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

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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.

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- **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

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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

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- 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)

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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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Assessment of Patients with Virologic Failure of Antiretroviral Treatment (Last updated November 1, 2012; last reviewed November 1, 2012)

Panel's Recommendations
• Assess adherence to therapy; address barriers and develop interventions to improve adherence **(AII)**. • Assess medication intolerance **(AIII)**. • Assess issues related to pharmacokinetics because developmental and individual differences in drug absorption, distribution, metabolism, and elimination can cause inadequate antiretroviral (ARV) drug exposure that can result in combination antiretroviral therapy failure **(AII)**. • Perform ARV drug-resistance testing when virologic failure occurs, while a patient is still taking the failing regimen and before changing to a new regimen **(AI*)**. • Perform assessment 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*

Each patient with an incomplete virologic response to therapy should be assessed to determine the cause of treatment failure because the approach to management and subsequent treatment may differ depending on the etiology of the problem. In most instances, treatment failure is multifactorial. Assessment of a child with suspicion of virologic treatment failure should include evaluation of adherence to therapy, medication intolerance, issues related to pharmacokinetics (PK) that could result in low drug levels or elevated, potentially toxic levels, and evaluation of suspected drug resistance. The main barrier to long-term maintenance of undetectable plasma viral load 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 antiretroviral (ARV) regimen.

Table 19 outlines a comprehensive approach to evaluating causes of virologic treatment failure in children, with particular attention to adherence. An extensive history should focus on the details of drug administration as well as changes in the social and psychological circumstances of the family likely to impact the child's ability to adhere to therapy. In some situations, it may be necessary to directly observe drug-taking behaviors either in the clinic, at home, or in the hospital because history alone may not fully identify the barriers to complete adherence.[1, 2]

Adherence Problems (For more details, see Adherence to Antiretroviral Therapy in HIV-Infected Children and Adolescents and Table 11.)

When treatment failure is observed, clinicians need to assess the likely contribution of adherence problems to the failure of the current regimen. In patients on initial therapy, poor virologic response or widely fluctuating

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viral loads—particularly in the presence of susceptible virus—are commonly an indication of poor adherence. Depending on the specific drug regimen, even small lapses in adherence can lead to cART failure.[3-8] Although adherence should be addressed at each medical visit for all children receiving cART, suspicion of treatment failure warrants increased scrutiny of adherence. Patterns of adherence can change over time and may be influenced by a large number of factors inherent to the drugs as well as social and psychological issues of children and their families.

It is important to evaluate whether adherence problems are related to drug formulation, number of pills, drug dose timing and frequency, food or fasting requirements, or drug side effects in order to determine changes best suited to the individual requirements of a child and his or her family. Family education concerning adherence should be intensive and include training in the administration of prescribed medications with emphasis on the importance of adherence to the drug regimen. Familial or social issues that impede adherence may need to be addressed before adherence can be improved. Issues to be addressed include financial or housing insecurity, concomitant mental health problems, need for substance abuse treatment, and fear of HIV disclosure. In some situations, clinicians may need to involve outside agencies, such as child protective services, to ensure support of a child's treatment. Various interventions should be considered if problems within the household are extreme and unlikely to resolve in favor of successfully supporting a child's treatment. Frequent patient visits and intensive follow-up may be necessary to support new adherence interventions and efforts by the child and the family to improve adherence to the current or new regimen. Directly observed therapy (DOT) may be used to identify additional factors impeding adherence as well as to confirm drug administration; however, durability of adherence improvement is variable after DOT is discontinued.[9]

Pharmacokinetic Factors

Treatment failure can result from inadequate drug exposure as well as poor adherence.[10] Children consistently require higher weight-based dosing of ARV drugs than do adults because of developmental differences in absorption, body composition, and metabolic activity through the pediatric age range.[11] Causes of subtherapeutic drug levels may include failure to increase dosing to accommodate for a child's rapid growth or impaired absorption because of gastrointestinal symptoms such as vomiting or diarrhea. Because drug exposure can be enhanced or reduced by administering medications with food, a clinician should review the food/fasting requirements of a regimen with both patient and caregiver. Drug interactions can alter drug metabolism; therefore, all concomitant medications, including over-the-counter medications and nutritional and herbal supplements, should be reviewed to evaluate whether they may be contributing to poor treatment response (see the *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*). Several studies suggest that genetic polymorphisms may influence PK and therapeutic response for a number of antiretroviral (ARV) medications.[12-14] In some circumstances, therapeutic drug monitoring can be considered for children receiving selected drugs (see Role of Therapeutic Drug Monitoring in Management of Treatment Failure).

Suspected Drug Resistance (See Antiretroviral Drug-Resistance Testing)

ARV drug resistance may develop in children who are taking ARV drugs in the context of inadequate viral suppression. Genotypic resistance testing can help assess adherence to therapy. If testing reveals no resistance-associated mutations to the drugs in the current regimen, it is unlikely that the child is currently taking these medications. The presence of mutations that confer resistance to one or more drugs in the regimen is consistent with patient adherence (partial or full) to the regimen at that time, but failure of the regimen to adequately suppress viral replication because of drug resistance. Because virus variants harboring resistance mutations may decrease in frequency to below the limits of detection of standard resistance assays in the absence of the selective pressure of ARV drugs, ARV resistance testing should be performed while a patient is still taking the failing regimen or within 4 weeks of discontinuing the regimen. Resistance testing can be used to assess reasons for current virologic failure and to identify active ARV medications for future regimens. (See Antiretroviral Drug-Resistance Testing.)

