Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Management of Medication Toxicity or Intolerance  
(Last updated May 22, 2018; last reviewed May 22, 2018)

<table>
<thead>
<tr>
<th>Panel’s Recommendations</th>
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<tbody>
<tr>
<td>• In children who have severe or life-threatening toxicity (e.g., a hypersensitivity reaction), all antiretroviral (ARV) drugs should be stopped immediately (AII). Once symptoms of toxicity have resolved, antiretroviral therapy should be resumed with substitution of a different ARV drug or drugs for the offending agent(s) (AII*).</td>
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<tr>
<td>• When modifying therapy because of toxicity or intolerance to a specific drug in children with virologic suppression, changing one drug in a multidrug regimen is permissible; if possible, an agent with a different toxicity and side-effect profile should be chosen (AI*).</td>
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<td>• The toxicity and the medication presumed responsible should be documented in the medical record and the caregiver and patient should be advised of the drug-related toxicity (AIII).</td>
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<td>• In general, dose reduction is not a recommended option for management of ARV toxicity (AII*).</td>
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</tbody>
</table>

**Rating of Recommendations:** A = Strong; B = Moderate; C = Optional

**Rating of Evidence:** I = One or more randomized trials in children with clinical outcomes and/or validated endpoints; I* = One or more randomized trials in adults with clinical outcomes and/or validated laboratory endpoints with accompanying data in children from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies in children with long-term outcomes; II* = One or more well-designed, nonrandomized trials or observational studies in adults with long-term clinical outcomes with accompanying data in children from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion

† Studies that include children or children/adolescents but not studies limited to post-pubertal adolescents

**Medication Toxicity or Intolerance**

The overall benefits of viral suppression and improved immune function as a result of effective antiretroviral therapy (ART) far outweigh the risks associated with the adverse effects (AEs) of some antiretroviral (ARV) drugs. However, AEs have been reported with the use of all ARV drugs and—in the mid-1990s when combination ART was introduced—were among the most common reasons for switching or discontinuing therapy and for medication nonadherence (see the Adult and Adolescent Guidelines).1

Fortunately, currently recommended ARV regimens are associated with fewer serious and intolerable AEs than regimens used in the past. Generally, <10% of ART-naive patients enrolled in randomized trials have treatment-limiting AEs.2-11 Some longer-term complications of ART (e.g., bone or renal toxicity, dyslipidemia, accelerated cardiovascular disease) may be underestimated because most clinical trials enroll a select group of patients based on highly specific inclusion criteria and the duration of participant follow-up is relatively short. To achieve sustained viral suppression over a child’s lifetime, both short-term and long-term ART toxicities must be anticipated. The clinician must consider potential AEs and issues with medication palatability when selecting an ARV regimen, as well as the individual child’s comorbidities, concomitant medications, and prior history of drug intolerance or viral resistance.

ARV drug-related AEs can vary from mild, more common symptoms (e.g., gastrointestinal intolerance, fatigue) to infrequent, but severe and life-threatening, illness. Drug-related toxicity can be acute (occurring soon after a drug has been administered), subacute (occurring within 1 to 2 days of administration), or late (occurring after prolonged drug administration). For a few ARV medications, pharmacogenetic markers associated with risk of early toxicity have been identified, but the only such screen in routine clinical use is HLA-B*5701 as a marker for abacavir hypersensitivity.12-14 For selected children aged <3 years who require treatment with efavirenz, an additional pharmacogenetic marker, CYP2B6 genotype, should be assessed in an attempt to prevent toxicity (see Efavirenz in Appendix A: Pediatric Antiretroviral Drug Information).15-17 For agents such as efavirenz, therapeutic ranges for plasma concentrations as determined by therapeutic drug monitoring (TDM) may indicate the need for dose reduction or modification of ART in patients experiencing central nervous system (CNS) AEs (see below).
The most common acute and chronic AEs associated with ARV drugs or drug classes are presented in the Management of Medication Toxicity or Intolerance tables. The tables include information on common causative drugs, estimated frequency of occurrence, timing of symptoms, risk factors, potential preventive measures, and suggested clinical management strategies. The tables also provide selected references regarding these toxicities in pediatric patients.

