Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Considerations About Interruptions in Antiretroviral Therapy  (Last updated May 22, 2018, last reviewed May 22, 2018)

Panel’s Recommendations

• Outside the context of clinical trials, structured interruptions of antiretroviral therapy are not recommended for children (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

Unplanned Interruptions

Temporary discontinuation of antiretroviral therapy (ART) may be unavoidable in some situations, such as in cases of serious treatment-related toxicity or acute illnesses or planned surgeries that preclude oral intake. Lack of available medication may also require temporary ART discontinuation. Children from limited-resource settings often experience interruptions due to drugs being out of stock locally or poor access to medication during the immigration process. Prolonged interruptions of ART can also result from disengagement from care or other social or psychologic issues that affect adherence. Observational studies of children and youth with unplanned or nonprescribed treatment interruptions suggest that interruptions are common, that most patients will experience immunologic decline during the treatment interruption, and that most patients restart therapy.1-3 In a retrospective study of 483 children in the ANRS French national pediatric cohort, 42% of participants had treatment interruptions of ≥3 months (median 12.1 months). Interruption was associated with lower CD4 T lymphocyte cell (CD4) percentages at 4 years, even in those who restarted therapy.4 A similar retrospective study of 136 youth (median age 12.9 years) in the United States found that 38 participants (28%) with histories of treatment interruption had lower CD4 counts and higher HIV RNA levels than participants with continuous treatment.5 Whether unplanned interruptions occur by accident or necessity (e.g., because of toxicity), all efforts should be made to minimize their duration. To prevent interruptions in children planning extended travel, such as immigrant children returning to home countries, local drug access or multiple-month drug dispensation should be arranged ahead of time. Additional guidance on supporting adherence can be found in Adherence to Antiretroviral Therapy in Children and Adolescents Living with HIV.

Structured Treatment Interruptions

Planned periods during which ART is not given, also known as “structured treatment interruptions,” were historically considered as a potential strategy to reduce toxicity, costs, and drug-related failure associated with ART.

Adult trials demonstrated significantly higher morbidity and mortality in participants randomized to undergo structured treatment interruptions than in participants who received continuous ART.6 Current Department of Health and Human Services guidelines recommend against planned long-term structured treatment interruptions in adults (see Discontinuation or Interruption of Antiretroviral Therapy in the Adult and Adolescent Guidelines).

There have been fewer studies in children of long-term structured treatment interruption. In one study, children with controlled viral load (i.e., HIV RNA <400 copies/mL for >12 months) were subjected to increasing durations of treatment interruption. Of 14 children studied, four 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 three out of 14 children in the structured treatment interruption study. In a European trial (PENTA 11), 109 children with virologic suppression on ART were randomized to receive continuous therapy (CT) or treatment interruption with CD4-guided re-initiation of ART. On average, CD4 values decreased sharply in the first 10 weeks after structured treatment interruption. However, only 34% (19/56) of children in the structured treatment interruption arm reached the required CD4 criteria to restart therapy within 48 weeks. 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 the ARROW trial, every month of treatment interruption among children was associated with 2% lower CD4 percentage (with a range of 1% to 3%, \( P = 0.001 \)) at 3 years of follow-up; having any interruption of treatment was associated with an increased risk of mortality during that time period [hazard ratio: 2.6 (95% CI, 0.7–10.4)]. In some populations of children, structured treatment interruption has been more specifically considered. The CHER trial in South Africa was designed to answer whether infants who initiated ART early could safely discontinue therapy at some point and re-initiate treatment based on CD4 cell decline. The study assessed outcomes in infants randomized to receive deferred ART (initiation driven by Centers for Disease Control and Prevention [CDC] stage and CD4 status), immediate ART with interruption after 40 weeks, or immediate ART with interruption after 96 weeks. While the two arms that received immediate ART followed by interrupted therapy had better outcomes than the deferred arms, up to 80% of infants had to restart therapy by the end of follow-up. In another trial, 42 children who had initiated ART at age <13 months (and had CD4 percentages >25% with normal growth) were randomized to undergo treatment interruption or to continue ART. Treatment was re-initiated in the treatment interruption arm if children met what were World Health Organization ART eligibility criteria at the time. Of the 21 infants in the treatment interruption arm, 12 met ART restart criteria within 3 months and randomization was stopped by the Data Safety Monitoring Board. No differences in CD4 percentage, virologic control, or morbidity were seen at 18 months. The long-term outcomes of infants in both trials are unknown.