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Table 19. Assessment of Causes of Virologic Antiretroviral Treatment Failure (page 1 of 2)

Cause of Virologic Treatment Failure	Assessment Method	Intervention
Non-Adherence	1. Interview child and caretaker • Take 24-hour or 7-day recall • Obtain description of: • *WHO* gives medications • *WHEN* medications are taken/given • *WHAT* medications are taken/given (names, doses) • *WHERE* medications are kept/administered • Have open-ended discussion of experiences taking/giving medications and barriers/challenges	• Identify or re-engage family members to support/supervise adherence • Establish fixed daily times and routines for medication administration • To avoid any patient/caregiver confusion with drug names, explain that drug therapies have generic names and trade names, and many agents are co-formulated under a third or fourth name. • Explore opportunities for facility or home-based DOT
	2. Review pharmacy records • Assess timeliness of refills	
	3. Observe medication administration • Observe dosing/administration in clinic • Conduct home-based observation by visiting health professional • Admit to hospital for trial of therapy • Observe administration/tolerance • Monitor treatment response	• Simplify medication regimen, if feasible • Substitute new agents if single ARV is poorly tolerated • Consider gastric tube placement to facilitate adherence • Consider DOT • Use tools to simplify administration (e.g., pill boxes, reminders [including alarms], integrated medication packaging for AM or PM dosing) • Suggest relaxation techniques
	4. Conduct psychosocial assessment • Make a comprehensive family-focused assessment of factors likely to impact adherence with particular attention to recent changes: • Status of caregiver, housing, financial stability of household, child/caretaker relationships, school, and child's achievement level • Substance abuse (child, caretaker, family members) • Mental health and behavior • Child/youth and caretaker beliefs about cART • Disclosure status (to child and others)	• Address competing needs through appropriate social services • Address and treat concomitant mental illness and behavioral disorders • Initiate disclosure discussions with family/child • Consider need for child protective services and alternate care settings when necessary

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Table 19. Assessment of Causes of Virologic Antiretroviral Treatment Failure (page 2 of 2)

Cause of Virologic Treatment Failure	Assessment Method	Intervention
Pharmaco-kinetics and Dosing Issues	1. Recalculate doses for individual medications using weight or body surface area. 2. Identify concomitant medications including prescription, over-the-counter, and recreational substances; assess for drug-drug interactions. 3. Consider drug levels for specific ARV drugs (see Role of Therapeutic Drug Monitoring in Management of Treatment Failure).	• Adjust drug doses • Discontinue or substitute competing medications • Reinforce applicable food restrictions
ARV Drug Resistance	1. Perform resistance testing, as appropriate (see Antiretroviral Drug- Resistance Testing).	• If minimal or no resistance detected to current drugs, focus on improving adherence • If resistance to current regimen detected, optimize adherence and evaluate potential for new regimen (see Approach to the Management of Virologic Failure of Antiretroviral Treatment).

Key to Acronyms: ARV = antiretroviral, cART = combination antiretroviral therapy, DOT = directly observed therapy

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Approach to the Management of Virologic Failure of Antiretroviral Treatment (Last updated November 1, 2012; last reviewed November 1, 2012)

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)**. • When deciding how to treat a child with virologic treatment failure, the probability of achieving durable virologic suppression should be considered, as well as the future options for treatment, should durable suppression not be achieved **(AII)**. • Children who experience 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*

General

Note: This section will focus only on the management of virologic treatment failure. For patients with immunologic failure or clinical failure in the setting of virologic suppression, non-HIV-related causes of immunologic or clinical failure should be identified and addressed, though frequently no specific etiology is identified. There is no consensus about the best management of immunologic or clinical failure in the setting of sustained virologic suppression.

Once the potential causes of virologic treatment failure have been identified and addressed, the child should be assessed to determine whether a change in antiretroviral (ARV) drug regimen is necessary and advisable. This will depend on the urgency and likelihood of achieving and sustaining an undetectable plasma viral load. The urgency of implementing a more effective treatment regimen depends on a child's immunologic status, with the greatest urgency in patients with clinical disease progression or clinical failure. The likelihood of achieving and maintaining undetectable plasma viral load depends on the extent of drug resistance, the number and quality of available agents that are active against a child's virus, and the likelihood of adherence to the new regimen. If poor adherence has been a major contributor to virologic treatment failure, and factors contributing to poor adherence have not been adequately addressed, changing the ARV drug regimen may not be advisable because it is not likely to result in virologic suppression and is likely to promote accumulation of additional drug resistance mutations.

Timing of Initiation of a New Regimen: Relative Importance of Virologic Suppression and Immunologic Improvement

Because immunologic improvement typically results from achieving undetectable plasma viral load,[1] the urgency of re-establishing virologic suppression depends on a child's clinical and immunologic status. For example, for older children or adolescents with severe immunosuppression (such as CD4 T lymphocyte [CD4 cell] counts <200 cells/mm^3), a change in therapy may be critical to prevent further immunologic

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decline or clinical disease progression and is strongly recommended. A patient with less immunosuppression is likely at less risk of clinical disease progression in the short term, so an immediate change in therapy is less urgent. However, continued treatment of a child with persistently detectable viremia increases the risk of immunologic decline or clinical disease progression and leads to further accumulation of resistance mutations, possibly further limiting future treatment options.[2, 3] Finally, even in children with advanced clinical and/or immunologic status, initiating a new regimen in the face of persistent adherence difficulties is unlikely to result in virologic suppression, and it is likely to promote accumulation of additional resistance.

