Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Management of Treatment-Experienced Infants, Children, and Adolescents (Last updated November 1, 2012; last reviewed November 1, 2012)

Panel's Recommendations

- 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 quantification 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 lymphocyte values), prevent clinical disease progression, and prevent development of additional drug resistance that could further limit future antiretroviral options **(AII)**.
- Not all instances of treatment failure require an immediate change in therapy; careful assessment, especially of adherence, is required to evaluate the etiology of the treatment failure and determine an appropriate management strategy **(AII)**.
- Children who require evaluation for treatment failure should be managed 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 and adolescents but not studies limited to postpubertal adolescents

Overview

Although many children remain on stable antiretroviral therapy (ART) for several years,[1-4] reassessment of a therapeutic regimen will often become necessary over time.[5]

Treatment failure is defined as suboptimal response or a lack of sustained response to therapy using virologic, immunologic, and clinical criteria. A careful assessment is required to evaluate the etiology of treatment failure and determine the appropriate management strategy. Not all instances of treatment failure require an immediate change in ART; in many cases, treatment efficacy can be restored by improving adherence or addressing other comorbidities. The approach to treatment failure in children and adolescents who have received more than one ARV regimen is often more complex than the approach in those receiving their first regimen. However, with the availability of an increasing number of antiretroviral (ARV) agents, including those directed at new viral targets, the goals of treatment for all patients—whether on initial, second, or subsequent regimens—remain the same: complete virologic suppression, combined with recovery or maintenance of immunologic function, and attainment or preservation of optimal clinical status, while preventing emergence of new viral drug-resistance mutations (see Assessment of Patients with Antiretroviral Treatment Failure and Management of Medication Toxicity or Intolerance). Decisions regarding changing ART should be individualized and should take into consideration a child's treatment history, including any ARV-associated toxicities; current virologic, immunologic, and clinical status; and ability to adhere to a new regimen as well as prior and current detection of drug-resistant virus and available treatment options. Given these complexities, all children being evaluated

for treatment failure should be managed in collaboration with a pediatric HIV specialist.

Developmental and behavioral characteristics distinguish adolescents from adults and affect decisions concerning management of treatment failure (see Specific Issues in Antiretroviral Therapy for HIV-Infected Adolescents). Drug metabolism may vary during puberty,[6] necessitating a reassessment of medication dosing throughout adolescence. In some instances, young adults may require larger doses by weight or by surface area than older adults (such as atazanavir; see Appendix A: Pediatric Antiretroviral Drug Information). In addition, dosing recommendations for adolescents have not been established for a number of new ARV medications now used in adults. Dosing guidance for children and adolescents for all ARV agents can be found in Appendix A: Pediatric Antiretroviral Drug Information. The *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents* can provide additional information to help inform management of ARV treatment failure in adolescents.

Definitions of Treatment Failure (see Table 18. Definitions of Treatment Failure in Human Immunodeficiency Virus (HIV)-Infected Children)

Treatment failure can be categorized as virologic failure, immunologic failure, or clinical failure (or some combination of the three). Laboratory results must be confirmed with repeat testing before a final assessment of virologic or immunologic treatment failure is made.

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 HIV RNA below the level of quantification using the most sensitive assay (<20–75 copies/mL). Older assays with lower limits of 200 or 400 copies/mL are acceptable if they are the only option; levels reported as detectable but below the level of quantification should not be considered evidence of virologic failure.

