Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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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. 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, 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. 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. 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. 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.

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. 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.
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. Interruption of cART was also associated with elevations in biomarkers of inflammation that were predictive of morbidity and mortality independent of CD4 cell count. Similarly, in the TRIVICAN trials, which used the same CD4 cell count triggers to stop and restart therapy, STI was shown to be inferior. 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. However, another large cohort study in Italy showed an increased risk of disease progression after interruption of first-line therapy. 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. 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. 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.

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. 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. 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.

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.

References


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