Likelihood of Viral Suppression Below the Limit of Detection Using the Most Sensitive Assay

When deciding whether to change a child's ARV drug regimen, a clinician must assess the likelihood that the new regimen will achieve significantly better virologic control than the current regimen. Although complete virologic suppression should be the goal, this may not always be achievable in HIV-infected children and adolescents. Clinical benefit may be observed with decrements in HIV RNA levels that do not result in undetectable levels.[1] However, failure to maximally suppress plasma viral load is associated with an increased probability of acquiring mutations associated with resistance.[4] It is important that the clinician alert the patient to potential toxicities and discuss strategies to minimize their impact. The likelihood of adherence to a new regimen plays a significant role in determining whether to change an ARV regimen; if a child is unlikely to adhere to a new regimen, resistance will develop and sustainable virologic suppression will not be achieved. Although studies differ on the exact predictors of adherence, several contributing factors have been noted. These include medication characteristics,[5] psychosocial stressors,[6, 7] health beliefs,[8] and prior adherence to medication (see Adherence to Antiretroviral Therapy in HIV-Infected Children and Adolescents for more detail). Importantly, adherence to combination antiretroviral therapy (cART) may change rapidly and unexpectedly with a change in family circumstances or as a child moves through progressive developmental stages. Thus, a clinician may choose to target a new ARV regimen to start at a time when a child and his or her family are most likely to adhere to the new regimen for a sustained period.

Categories of Children with Treatment Failure and Approaches to Consider

No Viral Drug Resistance Identified

Persistent viremia in the absence of detectable viral resistance to current medications suggests that the virus is not being exposed to the ARV agents. This lack of ARV drug exposure 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 undetectable plasma levels. Resistance testing should take place while a child is on therapy. After discontinuation of therapy, predominant plasma viral strains may quickly revert to wild-type and re-emerge as the predominant viral population, in which case resistance testing may fail to reveal drug-resistant virus (see Antiretroviral Drug-Resistance Testing). Thus, if a child on cART develops resistant virus and then stops therapy, sensitive virus will dominate in the absence of therapy. In this situation, resuming the prior therapy would fail to suppress the virus because the resistant virus would again emerge. 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 plasma virus is undetectable with the most sensitive assays, the virus is likely to be susceptible to the current therapy.

Viral Resistance to Current Antiretroviral Therapy

The recommendation in this situation is to start a new cART regimen in order to fully suppress and sustain plasma viral load below the limits of detection and prevent emergence of virus with additional resistance mutations. This requires a regimen that includes at least two, and preferably three, fully active agents. The choice of new agents should be based on current and past resistance testing (see Antiretroviral Drug-

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Resistance Testing), ART history, availability of new drugs and classes of agents, and consideration of potential toxicities. Some ARV drugs (such as nucleoside reverse transcriptase inhibitors [NRTIs]) may contribute partial ARV activity to an ARV regimen, despite drug resistance. Because of the potential for cross resistance of some drugs within a single class, substituting a new drug from the same previously used class does not ensure that the replacement drug will be fully active. This is particularly true for the non-nucleoside reverse transcriptase inhibitors (NNRTIs) nevirapine and efavirenz, for which cross-resistance with drug mutations is uniformly seen.

The availability of an increasing number of ARV drugs, including some with new viral targets, makes complete virologic suppression achievable for many patients with treatment failure. Unfortunately, the lack of pediatric formulations and dosing information for some of these agents limits the number of options available for younger children. Thus, it remains difficult to identify a new, active regimen for many children with extensive prior therapy (see The Use of Antiretroviral Agents Not Approved for Use in Children).

If difficulties contributing to poor adherence with the current regimen are likely to continue, emphasis and effort should be placed on improving adherence before initiating a new regimen (see next section).

Extensive Viral Drug Resistance Such That Two Fully Active Agents Cannot be Identified or Administered

In children for whom undetectable plasma virus is not achievable because two or more fully active agents cannot be identified, the goal is to preserve immunologic function and prevent clinical disease progression while preserving future options for new agents that are not yet available. Adult cohort studies suggest that maintaining HIV viral load at <10,000 to 20,000 copies/mL may offer ongoing immunologic and clinical benefit;[9, 10] pediatric studies suggest that children receiving cART with viral load <1,000 to 5,000 copies/mL may not achieve significantly better clinical and immunologic outcomes by changing therapy.[3, 4, 11] Several cohort studies show a clinical benefit of remaining on cART, regardless of whether it leads to a decrease in viral load. The principal risk associated with continuing a failing regimen when no suppressive regimen is available is the development of additional resistance mutations that can limit future treatment options. This risk is especially true for NNRTI-containing regimens but also occurs with prolonged use of non-suppressive protease inhibitor-containing regimens.[2, 4, 12]

The goal of continued treatment with an incompletely suppressive regimen is to select for resistant virus with reduced viral fitness that will cause slower disease progression while minimizing risk of drug toxicity and development of new resistance mutations to multiple classes of drugs. Simplified (often all-NRTI) "holding regimens" are sometimes used in place of continuing a failing cART regimen (see Choice of Therapy When Two Agents Cannot be Identified). The overall goal of these alternative strategies is to prevent clinical and immunological progression until additional active drugs are available that can be used to design a regimen that is expected to achieve undetectable plasma viral load.[1, 13-21] This approach should be regarded as acceptable but not ideal; these patients should be followed more closely than those with stable virologic status and the potential for successful initiation of a fully suppressive ARV drug regimen should be reassessed at every opportunity. Interrupting therapy completely will avoid new drug resistance, but potentially at higher risk of immunologic or clinical progression (see Treatment Interruption).