- **Incomplete virologic response to therapy:** Incomplete virologic response to therapy is defined for all children as a <1.0 $\log_{10}$ decrease in HIV RNA copy number from baseline after 8 to 12 weeks of therapy, plasma HIV RNA >200 copies/mL after 6 months of therapy, or repeated plasma HIV RNA greater than the level of quantification using the most sensitive assay after 12 months of therapy. Occasionally, infants with high plasma HIV RNA levels at initiation of therapy have HIV RNA levels that are declining but remain >200 copies/mL after 6 months of therapy. Among many of those receiving lopinavir/ritonavir, suppression can be achieved without regimen change if efforts are made to improve adherence.[7] However, ongoing non-suppression—especially with non-nucleoside reverse transcriptor inhibitor-based regimens—increases risk of drug resistance.[8] HIV-infected adults with detectable HIV RNA and a quantified result <200 copies/mL after 6 months of combination ART (cART) often ultimately achieve virologic suppression without regimen change.[9]
- **Viral rebound:** For children whose plasma HIV RNA level was previously virologically suppressed in response to therapy, viral rebound is defined as subsequent, repeated detection of plasma HIV RNA above the level of quantification. "Blips," defined as isolated episodes of plasma HIV RNA <1,000 copies/mL followed by return to viral suppression, are common and not generally reflective of virologic failure.[10, 11] Repeated or persistent plasma HIV RNA detection above the level of quantification (especially if >1,000 copies/mL) more likely represents viral rebound.[12, 13]

Immunologic Failure: Immunologic failure is defined as an incomplete immunologic response to therapy or an immunologic decline while on therapy. Evaluation of immune response in children is complicated by the normal age-related changes in CD4 T lymphocyte (CD4 cell) count discussed previously (see Immunologic Monitoring in Children). Thus, the normal decline in CD4 values with age needs to be considered when evaluating declines in CD4 parameters. CD4 percentage tends to vary less with age. At about age 5 years, absolute CD4 count values in children approach those of adults; consequently, changes in absolute count can be used in children aged ≥5 years.

- **Incomplete immunologic response to therapy:** Incomplete immunologic response to therapy is defined as the failure of CD4 percentage to increase by ≥5 percentage points in a child aged <5 years with severe immune suppression (CD4 percentage <15%) or as the failure of absolute CD4 cell count to increase by ≥50 cells/mm^3 above baseline within the first year of therapy in a child ≥5 years of age with severe immune suppression (CD4 <200 cells/mm^3).
- **Immunologic decline:** Immunologic decline is defined as a sustained decline to 5 CD4 percentage points below the pre-therapy baseline at any age or a decline in absolute CD4 cell count to below pre-therapy baseline in children aged ≥5 years. Declines that represent a change to a more advanced category of immunosuppression compared with baseline (e.g., from CD4 percentage of 28% to 23% or from CD4 cell count of 250 cells/mm^3 to 150 cells/mm^3) or to more severe immunosuppression in children already suppressed at baseline (e.g., from CD4 percentage of 14% to 9% or from CD4 cell count of 150 cells/mm^3 to 100 cells/mm^3) are of particular concern.

Clinical Failure: Clinical failure is defined as the occurrence of new opportunistic infections (OIs) and/or other clinical evidence of HIV disease progression during therapy. Clinical failure represents the most urgent and concerning type of treatment failure and should prompt an immediate evaluation. Clinical findings should be viewed in the context of virologic and immunologic response to therapy; in patients with stable virologic and immunologic parameters, development of clinical symptoms may not represent treatment failure. Clinical events occurring in the first several months after cART initiation often do not represent cART failure. For example, the development or worsening of an OI in a patient who recently initiated cART may reflect a degree of persistent immune dysfunction in the context of early recovery, or, conversely be a result of immune reconstitution inflammatory syndrome (IRIS). However, the occurrence of significant clinical disease progression, such as noted below, should prompt strong consideration that the current treatment regimen is failing:

- **Progressive neurodevelopmental deterioration.** The presence of two or more of the following findings documented on repeated assessments: Impairment in brain growth (e.g., lack of expected increase in head circumference in infants and young children), decline in cognitive function documented by psychometric testing, or clinical motor dysfunction.
- **Growth failure.** Persistent decline in weight-growth velocity despite adequate nutritional support and without other explanation.
- **Severe or recurrent infection or illness.** Recurrence or persistence of AIDS-defining conditions or other serious infections.

Children who experience treatment failure do not always require an immediate change in therapy; careful assessment is required to evaluate the etiology of the treatment failure and determine an appropriate management strategy (see Assessment of Patients with Antiretroviral Treatment Failure).

