Management of Medication Toxicity or Intolerance (Last updated April 14, 2020; last reviewed April 14, 2020)

Panel's Recommendations

- In children 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 therapy because of toxicity or intolerance to a specific drug in children with virologic suppression, changing one drug in a multidrug regimen is permissible; an agent with a different toxicity and side-effect profile should be chosen **(AI*)**.
- The toxicity and the medication presumed to be responsible should be documented in the medical record and the caregiver and patient should be advised of the drug-related toxicity **(AIII)**.
- In general, dose reduction **is not recommended** 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 post-pubertal adolescents

Medication Toxicity or Intolerance

Effective antiretroviral therapy (ART) results in viral suppression and improved immune function. These benefits 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. 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 (see Adverse Effects of Antiretroviral Agents in the Adult and Adolescent Antiretroviral Guidelines).[1] In recent clinical trials with newer ARV drugs, however, <10% of ARV-treated patients had treatment-limiting AEs.[2-9]

The incidence of 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.[2,4,5,10-13] Unexpected AEs may emerge with additional clinical experience with newer ARV drugs. The prevalence and the relationship of these AEs to newer ARV drugs can be unclear (e.g., weight gain with the use of integrase strand transfer inhibitors [INSTIs]; see Table 15h).[14,15] To achieve sustained viral suppression throughout 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 history of drug intolerance or viral resistance.

The AEs caused by ARV drugs can vary from mild, more common symptoms (e.g., gastrointestinal [GI] 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 that are 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.[16] For certain children aged <3 years who require treatment with efavirenz (EFV), an additional pharmacogenetic marker, cytochrome P450 2B6 genotype, should be assessed in an attempt to prevent toxicity (see the Efavirenz

section in Appendix A: Pediatric Antiretroviral Drug Information).[16-20]

The most common acute and chronic AEs that are associated with currently recommended 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 include selected references that provide further information about these toxicities in pediatric patients.

As new ARV drugs are approved for use in children, many of the older ARV drugs **are no longer recommended** because they have unacceptable toxicities, inferior virologic efficacy, a high pill burden, pharmacologic concerns, and/or a limited amount of pediatric data. The following older ARV drugs have therefore been removed from the Management of Medication Toxicity or Intolerance tables:

- Didanosine (ddI)
- Enfuvirtide
- Fosamprenavir
- Indinavir
- Nelfinavir
- Saquinavir
- Stavudine (d4T)
- Tipranavir

Information on the toxicities that are associated with these agents can be found in archived versions of the toxicity tables and archived drug sections. Because peripheral nervous system toxicity is primarily associated with some of the older drugs that were removed from the toxicity tables (e.g., ddI, d4T), that toxicity table has also been archived.

Management

ART-associated AEs can range from acute and potentially life-threatening to chronic and insidious. Serious life-threatening events (e.g., a hypersensitivity reaction [HSR] 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) 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 suspected 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, the child's viral suppression status, and the available ARV drug 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 GI 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. Central nervous system (CNS) AEs are commonly encountered 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.[21,22] In addition, mild rash can be ameliorated with drugs such as antihistamines. Addressing AEs is essential, as 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 resistance.[23,24]

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.[7,25,26] For mild to moderate toxicities, changing to a drug with a different toxicity profile may be sufficient; discontinuing all therapy may 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 reverse transcriptase inhibitor backbone, due to the long half-life of NNRTI drugs. However, patients who have a severe or life-threatening toxicity (e.g., HSR—see Table 15k) should stop all components of the drug regimen simultaneously, regardless of drug half-life. Once the cause of the AE has been determined, clinicians can either initiate a new ARV regimen that does not contain the offending drug or resume 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 an ARV regimen 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.[27-30] 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 only permissible for patients whose viral loads are undetectable.

In general, dose reduction is not a recommended strategy for toxicity management, as inadequate ARV drug levels may lead to decreased virologic efficacy. Therapeutic drug monitoring (TDM) is not routinely recommended; however, it may be used in cases where mild or moderate toxicity is thought to be the result of a drug concentration exceeding the normal therapeutic range.[31,32] An expert in the management of pediatric HIV should be consulted when dose reduction is being considered based on the results of TDM. Dose reduction after TDM has been studied most extensively with EFV, since increased CNS toxicity has clearly been associated with higher levels of EFV (see the Efavirenz section 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., switching to ABC for zidovudine-related anemia or to a PI or INSTI for EFV-related CNS symptoms).
- Using dose reduction, guided by TDM, after consulting with an expert in pediatric HIV.

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