Misinterpretation of normal, age-related CD4 decline (i.e., immunologic response not actually poor) • Low pretreatment CD4 cell count or percentage • Adverse effects of use of ZDV or the combination of TDF and didanosine • Use of systemic corticosteroids or chemotherapeutic agents • Conditions that can cause low CD4 values, such as HCV, TB, malnutrition, Sjogren's syndrome, sarcoidosis, and syphilis <p>Poor Immunologic and Clinical Responses Despite Virologic Suppression:</p> <ul style="list-style-type: none"> • Lab error • Falsely low viral load result for HIV strain/type 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 tuberculosis • Malignancy
Differential Diagnosis of Poor Clinical Response Despite Adequate Virologic and Immunologic Responses
<ul style="list-style-type: none"> • IRIS • Previously unrecognized preexisting infection or condition (e.g., TB, malignancy) • Malnutrition • Clinical manifestations of previous organ damage: brain (e.g., strokes, vasculopathy), lungs (e.g., bronchiectasis) • New clinical event due to non-HIV illness or condition • 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; TDF = tenofovir disoproxil fumarate; ZDV = zidovudine

Management of Virologic Treatment Failure

The approach to management and subsequent treatment of virologic treatment failure will differ depending on the etiology of the problem. While the causes of virologic treatment failure may be multifactorial, nonadherence plays a role in most cases. Assessment of a child with suspicion of virologic treatment failure should include evaluation of adherence to therapy and medication intolerance, **confirmation that prescribed dosing is correct 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 [Antiretroviral Drug-Resistance Testing](#) in the [Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents](#)). The main barrier to long-term maintenance of sustained virologic

suppression in adults and children is incomplete adherence to medication regimens, with subsequent emergence of viral mutations conferring partial or complete resistance to one or more of the components of the ART regimen. **Please see guidance on assessment of [adherence](#) and strategies to improve adherence.**

Virologic Treatment Failure with No Viral 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 [Antiretroviral Drug-Resistance Testing](#) in the [Adult and Adolescent Antiretroviral Guidelines](#)). An approach to identifying resistance in this situation is to restart the prior medications while emphasizing adherence, and repeat resistance testing in 4 weeks if plasma virus remains detectable. If the HIV plasma viral load becomes undetectable, nonadherence was likely the original cause of virologic treatment failure.

Virologic failure of boosted protease inhibitor (PI)-based regimens (in the absence of prior treatment with full-dose ritonavir) is frequently associated with no detectable major PI resistance mutations, and virologic suppression may be achieved with continuation of the PI-based regimen accompanied by adherence improvement measures.^{23,24}

In some cases, the availability of a new regimen for which the convenience (e.g., single fixed-dose tablet once daily) is anticipated to address the main barrier to adherence may make it reasonable to change to this new regimen with close adherence and viral load monitoring. In most cases, however, when there is evidence of poor adherence to the current regimen and an assessment that good adherence to a new regimen is unlikely, emphasis and effort should be placed on improving adherence before initiating a new regimen (see [Adherence](#)).

Virologic Treatment Failure with Viral Drug Resistance Identified

After reaching a decision that a change in therapy is needed, a clinician should attempt to identify at least 2, but preferably 3, fully active ARV agents from at least 2 different classes on the basis of resistance test results, prior ARV exposure, acceptability to the patient, and likelihood of adherence.²⁵⁻²⁹ This 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 because of the presence of drug-resistance mutations that confer cross-resistance within a drug class.

A change to a new regimen must include an extensive discussion of treatment adherence and potential toxicity with a patient in an age- and development-appropriate manner and with a patient's caregivers. Clinicians must recognize that conflicting requirements of some medications with respect to food and concomitant medication restrictions may complicate administration of a regimen. Timing of medication administration is particularly important to ensure adequate ARV drug exposures throughout the day. Palatability, size and number of pills, and dosing frequency all need to be considered when choosing a new regimen.³⁰

Therapeutic Options After Virologic Treatment Failure with Goal of Complete Virologic Suppression

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 treatment history and [drug-resistance testing](#) to optimize ARV drug potency in the new regimen. A general strategy for regimen change is shown in [Table 16](#), although 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 has **failed** initial therapy with an NNRTI-based regimen, a change to a PI-based regimen is generally effective. Since there is no evidence of better outcomes (from studies in adults) of a boosted PI regimen including raltegravir compared to a boosted PI regimen containing 2 NRTIs, most children failing an initial NNRTI-based regimen should be changed to a regimen of a boosted PI plus 2 NRTIs.^{31,32} Limited data support use of 2 NRTIs plus an INSTI following failure of an NNRTI-based regimen,^{33,34} but there is concern about this approach (especially with INSTIs with lower barrier to resistance such as raltegravir), because children failing NNRTI-based regimens often have substantial NRTI resistance.³⁵ Resistance to the NNRTI nevirapine results in cross-resistance to the NNRTI efavirenz, and vice versa. However, the NNRTIs etravirine and rilpivirine can retain activity against nevirapine- 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 fails initial therapy with a PI-based regimen, there is often limited resistance detected,^{35,36} in which case 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.³⁷⁻³⁹ Darunavir/r-based therapy has also been used.^{40,41} Based on more limited data, a change to an INSTI-based regimen can be effective.^{33,42}

The availability of newer drugs in existing classes and newer classes of drugs increases the likelihood of finding 3 active drugs, even for children with extensive drug resistance (see [Table 16](#)). As discussed, INSTI-based regimens are increasingly used for children who have failed NNRTI- or PI-based regimens.^{33,42} The INSTI with the greatest experience in children is raltegravir but dolutegravir (see [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, including activity in patients who have failed raltegravir-based therapy. Maraviroc, a CCR5 antagonist, provides a new class but many treatment-experienced children already harbor X4-tropic virus that precludes its use.⁴³ Regimens including an INSTI and potent, boosted PI plus or minus etravirine have been effective in small studies of extensively ARV-experienced patients with multi-class drug resistance.⁴⁴⁻⁴⁷ It is important to review individual drug profiles for information about drug interactions and dose adjustment when devising a regimen for children with multi-class drug resistance. [Appendix A: Pediatric Antiretroviral Drug Information](#) provides more detailed information on drug formulation, pediatric and adult dosing, and toxicity, as well as discussion of available pediatric data for the approved ARV drugs.