Discordance Between Viral, Immune, and Clinical Responses

In general, cART that results in virologic suppression also leads to immune restoration or preservation as well as to prevention of HIV-related illnesses. The converse is also generally true: ineffective cART that fails to suppress viremia is commonly accompanied by immunologic and clinical failure.[14] However, patients may also present with failure in one domain (e.g., immunologic failure) but with a good response in the other domains (e.g., virologic and clinical response). In fact, the discordance in responses to cART can occur in any of these three domains in relation to the other two. It is essential to consider potential alternative causes of discordant responses before concluding that ART failure has truly occurred.

Incomplete Virologic Response Despite Adequate Clinical and Immunologic Responses: Some patients who are maintained on cART may sustain immunologic and clinical benefit for up to 3 years despite

persistent viremia.[15-24] This observation is the rationale for continuing non-suppressive ART for immunologic and clinical benefit in selected patients for whom a completely suppressive regimen is not available or practical. The risks, benefits, and indications for this approach are discussed in Approach to the Management of Antiretroviral Treatment Failure and Choice of Next Antiretroviral Regimen for Treatment Failure with Evidence of Drug Resistance. The proposed mechanisms for immunologic and clinical benefit without complete virologic suppression are maintenance of a lower viral load or selection for strains harboring drug-resistance mutations that impair viral replication or virulence. Another potential explanation for this discordance is that some of these children may have host genetic and/or virologic characteristics that would have allowed them to be either "slow-progressors" or "long-term non-progressors" without therapy.

Poor Immunologic Response Despite Virologic Suppression Regardless of Clinical Response: Poor immunologic response despite virologic suppression can occur in the context of adequate or poor clinical response. 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 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 (such as HIV-1 non-M groups or non-B subtypes, HIV-2), resulting in falsely low or negative viral load results (see Diagnosis of HIV Infection in Infants and Laboratory Monitoring of Pediatric HIV Infection). Once lab results are confirmed, evaluation for adverse drug effects, medical conditions, and other factors that can result in lower CD4 values is necessary.

In addition, it is common for patients with baseline severe immunosuppression to achieve virologic suppression weeks to months before achieving immunologic recovery, resulting in a transient early treatment period of persistent immunosuppression during which additional clinical disease progression can occur. Patients who have very low baseline CD4 values before initiating combination therapy are at higher risk of an impaired CD4 lymphocyte response to cART and, based on adult studies, may be at higher risk of death and AIDS-defining illnesses, despite virologic suppression.[25-29]

Certain ARV agents or combinations may be associated with a blunted CD4 response. For example, treatment with a regimen containing tenofovir and didanosine can blunt the CD4 response, especially if the didanosine dose is not reduced[30] and this combination is not recommended as part of initial therapy. Dosing of didanosine should be adjusted when co-administered with tenofovir. In adults, ARV regimens containing zidovudine may also impair rise in CD4 cell count but not CD4 percentage, perhaps through the myelosuppressive effects of zidovudine.[31] Fortunately, this ARV drug-related suboptimal CD4 cell count response to therapy does not seem to confer an increased risk of clinical events. It is not clear whether this scenario warrants substitution of zidovudine with another drug.

Several drugs (e.g., corticosteroids, chemotherapeutic agents) and other conditions (e.g., hepatitis C, tuberculosis, malnutrition, Sjogren's syndrome, sarcoidosis, syphilis) are independently associated with low CD4 values. Occasional cases of idiopathic CD4 lymphocytopenia have also been reported in HIV-uninfected adults.[32]

Differential Diagnosis of Poor Immunologic Response Despite Virologic Suppression:

Poor Immunologic Response Despite Virologic Suppression and Good Clinical Response

- Lab error (in CD4 lymphocyte or viral load result)
- Normal age-related CD4 lymphocyte decline (i.e., immunologic response not actually poor)
- Low pretreatment CD4 cell count or percentage
- Adverse effects of use of zidovudine or the combination of tenofovir and didanosine
- Use of systemic corticosteroids or chemotherapeutic agents