The case of an infant from Mississippi who initiated ART soon after birth and had a prolonged period of time without viremia after an unplanned treatment interruption raised the hope that it may be possible to stop or reduce ART in some infants (see Antiretroviral Management of Newborns). However, that infant eventually experienced viral rebound, and there have been other reports of infants who have experienced immediate rebound of viral load after cessation of ART despite having undetectable HIV DNA and RNA while on ART. The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) does not recommend treatment interruption as a strategy to confirm diagnosis or to assess for remission or cure in infants who revert to negative serology or negative HIV DNA testing.

Short-Cycle Treatment Strategies
One approach, called short-cycle therapy (SCT), schedules 4-day treatment interruptions, rather than waiting to restart ART after CD4 decline or other adverse events. In one proof-of-concept study (ATN015), 32 participants (aged 12–24 years) underwent short cycles of 4 days on/3 days off ART. Participants had at least 6 months of documented viral suppression below 400 copies/mL and CD4 count above 350 cells/mm³ and were receiving protease inhibitor-based ART. Participants demonstrated good adherence to the schedule, but 12 participants (37.5%) developed confirmed viral load rebound >400 copies and a total of 18 participants (56%) came off study; there was no impact on the CD4 counts.

A more recent study suggests that shorter cycles off ART may result in better outcomes. BREATHER (PENTA 16) was a noninferiority trial that randomized 199 children (aged 8–24 years) years to receive SCT (5 days on/2 days off) or CT. At enrollment, participants were virologically suppressed (viral load <50 copies/mL for >12 months) and receiving efavirenz plus two nucleoside reverse transcriptase inhibitors. By 48 weeks, six participants (6%) in the SCT arm and seven participants (7%) in the CT arm had a confirmed
virological failure (viral load >50 copies/mL) [difference -1.2%, 90% CI, -7.3% to 4.9%]. Of the six participants in the SCT arm with failure, five resuppressed. Three of those participants resuppressed on the same regimen and two resuppressed with a regimen switch; two others on SCT resumed daily ART for other reasons. Seven participants (SCT, n = 2; CT, n = 5) had major non-nucleoside reverse transcriptase inhibitor mutations at the time of virologic failure. At 48 weeks, the SCT arm had higher d-dimer levels but no other evidence of increased inflammation across a number of other biomarkers. Participants generally appreciated the option of SCT. A preliminary report about long-term follow-up of children in the BREATHER study (which included 194 of the original 199 children) suggests comparable virological failure rates between the SCT and CT arms (both arms had a failure rate of approximately 16%) after a median 3.6 years. The participants in the SCT arm experienced a greater number of serious adverse events than participants in the CT arm (21 serious adverse events in the SCT arm vs. eight in the CT arm, driven by hospitalizations), but both arms experienced comparable rates of CDC-stage and Grade 3 or 4 adverse events. In summary, the BREATHER trial suggests that SCT with efavirenz-based ART may be safe in some adolescents and may yield increased satisfaction that could lead to better long-term adherence. However, the Panel believes that additional data are needed to decide whether this strategy would be safe in different patient populations, with different ART regimens, outside of the context trial, and over longer periods of time.

Conclusion
Most studies have shown that treatment interruption in children appears to result in only short periods of time off ART and yields only minimal potential benefits to counterbalance the risks and limited long-term follow-up data. Lower toxicity of current antiretroviral agents decreases the potential benefits of treatment interruptions. It is possible that short-cycle treatment strategies may be safe for some patients, but additional data are needed. At the present time, the Panel does not recommend structured treatment interruption in the clinical care of children with HIV; additional studies of treatment interruption strategies in specific situations may be warranted.

References