Management

ART-associated AEs can range from acute and potentially life-threatening to chronic and insidious. Serious life-threatening events (e.g., hypersensitivity reaction [HSR] due to abacavir, symptomatic hepatotoxicity, or severe cutaneous reactions) require the immediate discontinuation of all ARV drugs and reinitiation of an alternative regimen without overlapping toxicity. Toxicities that are not life-threatening (e.g., urolithiasis caused by atazanavir, renal tubulopathy caused by tenofovir disoproxil fumarate) can usually be managed by substituting another ARV agent for the presumed causative agent without interrupting ART. Other chronic, non-life-threatening AEs (e.g., dyslipidemia) can be addressed either by switching the potentially causative agent for another agent or by managing the AE with additional pharmacological or nonpharmacological interventions.

Management strategies must be individualized for each child, taking into account the severity of the toxicity, viral suppression status, and available ARV options. Clinicians should anticipate the appearance of common, self-limited AEs, and reassure patients that many AEs will resolve after the first few weeks of ART. For example, when initiating therapy with boosted protease inhibitors (PIs), many patients experience gastrointestinal AEs such as nausea, vomiting, diarrhea, and abdominal pain. Instructing patients to take PIs with food may help minimize these AEs. Some patients may require antiemetics and antidiarrheal agents for symptom management. CNS AEs are commonly encountered when initiating therapy with efavirenz. Symptoms can include dizziness, drowsiness, vivid dreams, or insomnia. Patients should be instructed to take efavirenz-containing regimens at bedtime, on an empty stomach, to help minimize these AEs. Patients should be advised that these AEs usually diminish in general within 2 to 4 weeks of initiating therapy in most people, but may persist for months in some, and may require a medication change. In addition, mild rash can be ameliorated with drugs such as antihistamines.

Addressing AEs is essential, as continued use of an ARV that a patient finds intolerable may lead the patient to stop their treatment, risking viral rebound and the development of resistance.

In patients who experience unacceptable AEs from ART, every attempt should be made to identify the offending agent and to replace the drug with another effective agent as soon as possible. For mild to moderate toxicities, changing to a drug with a different toxicity profile may be sufficient, and discontinuation of all therapy may not be required. When interrupting a non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimen, many experts will stop the NNRTI 7 to 14 days before stopping the dual nucleoside analogue reverse transcriptase backbone, due to the long half-life of NNRTI drugs. However, patients who have a severe or life-threatening toxicity (e.g., HSR—see Hypersensitivity Reaction, Table 15) should stop all components of the drug regimen simultaneously, regardless of drug half-life. Once the offending drug or alternative cause for the AE has been determined, planning can begin for:

- Resuming therapy with a new ARV regimen that does not contain the offending drug, or
- Resuming therapy with the original regimen, if the event is attributable to another cause.

All drugs in the ARV regimen should then be started simultaneously, rather than one at a time, with observation for AEs.

When therapy is changed because of toxicity or intolerance in a patient with virologic suppression, agents with different toxicity and side-effect profiles should be chosen, when possible. Clinicians should have comprehensive knowledge of the toxicity profile of each agent before selecting a new regimen. In the event of drug intolerance, changing a single drug in a multidrug regimen is permissible for patients whose viral loads are undetectable. However, substitution of a single active agent for a single drug in a failing multidrug regimen...
(e.g., a patient with virologic failure) is generally not recommended because of concern for development of resistance (see Recognizing and Managing Antiretroviral Treatment Failure in Management of Children Receiving Antiretroviral Therapy).

In general, dose-reduction is not recommended for toxicity management, as inadequate ARV drug levels may lead to decreased virologic efficacy. Although TDM is not routinely recommended, it may be used in the management of a child with mild or moderate toxicity if the toxicity is thought to be the result of a drug concentration exceeding the normal therapeutic range. An expert in the management of pediatric HIV should be consulted when considering dose reduction based on the results of TDM. Dose-reduction after TDM has the most data for efavirenz, where increased CNS toxicity has clearly been associated with higher drug levels (see Efavirenz in Appendix A: Pediatric Antiretroviral Drug Information).

To summarize, management strategies for drug intolerance include:

• Symptomatic treatment of mild to moderate transient AEs.
• Switching one drug for another drug that is active against a patient’s virus (e.g., changing to abacavir for zidovudine-related anemia or to a PI or integrase strand transfer inhibitor [INSTI] for efavirenz-related CNS symptoms).
• Using dose reduction as guided by TDM in consultation with an expert in pediatric HIV.

References