When managing disease progression in patients with advanced disease and extensive resistance, quality of life must be considered. The relative benefits (e.g., reduced viral fitness, continued clinical benefit despite resistance) and burdens of continuing a failing ARV drug regimen should be discussed. Decisions to continue, discontinue, or simplify cART should be made collaboratively with patients, families, and clinicians and should be consistent with the patients' or families' stated values and goals for care.

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Children with Ongoing Adherence Problems as a Major Reason for Virologic Treatment Failure

If 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). Adherence in infants and younger children depends completely on their caregivers. When other intensive measures to address adherence problems have failed and caretakers appear unable or unwilling to administer medications, child protective services may need to be requested to assess the need for additional support for current caretakers or for a change in caretaker. When efforts to improve adherence will require several weeks or months, some clinicians may choose to continue the current non-suppressive regimen or use a simplified, NRTI-only, non-suppressive regimen that may provide some clinical and immunologic benefit while preserving future ARV drug choices (see Choice of Therapy with Extensive Drug Resistance Such That Two Fully Active Agents Cannot Be Identified or Administered).[13, 22, 23] Treatment with non-suppressive regimens in such situations should be regarded as an acceptable but not ideal interim strategy to prevent immunologic and clinical deterioration while working on adherence. Such patients should be followed more closely than those with stable virologic status, and the potential to successfully initiate a fully suppressive ARV drug regimen should be reassessed at every opportunity.

Complete treatment interruption for a persistently nonadherent patient should prevent accumulation of additional drug resistance but has been associated with immunologic declines and poor clinical outcomes.[24] However, the strategy of complete treatment interruption has not been fully evaluated in children. Although complete treatment interruption is not recommended for cases of ongoing poor adherence, it is recognized that some patients may decide on their own to stop all medications. Although careful monitoring and open communication between provider and patient are always important, they are especially critical in these situations (see Treatment Interruption).

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Choice of Next Antiretroviral Regimen for Virologic Treatment Failure with Evidence of Drug Resistance (Last updated November 1, 2012; last reviewed November 1, 2012)

Panel's Recommendations

- Antiretroviral (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 two, but preferably three, fully active ARV medications with assessment of anticipated ARV activity based on past treatment history and resistance test results **(AII*)**.
- Interpretation of resistance test results showing complex combinations of mutations and assessment of future treatment options should be made in collaboration with a pediatric HIV specialist **(AI*)**.
- Use of novel agents with limited available pharmacokinetic and/or safety data in pediatric populations should be undertaken only 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 and adolescents but not studies limited to postpubertal adolescents

General

After reaching a decision that a change in therapy is needed, a clinician should attempt to identify at least two, but preferably three, fully active antiretroviral (ARV) agents from at least two different classes on the basis of resistance test results, prior ARV exposure, acceptability to the patient, and likelihood of adherence.[1-5] 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 should not be done 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. In children who are changing therapy owing to the occurrence or progression of abnormal neurodevelopment, the new treatment regimen should include agents (such as zidovudine) that are known to achieve higher concentrations in the central nervous system.[6-10]

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.[11]

Choice of Therapy with Viral Resistance to Current Therapy: Goal of Complete Virologic Suppression

Determination of a new regimen with the best chance for complete virologic suppression in children who

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have already experienced treatment failure should be made 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 20, 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 received initial therapy with a non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimen, a change to a protease inhibitor (PI)-based regimen is recommended. Resistance to the NNRTI nevirapine results in cross-resistance to the NNRTI efavirenz, and vice versa. However, the newer NNRTI etravirine retains activity against nevirapine- or efavirenz-resistant virus (see below). If a child received initial therapy with a PI-based regimen, a change to an NNRTI-based regimen is generally recommended. Lopinavir/ritonavir-based regimens have also been shown to have durable ARV activity in some PI-experienced children.[12-14] Choice of the new dual-nucleoside reverse transcriptase inhibitor (NRTI) component is particularly important when constructing a regimen because the choice of an insufficiently potent NRTI may result in selection of additional NRTI-related drug-resistance mutations. Resistance testing is essential to properly select a potent NRTI combination, and interpretation of these results should take place in collaboration with an expert in pediatric HIV infection (see Antiretroviral Drug-Resistance Testing).

The availability of new drugs in existing classes (e.g., the NNRTI etravirine) and new classes of drugs (e.g., integrase inhibitors) increases the likelihood of finding three active drugs, even for children with extensive drug resistance (Table 20). In studies of adults, etravirine retains activity against nevirapine- or efavirenz-resistant viruses when used in a regimen that also contains darunavir/ritonavir and if the number of NNRTI resistance-associated mutations is limited.[15, 16] Etravirine in combination with ritonavir-boosted darunavir, as part of a new combination antiretroviral therapy (cART) regimen, has been shown to be a safe and effective option for children in whom cART fails.[17, 18] Etravirine is approved for use in children aged ≥6 years;[17, 19] studies in younger children are under way. Studies of treatment-experienced adult and adolescent patients have shown that using one or more new class(es) of drug (e.g., integrase inhibitors, entry inhibitors), often coupled with a ritonavir-boosted PI (e.g., darunavir) in PI-experienced patients with multidrug-resistant virus, is associated with good virologic responses.[20-23] Raltegravir, in combination with optimized background therapy, was safe and effective in treatment-experienced children aged 2 to 16 years,[24] for whom it is Food and Drug Administration (FDA)-approved. Use of newer agents in novel combinations is becoming more common in aging perinatally infected youth in the United States.[25] 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, including new drugs in existing classes such as darunavir and agents in new classes of drugs such as CCR5 antagonists (e.g., maraviroc, approved for use in adolescents aged ≥16 years) and integrase inhibitors (e.g., raltegravir, approved for use in children aged ≥2 years [FDA, December 21, 2011]).

