Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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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

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-

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.

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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