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 from a liquid to a pill formulation or to a new formulation [e.g., ritonavir tablet]). Limited data in adults suggest that continuation of lamivudine can contribute to suppression of HIV replication despite the presence of lamivudine resistance mutations and can maintain lamivudine mutations (184V) that can partially reverse the effect of other mutations conferring resistance to zidovudine, stavudine, and tenofovir disoproxil fumarate.⁴⁸⁻⁵⁰ The use of new drugs that have been evaluated in adults but have not been fully evaluated in children may be justified, and ideally would be done in the framework of a clinical trial. Expanded access programs or clinical trials may be available (see www.clinicaltrials.gov). New drugs should be used in combination with at least 1, and ideally 2, additional active agents.

Enfuvirtide has been Food and Drug Administration-approved for treatment-experienced children aged ≥ 6 years but must be administered by subcutaneous injection twice daily.^{51,52} PK studies of certain dual-boosted PI regimens (LPV/r with saquinavir) suggest that PK targets for both PIs can be achieved or exceeded when used in combination in children.⁵³⁻⁵⁵ Multidrug regimens (up to 3 PIs and/or 2 NNRTIs) have shown efficacy in a pediatric case series, but they are complex, often poorly tolerated, and subject to unfavorable drug-drug interactions.⁵⁶ Availability of newer PIs (e.g., darunavir **for children aged ≥ 3 years**) and new classes of ARV drugs (integrase and CCR5 inhibitors) have lessened the need for use of enfuvirtide, dual-PI regimens, and regimens of 4 or more drugs.

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,^{57,58} and one of these studies reported higher mortality in adults randomized to a regimen with NRTIs compared to adults randomized to an NRTI-sparing regimen.⁵⁸ There are no studies of NRTI-sparing regimens in children with virologic failure and multidrug resistance, but that may be a reasonable option for children with extensive NRTI resistance.

When searching for at least 2 fully active agents in cases of extensive drug resistance, clinicians should consider the potential availability and future use of newer therapeutic agents that may not be studied or approved in children or may be in clinical development. Information concerning potential clinical trials can be found at http://aidsinfo.nih.gov/clinical_trials and through collaboration with 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.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

Use of ARV agents that do not have a pediatric indication (i.e., off-label) may be necessary for children with HIV who have limited ARV options. In this circumstance, consultation with 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 non-suppressive regimen must be made on an individual basis, weighing potential benefits and costs. Specifically, HIV providers must balance the inherent tension between the benefits of virologic suppression and the risks of continued viral replication and potential evolution of viral drug resistance in the setting of inadequate ARV drug exposure (i.e., nonadherence, non-suppressive suboptimal regimen). Non-suppressive 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.⁶¹ However, persistent viremia in the context of ARV 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 continuing non-suppressive regimens should be followed more closely than those with stable virologic status, 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 complete interruption of therapy is not recommended. In a trial (IMPAACT P1094) randomizing children harboring the M184V resistance mutation with persistent nonadherence and virologic failure to continue their non-suppressive, non-NNRTI-based ART regimen versus switching 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 4. Only patients in the lamivudine/emtricitabine arm experienced the primary outcome.⁶² Although this was a small study (N = 33), it is the only study ever to randomize patients to continuing non-suppressive ART versus lamivudine/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^{63,64} (see Treatment Interruption).

Table 16. Options for Regimens with at Least Two Fully Active Agents with Goal of Virologic Suppression in Patients with Failed Antiretroviral Therapy and Evidence of Viral Resistance^a

Prior Regimen	New Regimen Options ^a
2 NRTIs plus NNRTI	<ul style="list-style-type: none"> • 2 NRTIs plus PI • 2 NRTIs plus INSTI
2 NRTIs plus PI	<ul style="list-style-type: none"> • 2 NRTIs plus INSTI • 2 NRTIs plus different RTV-boosted PI • INSTI plus different RTV-boosted PI +/- NNRTI +/- NRTI(s)
2 NRTIs plus INSTI	<ul style="list-style-type: none"> • 2 NRTIs plus RTV-boosted PI • DTG (if not used in the prior regimen) + RTV-boosted PI +/- 1-2 NRTIs
Failed Regimen(s) That Included NRTI(s), NNRTI(s), and PI(s)	<ul style="list-style-type: none"> • INSTI + 2 NRTIs (if NRTIs are fully active) • INSTI + 2 NRTIs + RTV-boosted PI (if NRTIs are not fully active) • INSTI + RTV-boosted PI plus +/-ETR or RPV +/- NRTI(s) (if minimal NRTI activity) (consider adding T20 and/or MVC if additional active drug[s] needed)

^a ARV regimens should be chosen based on treatment history and drug-resistance testing to optimize ARV drug effectiveness. This is particularly important in selecting 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 2, but preferably 3, fully active drugs for durable, potent virologic suppression. **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 adjustment when devising a regimen for children with multi-class drug resistance.** Collaboration with a pediatric HIV specialist is especially important when choosing regimens for children with multi-class drug resistance. Regimens in this table are provided as examples, but the list is not exhaustive.

Key to Acronyms: DTG = dolutegravir; ETR = etravirine; 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; T20 = enfuvirtide

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