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 (such as by switching from a liquid to pill formulation or to a new formulation [such as 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.[26-28] The use of new drugs that have been evaluated in adults but have not been fully evaluated in children may be justified and ideally is done in the framework of a clinical trial (see The Use of Antiretroviral Agents Not Approved for Use in Children). Expanded access programs or clinical trials may be available. New drugs should be used in combination with at least one, and ideally two, additional active agents.

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The HIV entry inhibitor enfuvirtide is approved for use in heavily treatment-experienced patients based on potent ARV activity in heavily treatment-experienced adults; it has been approved for use in children aged ≥6 years.[29, 30] Studies have helped establish safety, appropriate dosing, and efficacy of enfuvirtide in treatment-experienced children aged ≥6 years.[31, 32] Enfuvirtide must be administered by subcutaneous injection twice daily, a disadvantage that presents a greater challenge to adherence in adolescents than in younger children. Enfuvirtide can be considered an option when designing a new regimen for children in whom multiple classes of ARV medications have failed, but newer and better tolerated agents have largely supplanted use of enfuvirtide.

Pharmacokinetic (PK) studies of certain dual-boosted PI regimens (lopinavir/ritonavir with saquinavir and lopinavir/ritonavir with atazanavir/ritonavir) suggest that PK targets for both PIs can be achieved or exceeded when used in combination in adults[33-35] and in children.[36-38] PK studies of other dual-boosted PI combinations are limited but suggest inadequate drug levels of one or both PIs.[39, 40] A study in Thailand of 50 PI-naive but NRTI +/- NNRTI-experienced children treated with a combination of lopinavir/ritonavir (230/57.5 mg/m^2 twice daily) and saquinavir (50 mg/kg twice daily, maximum dose 1000 mg) demonstrated trough levels of both PIs at or above therapeutic targets and complete viral suppression at 48 weeks in ≥50% of patients. The use of multidrug regimens, sometimes including up to 3 PIs and/or 2 NNRTIs, has shown efficacy in a pediatric case series;[41] however, multidrug regimens should be used cautiously because of their complexity, poor tolerability, and unfavorable drug-drug interactions. Therapeutic drug monitoring may be helpful for confirming therapeutic PI levels when using PIs in combinations that result in complex drug interactions or when there is partially reduced PI activity because of the presence of drug-resistance mutations (see Role of Therapeutic Drug Monitoring in Management of Treatment Failure). Availability of newer potent PIs and new classes of ARV drugs (integrase and CCR5 inhibitors) may lessen the need for dual-PI regimens.

When searching for at least two 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 (see The Use of Antiretroviral Agents Not Approved for Use in Children). 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.

Therapeutic 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 extensive drug-resistant virus in a patient or because a patient is unable to adhere to or tolerate cART.

In such cases, non-suppressive regimens (or holding regimens) are sometimes used pending availability of additional active, tolerable drugs or improvement in ability to adhere. This interim strategy allows for the overall objective of preventing clinical and immunological deterioration until new agents are available to design a regimen that can be expected to achieve undetectable plasma viral load. This approach should be regarded as acceptable but not ideal. Such patients should be followed more closely than those with stable virologic status, and the potential to successfully initiate a fully suppressive cART regimen should be reassessed at every opportunity.

Even when NRTI drug-resistance mutations are present, patients can derive immunologic and clinical benefit despite persistent viremia from treatment with lamivudine monotherapy or with lamivudine or emtricitabine in combination with one or more other NRTIs, such as zidovudine, stavudine, abacavir, or tenofovir.[42, 43]

The newer NNRTI etravirine retains activity against many nevirapine- or efavirenz-resistant viruses with a limited number of NNRTI resistance-associated mutations. Ongoing use of efavirenz or nevirapine as part of a failing regimen should be avoided because it may lead to accumulation of additional NNRTI resistance

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mutations that will reduce etravirine activity and preclude its use in a future, suppressive regimen,[44] and it may allow for accumulation of additional NRTI resistance.[45]

Continued use of a PI in the face of persistent viremia can lead to accumulation of additional mutations conferring resistance to that PI as well as other, newer PIs. Such acquisition of additional PI drug resistance occurs slowly, especially if the viral load is relatively low.[46-49] However, continued PI use in the presence of resistance may limit viral replication and be beneficial to some patients.

When clinical or immunologic deterioration occurs while patients are receiving such holding regimens, it is important to re-assess patient readiness and regimen availability. It may be appropriate to use investigational agents or agents approved for older age groups as second fully active drugs in the new regimen (see The Use of Antiretroviral Agents Not Approved for Use in Children). In general, a single, new, fully active agent should not be added to non-suppressive holding regimens because resistance is likely to develop quickly.

