Management of Medication Toxicity or Intolerance

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Panel's Recommendations
• In children with HIV who have severe or life-threatening toxicity (e.g., a hypersensitivity reaction), all antiretroviral (ARV) drugs should be stopped immediately (AIII). Once symptoms of toxicity have resolved, ARV therapy should be resumed with substitution of a different ARV drug or drugs for the offending agent(s) (AII*). • When modifying ARV 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 adverse effect profile should be chosen (AI*). • The toxicity and the medication presumed responsible should be documented in the medical record of the patient, and the caregiver and patient should be advised of the drug-related toxicity (AIII). • In general, dose reduction is not a recommended option for management of ARV toxicity (AII*).
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 postpubertal adolescents*

Medication Toxicity or Intolerance

The overall benefits of viral suppression and improved immune function because of effective antiretroviral therapy (ART) far outweigh the risks associated with the adverse effects (AEs) of some antiretroviral (ARV) drugs. AEs have been reported, however, with the use of all ARV drugs. Currently recommended ARV regimens are associated with fewer serious and intolerable AEs than regimens used in the past. In the mid-1990s when combination ART was introduced, AEs were among the most common reasons for switching or discontinuing therapy and for medication nonadherence[1-3] (see Adverse Effects of Antiretroviral Agents in the Adult and Adolescent Antiretroviral Guidelines). In recent clinical trials, however, <10% of ARV-treated patients had treatment-limiting AEs.[4-14]

The incidence of some longer-term complications of ART (e.g., bone or renal toxicity, dyslipidemia, accelerated cardiovascular disease) might 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.[6,7,15-17] To achieve sustained viral suppression during a child's lifetime, both short- 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 history of drug intolerance or viral resistance.

The AEs caused by ARV drugs 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 (i.e., occurring soon after a drug has been administered), subacute (i.e., occurring within 1 day to 2 days after administration), or late (i.e., occurring after prolonged drug administration). For a few ARV medications, pharmacogenetic markers associated with the risk of early toxicity have been identified;

however, the only marker that is routinely screened for is HLA-B*5701, a marker for abacavir (ABC) hypersensitivity.[18] For selected children aged <3 years who require treatment with efavirenz (EFV), an additional pharmacogenetic marker, cytochrome P450 (CYP) 2B6 genotype, should be assessed in an attempt to prevent toxicity[18-22] (see Efavirenz in Appendix A: Pediatric Antiretroviral Drug Information). For agents such as EFV, 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 who experience central nervous system (CNS) AEs.

The most common acute and chronic AEs that are associated with currently recommended ARV drugs or drug classes are presented in Tables 17a–17k, which are listed below. These 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 include selected references that provide further information about these toxicities in pediatric patients.

- Table 17a. Central Nervous System Toxicity
- Table 17b. Dyslipidemia
- Table 17c. Gastrointestinal Effects
- Table 17d. Hematologic Effects
- Table 17e. Hepatic Events
- Table 17f. Insulin Resistance, Asymptomatic Hyperglycemia, and Diabetes Mellitus
- Table 17g. Lactic Acidosis
- Table 17h. Lipodystrophies and Weight Gain
- Table 17i. Nephrotoxic Effects
- Table 17j. Osteopenia and Osteoporosis
- Table 17k. Rash and Hypersensitivity Reactions

Information on toxicities associated with older ARV drugs that are no longer recommended can be found in the Archived Drugs section and archived toxicity tables.

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 ABC, symptomatic hepatotoxicity, severe cutaneous reactions) require the immediate discontinuation of all ARV drugs and re-initiation 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) usually can be managed by substituting another ARV agent for the presumed causative agent without interrupting ART. Other chronic, non–life-threatening AEs (e.g., dyslipidemia, weight gain) can be addressed either by switching the potentially causative agent for another agent or by managing the AE with additional pharmacological or nonpharmacological interventions, such as lifestyle modification.

Management strategies must be individualized for each child, taking into account the severity of the toxicity, the child's viral suppression status, and the 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 antiemetic and antidiarrheal agents for symptom management. CNS AEs are encountered commonly when initiating therapy with EFV. Symptoms can include dizziness, drowsiness, vivid dreams, or insomnia. Patients should be instructed to take EFV-containing regimens at bedtime and on an empty stomach to help minimize these AEs. Patients should be advised that these AEs usually diminish within 2 to 4 weeks of initiating therapy in most people; however, they may persist for months in some patients and may require a medication change.[23] In addition, mild rash can be ameliorated with drugs, such as antihistamines. Addressing AEs is essential, because continued use of an ARV agent that a patient finds intolerable may lead the patient to stop their treatment, risking viral rebound and the development of drug resistance.

In patients who experience intolerable 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.[9,24] For mild-to-moderate toxicities, changing to a drug with a different toxicity profile might be sufficient, and discontinuation of all therapy might not be required. When interrupting a non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimen, many experts will stop the NNRTI for 7 to 14 days before stopping the dual nucleoside analogue reverse transcriptase backbone, because of the long half-life of NNRTI drugs. However, patients who have a severe or life-threatening toxicity (e.g., HSR—see Table 17k. Rash and Hypersensitivity Reactions) 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, while observing the patient for AEs.

When therapy is changed because of toxicity or intolerance in a patient with virologic suppression, agents with different toxicity and AE profiles should be chosen, when possible.[25-28] 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 only for patients whose viral loads are undetectable.

In general, dose reduction is not a recommended strategy for toxicity management, because inadequate ARV drug levels may lead to decreased virologic efficacy and, for most agents, there is not a clear relationship between drug levels and the AE. Therefore, TDM is rarely recommended; however, it may be considered to assist in the management for 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 and other ARV options are limited.[29-31] 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 been studied most extensively with EFV, because increased CNS toxicity has clearly been associated with higher levels of EFV (see Efavirenz in Appendix A: Pediatric Antiretroviral Drug Information).

To summarize, management strategies for drug intolerance include the following:

- 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 ABC for zidovudine-related anemia or to a PI or integrase strand transfer inhibitor for EFV-related CNS

symptoms) (see Modifying Antiretroviral Regimens in Children With Sustained Virologic Suppression on Antiretroviral Therapy).

- Using dose reduction, guided by TDM, after consulting with an expert in pediatric HIV.

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