- Conditions that can cause low CD4 values, such as hepatitis C coinfection, tuberculosis, malnutrition, Sjogren's syndrome, sarcoidosis, and syphilis

Poor Immunologic and Clinical Responses Despite Virologic Suppression

- Lab error, including 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
- Loss of immunologic (CD4) reserve

Poor Clinical Response Despite Adequate Virologic and Immunologic Responses: Clinicians must carefully evaluate patients who experience clinical disease progression despite favorable immunological and virological responses to cART. 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 cART is IRIS, which does not represent cART failure and does not generally require discontinuation of cART.[33, 34] 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.[35] Such cases do not represent cART failure and, in these instances, children would not benefit from a change in ARV regimen. Before reaching a definitive conclusion of cART failure, 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 (such as *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. Although such cases are rare, they may represent cART failure and suggest that improvement in CD4 values may not necessarily represent the return of complete immunologic function.

Differential Diagnosis of Poor Clinical Response Despite Adequate Virologic and Immunologic Responses:

- IRIS
- Previously unrecognized pre-existing infection or condition (tuberculosis, malignancy)
- Malnutrition
- Clinical manifestations of previous organ damage: brain (strokes, vasculopathy), lungs (bronchiectasis)
- New clinical event due to non-HIV illness or condition
- New, otherwise unexplained HIV-related clinical event (treatment failure)

Table 18. Definitions of Treatment Failure in HIV-Infected Children

Virologic Failure[a]	• **Incomplete virologic response to therapy:** Incomplete virologic response to therapy is defined as:
	  • <1.0 $\log_{10}$ decrease in HIV RNA copy number from baseline after 8–12 weeks of therapy, or
	  • HIV RNA >200 copies/mL after 6 months of therapy, or
	  • repeated HIV RNA above the level of quantification using the most sensitive assay after 12 months of therapy.[a]
	• **Viral rebound:** Viral rebound is defined as repeated detection of plasma HIV RNA above the level of quantification after a child had achieved virologic suppression in response to therapy. Isolated episodes of plasma HIV RNA detection above the level of quantification but <1,000 copies/mL are common. They generally do not indicate virologic failure and may be transient blips, but should be followed up to confirm spontaneous resolution.

Immunologic Failure[b]	• **Incomplete immunologic response to therapy:** Failure in a child aged <5 years with severe immune suppression (CD4 percentage <15%) of CD4 percentage to increase by ≥5 percentage points or failure in a child aged ≥5 years with severe immune suppression (CD4 < 200 cells/mm^3) of absolute CD4 cell counts to increase by ≥50 cells/mm^3 above baseline within the first year of therapy. • **Immunologic decline:** Sustained decline of 5 percentage points in CD4 percentage below pre-therapy baseline at any age or decline to below pre-therapy baseline in absolute CD4 cell count in children aged ≥5 years.[c]
Clinical Failure	• **Progressive neurodevelopmental deterioration:** Two or more of the following on repeated assessments: impairment in brain growth, decline in cognitive function documented by psychometric testing, and clinical motor dysfunction. • **Growth failure:** Persistent decline in weight-growth velocity despite adequate nutritional support and without other explanation. • **Severe or recurrent infection or illness:** Recurrence or persistence of AIDS-defining conditions or other serious infections.

[a] Children with higher plasma HIV RNA levels at initiation of therapy, especially infants, may take longer to reach undetectable viral load.[7] HIV-infected adults with HIV RNA detectable above the level of quantification but <200 copies/mL after 6 months of cART often ultimately achieve virologic suppression without regimen change.[9]

[b] At least 2 measurements (taken at least 1 week apart) should be performed to confirm initial laboratory results.

[c] Declines that represent a change to a more advanced category of immunosuppression compared with baseline (such as from CD4 percentage of 28% to 23% or from CD4 cell count of 250 cells/mm^3 to 150 cells/mm^3) or to more severe immunosuppression in those already suppressed at baseline (such as from CD4 percentage of 14% to 9% or from CD4 cell count of 150 cells/mm^3 to 100 cells/mm^3) are of particular concern.

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