Table 20. 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	Recommended Change (in order of relative preference)[a]
2 NRTIs + NNRTI	• 2 NRTIs + PI • 2 NRTI + integrase inhibitor[b]
2 NRTIs + PI	• 2 NRTIs + NNRTI • 2 NRTIs + alternative RTV-boosted PI • 2 NRTIs + integrase inhibitor[b] • NRTI(s) + integrase inhibitor + (NNRTI *or* alternative RTV-boosted PI)
3 NRTIs	• 2 NRTIs + (NNRTI or PI) • 2 NRTIs + integrase inhibitor[b] • Integrase inhibitor[b] + 2 other active agents (chosen from NNRTI, PI, NRTI[s])
Failed regimen(s) that included NRTI(s), NNRTI(s), and PI(s)	• > 1 NRTI + RTV-boosted PI • NRTI(s) + RTV-boosted PI + integrase inhibitor[b] (consider adding T-20 and/or MVC,[c] if additional active drug[s] needed) • NRTI(s) + RTV-boosted DRV, LPV or SQV + ETR (consider adding one or more of MVC,[c] T-20, or integrase inhibitor,[b] if additional active drug[s] needed) • > 1 NRTI + 2 RTV-boosted PIs (LPV/r + SQV, LPV/r + ATV) (consider adding T-20 or an integrase inhibitor[b] 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 two, but preferably three, fully active drugs for durable, potent virologic suppression. *Please see individual drug profiles for information about 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 listed in relative order of preference and are provided as examples but the list is not exhaustive.

[b] Caution advised when using raltegravir in children aged ≤6 years because pharmacokinetic and efficacy data are particularly limited in this age group.

[c] No current FDA-approved pediatric indication for maraviroc.

Key to Acronyms: ATV = atazanavir, DRV = darunavir, ETR = etravirine, LPV = lopinavir, LPV/r = lopinavir/ritonavir, MVC = maraviroc, NNRTI = non-nucleoside reverse transcriptase inhibitor, NRTI = nucleoside reverse transcriptase inhibitor, PI = protease inhibitor, RTV = ritonavir, SQV = saquinavir, T-20 = enfuvirtide

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The Use of Antiretroviral Agents Not Approved for Use In Children (Last updated November 1, 2012; last reviewed November 1, 2012)

Panel's Recommendations

- Children may need to use antiretroviral (ARV) drugs that are not yet approved for their age because many of the recently approved, more convenient, and potent agents are approved for use in adults before pharmacokinetic (PK), safety, and efficacy data are available in children **(AII)**.
- Dosing in a child of ARVs only approved for adults cannot simply be inferred from a simple calculation using the adult dose and the child's weight **(AII)**. Such use of ARVs should always be done in collaboration with a pediatric HIV specialist, who may have access to unpublished data about safety and PKs of ARVs that are not yet Food and Drug Administration (FDA)-approved for children **(AI*)**.
- Whenever possible, use of ARVs that are not yet FDA-approved for children should be done in the context of clinical trials that can generate the data needed for pediatric approval **(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 and adolescents but not studies limited to postpubertal adolescents

It has long been the practice of physicians, especially pediatricians, to prescribe medications in off-label situations, meaning for indications or populations that do not fall within the official, Food and Drug Administration (FDA)-approved indication.[1] The relatively small market for pediatric antiretroviral (ARV) drugs and few children available to participate in clinical trials have delayed or prevented studies to obtain an FDA pediatric label indication for some ARV drugs at the same time their use in adults is approved. Pediatric HIV specialists may need to prescribe these agents because drugs currently available for pediatric use afford few options for heavily treated children and adolescents with high levels of resistance and because the newer agents offer improvements in tolerability and ease of adherence with less frequent dosing.

One distinct advantage of some of the newer medications is improved tolerability. Examples include a reduction in frequency or severity of side effects with newer protease inhibitors (PIs) and the ability to create simpler regimens using fixed-dose combination tablets or once-daily preparations. The incentive to use these drugs to avoid toxicities and simplify regimens is that these regimens will lead to improved adherence, and thus, better long-term outcomes.

Another major factor leading to off-label use of ARVs has been the development of new drugs belonging to novel classes of agents effective against resistant virus. In the United States, many older perinatally infected children have extensive drug resistance resulting from treatment with multiple non-suppressive regimens. Cross resistance between fully approved ARVs within a class makes it difficult to find a combination of agents likely to fully suppress the virus. In an effort to create a regimen likely to achieve complete virologic suppression in an individual patient, providers must identify at least two and preferably three drugs with demonstrated activity against the patient's virus. Success is almost impossible in heavily treatment-experienced children using only drugs with approved pediatric label indications; thus providers may use

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drugs not yet approved for children in order to provide optimal virologic response.

The use of agents not yet approved for pediatric use causes some difficulties. One of the major issues is lack of data on appropriate dosing in children. Agents are approved for adult use before being approved for pediatric use because safety and pharmacokinetic (PK) studies in children have not yet been completed. Sometimes studies in children are ongoing and some data are available, but other times, pediatric studies have not yet begun. It is essential for providers prescribing agents for off-label use to consult with pediatric HIV experts to avail themselves of the latest information from ongoing studies.

The possibility of age-related side effects is another concern when initiating off-label ARV use. To date, no ARV has been found to have adverse effects that preclude use uniquely in children, but until an agent has been tested in children, it cannot be considered to be free of such an effect. In addition, adverse effects noted in adults may be of more substantial concern in a growing and developing child.

Difficulties in pediatric dosing for off-label use of ARV drugs are even more problematic than the potential for adverse effects. As absorption, hepatic metabolism, and excretion change with age, so will drug levels change in children.[2] The difficulty in dosing children as they increase in weight is exacerbated by changing PKs. 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.[3]

In summary, use of ARV agents without a pediatric indication is an absolute necessity for treatment of some HIV-infected children, but such off-label use must be done with care. **It is essential that a provider consult with a pediatric HIV specialist to identify any particular concerns with each agent, to access any available data from clinical trials or other limited off-label pediatric use, and to investigate the availability of suitable clinical trials.**

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Role of Therapeutic Drug Monitoring in Management of Treatment Failure (Last updated August 11, 2011; last reviewed November 1, 2012)

Therapeutic drug monitoring (TDM) is use of plasma drug concentration measurements as part of a strategy to optimize drug dosing to minimize toxicity and maximize treatment benefit. TDM can be considered for use in combination antiretroviral therapy because:[1, 2]

- Interpatient variability in antiretroviral (ARV) exposure (i.e., plasma drug concentrations) using standard recommended doses is high;
- Low drug exposure can lead to suboptimal virologic response to therapy; and
- High plasma concentrations can be associated with increased risk of drug toxicity.

Developmental pharmacokinetic differences contribute to greater variability and a greater frequency of suboptimal ARV exposure in pediatric patients than in adults.[3] Pediatric dosing is designed to mimic adult exposure and rarely reflects the maximum tolerated ARV drug dose. Even when using dose recommendations from published pediatric guidelines, children often receive inadequate ARV doses.[4]

There are two main situations in which TDM may be useful in a child who is failing therapy. First, TDM can be used to rule out subtherapeutic drug levels as a cause of failure. Such inadequate drug levels could result from malabsorption, drug interactions, poor adherence, or increased drug metabolism or clearance. Second, drug levels can be used to optimize drug dosage when changing to a new regimen in a patient whose virus has reduced susceptibility to that drug.

For TDM to be useful, the relationship between ARV drug concentrations and anti-HIV effects must be clearly defined.[5-7] This association is strongest with protease inhibitors (PI) and non-nucleoside reverse transcriptase inhibitors (NNRTIs),[8] but maintaining adequate nucleoside reverse transcriptase inhibitor (NRTI) serum concentrations also has been shown to be important for maximal anti-HIV activity.[9] The exposure-toxicity response relationship is less well defined for NRTI drugs but has been determined for some agents.[7] Concentration-response relationships have been established with minimum plasma concentrations (C_{min} or C_{trough}) or area under the curve (AUC), but the optimal measure is not defined for all ARV drugs.[10]

Table 21 presents recommendations for the minimum target trough concentrations of PIs and NNRTIs in patients without evidence of resistance to those drugs. In ARV-experienced patients, the choice of minimum target trough concentration should be based on results of resistance testing.[11-13] Although it is intrinsically difficult to demonstrate benefit of TDM using double-blind studies, limited data suggest targeted concentrations can be achieved with TDM, clinical responses can be improved with increased or modified doses, and TDM information can be helpful in decision making.[8, 14-18] Clinicians should consult with a pediatric HIV specialist or pharmacologist in making these decisions.

TDM is not recommended for routine use but may be considered potentially useful for patients:

- In whom clinical response is different from that expected;
- Who are treatment experienced and infected with virus with reduced drug susceptibility, where a comparison of the drug susceptibility of the virus and the achieved drug concentrations may be useful;
- Who may experience potential difficulties with drug administration related to suboptimal dietary intake or malabsorption, incorrect dosing or caregiver measuring errors, or concerns surrounding adherence; and
- Who experience drug or food interactions, including interactions resulting from alteration of drug formulations by crushing medications or mixing them with various foods and liquids.

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Current limitations for pediatric ARV TDM include:

- Prolonged time for laboratory processing in the face of potentially diminishing benefit the longer a patient is on inadequate therapy;
- Difficulties in coordinating sample collections at appropriate times, which make determination of true C_{min} or AUC difficult;
- High intrapatient variability from single drug concentration measurements may complicate interpretation of results;[19, 20]
- Single trough measurements within the target range, which do not guarantee consistent adequacy of drug exposure or therapeutic success;
- Inadequate information on safety and effectiveness of dose adjustment strategies in children and adolescents;
- Limited availability of certified laboratories capable of assaying drug concentrations; and
- Lack of third-party reimbursement of costs associated with TDM.

Table 21. Suggested Minimum Target Trough Concentrations[a]

Drug	Concentration (ng/mL)
Atazanavir	150
Fosamprenavir	400 (measured as amprenavir concentration)
Indinavir	100
Lopinavir	1,000
Nelfinavir (measurable active [M8] metabolite)	800
Saquinavir	100–250
Efavirenz	1,000
Nevirapine	3,000
Recommendations applicable only to treatment-experienced persons who have resistant HIV-1 strains	
Maraviroc	>50
Tipranavir	20,500

[a] Reprinted from: *Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents*. Department of Health and Human Services. http://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf.

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Discontinuation or Interruption of Therapy (Last updated November 1, 2012; last reviewed November 1, 2012)

General

Discontinuation of combination antiretroviral therapy (cART) may be indicated in some situations, including serious treatment-related toxicity, acute illnesses or planned surgeries that preclude oral intake, lack of available medication, or patient or parent request. Observational studies of children and youth with unplanned or non-prescribed treatment interruptions suggest that interruptions are common, most patients will experience immunologic decline during the treatment interruption, and most restart therapy.[1-3] Although events precipitating ART interruptions are usually unplanned, planned discontinuation of therapy was considered as a potential strategy to reduce toxicity, costs, and drug-related failure associated with ART. While one trial of children randomized to structured treatment interruptions (STI) with CD4-guided resumption of cART reported no serious clinical outcomes,[4] adult trials have demonstrated significantly higher morbidity and mortality in adults randomized to STI compared with continuous cART.[5] Long-term STI as a drug-sparing strategy or to give patients "drug holidays" is not recommended for children or adults outside of a clinical trial. The discussion below provides more detailed guidance for interruption of cART and the risks and benefits in specific situations.

Short-Term Therapy Interruption

In children, short-term therapy interruptions are most often necessitated by acute illnesses that limit oral intake. These illnesses are often infectious diseases that result in vomiting and/or diarrhea. A clinician has no choice but to stop all therapy at the same time. Planned short-term interruption of therapy may also be required in the event of surgery or sedation for procedures; however, when possible, patients should be allowed to continue regular cART with minimal fluid intake. For a prolonged period of restricted oral intake, all drugs in an ARV regimen should be stopped at the same time if the medications have similar half-lives. In the case of serious or life-threatening ARV drug toxicity, all drugs should be stopped immediately.

Efavirenz and nevirapine have very long half-lives and can be detected for 21 days or longer after discontinuation.[6-9] As the other drugs with shorter half-lives are cleared, only nevirapine or efavirenz may persist, resulting in functional monotherapy, which can increase risk of selection of non-nucleoside reverse transcriptase inhibitors (NNRTI)-resistant mutations. Certain genetic polymorphisms that are more common in certain racial and ethnic groups (i.e., African Americans, Hispanics) may result in a slower rate of drug clearance.[8, 9] To prevent this functional monotherapy, some experts recommend stopping the NNRTI first and continuing the other ARV drugs (NRTI backbone or protease inhibitor [PI]) for a period of time.[7] An alternative is to substitute a PI for the NNRTI up to 4 weeks before interrupting all drugs; however, there are no data to support this practice. Studies are ongoing in adults to help determine an effective strategy, but information in children is unavailable and, because the PKs of these agents are different in children, the recommendations for adults may not be applicable.[10-12]

An additional consideration is reintroduction of nevirapine. Currently, a 2-week, half-dose escalation is recommended in patients who are started on nevirapine. Dose escalation is used because nevirapine induces its own metabolism by inducing CYP3A4 metabolic liver enzymes; thus, initial administration of the full therapeutic dose will result in elevated drug levels until metabolic enzyme induction has occurred. Lower rates of rash toxicity have been observed with the 2-week dose escalation.[10] In cases where nevirapine has been discontinued for more than 2 weeks, another 2-week dose escalation is recommended when the drug is reintroduced.

Long-Term Structured Treatment Interruptions

Strategies for STI for long periods of time traditionally have been proposed with the aim of reducing toxicities and costs associated with long-term cART.

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In adults, two large, randomized clinical trials have demonstrated increased morbidity when CD4 T lymphocyte (CD4 cell) count was used as an indication to stop and start therapy. The Strategies for Management of Antiretroviral Therapy (SMART) trial stopped cART when the CD4 cell count was >350 cells/mm^3 and reintroduced therapy when the count was <250 cells/mm^3. Compared with the group receiving continuous cART, the STI group had an increased risk of disease progression and death.[5] Interruption of cART was also associated with elevations in biomarkers of inflammation that were predictive of morbidity and mortality independent of CD4 cell count.[13] Similarly, in the TRIVICAN trials, which used the same CD4 cell count triggers to stop and restart therapy, STI was shown to be inferior.[14] Studies in adults using a CD4 cell count <350 cells/mm^3 as a trigger to restart therapy did not report significant differences in serious disease progression or death.[15, 16] However, another large cohort study in Italy showed an increased risk of disease progression after interruption of first-line therapy.[17] In light of these data, the current Department of Health and Human Services guidelines for adults recommend against planned long-term STI in adults (see *Adult and Adolescent Treatment Guidelines*).

In children, there have been fewer studies of long-term STI. In one study, children with controlled viral load (HIV RNA <400 copies/mL for >12 months) were subjected to increasing intervals of treatment interruption. Of 14 children studied, 4 maintained undetectable viral loads with interruptions of up to 27 days. It has been hypothesized that enhanced HIV-specific immune responses may play a role in the viral suppression.[18] However, new drug-resistance mutations were detected in 3 of 14 children in the STI study. In the European (PENTA) trial, 109 children with virologic suppression on cART were randomized to continuous therapy (CT) versus treatment interruption with CD4-guided re-initiation of cART. On average, CD4 values decreased sharply in the first 10 weeks after STI. However, most children in the STI arm (almost 60%) did not reach CD4 criteria to restart therapy over 48 weeks. Children in the STI arm spent significantly less time on cART than children in the CT arm.[4] None of the children in the trial experienced serious clinical illnesses or events, and the appearance of new drug-resistance mutations did not differ between the two arms.[4]

In some populations of children, STI has been more specifically considered. In the United States and other developed countries, most HIV-infected children begin cART during infancy.[19, 20] Many of them have had controlled viral replication for many years and are growing and developing normally. One trial was designed to answer whether infants who initiated cART early could safely discontinue therapy at some point and reinitiate treatment based on CD4 cell decline. The CHER study in South Africa assessed outcomes in infants randomized to deferred cART (initiation driven by CDC stage and CD4 status), immediate cART with interruption after 40 weeks, or immediate cART with interruption after 96 weeks.[21, 22] While the two arms of interrupted therapy led to better outcomes compared to the deferred arms, up to 80% of infants had to restart therapy by the end of follow-up. The long-term outcomes in children after this interruption remain unknown and it is unclear if the short period of time on cART saved by most children merits the potential risks associated with cessation. Another scenario often raised involves patients who have limited treatment options and who cannot achieve an undetectable viral load despite aggressive cART. In such cases, continuation of non-suppressive therapy is recommended because, despite detectable viral replication, immunologic benefit has been well documented.[23-26]

Given the increased availability of medications with less toxicity, the potential benefits of long-term STI may be decreasing. Current data do not support use of long-term STI in clinical care of HIV-infected children.

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