Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Considerations About Interruptions in Antiretroviral Therapy (Last updated April 27, 2017, last reviewed April 27, 2017)

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 necessary in some situations, including serious treatment-related toxicity, acute illnesses or planned surgeries that preclude oral intake, or lack of available medication. 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 non-prescribed treatment interruptions suggest that interruptions are common, most patients will experience immunologic decline during the treatment interruption, and most restart therapy.[1-3] In a retrospective study of 483 children in the ANRS French national pediatric cohort, 42% had treatment interruptions of ≥3 months (median 12.1 months), and interruption was associated with lower CD4 T lymphocyte cell (CD4) percentage at 4 years, even in those who restarted therapy.[4] Whether unplanned interruptions occur by accident or necessity (e.g., because of toxicity), all efforts should be made to minimize their duration. Specific guidance on supporting adherence can be found in the section, 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 those randomized to structured treatment interruptions compared with continuous ART.[5] Current Department of Health and Human Services guidelines for adults recommend against planned long-term structured treatment interruptions in adults (see the Adult and Adolescent Guidelines).

In children, there have been fewer studies of long-term structured treatment interruption. In 1 study, children with controlled viral load (i.e., 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.[6] However, new drug-resistance mutations were detected in 3 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 continuous therapy (CT) versus treatment interruption with CD4-guided re-initiation of ART.[7] 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 CD4 criteria to restart therapy within 48 weeks. Children in the structured treatment interruption arm spent significantly less time on ART 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 the ARROW trial, every month of treatment interruption among children was associated with 2% (1% to 3%, $P = 0.001$) lower CD4 percentage by 3 years of follow-up; having any interruption of treatment was associated with a trend to increased mortality [hazard ratio: 2.6 (95% CI, 0.7–10.4)].[8] In some populations of children, structured treatment interruption has been more specifically considered. One trial 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 CHER study in South Africa assessed outcomes in infants randomized to deferred ART (initiation driven by Centers for Disease Control and Prevention stage and CD4 status), immediate ART with interruption after 40 weeks, or immediate ART with interruption after 96 weeks.[9,10] While the 2 arms of immediate ART followed by 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. In another trial, 42 children who had initiated ART at age <13 months (and had CD4 percentage >25 with normal growth) were randomized to treatment interruption or to continue ART.[11] 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 had raised the hope that it may be possible to stop or reduce ART in some infants (see Special Considerations for Neonates).[12-14] However, viral rebound eventually appeared in that infant, 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.[15,16] The Panel recommends that treatment of infants who revert to negative serology or negative HIV DNA testing not be interrupted in an attempt to confirm diagnosis or to assess for remission or cure.

Short-Cycle Treatment Strategies

One approach, called short cycle therapy (SCT), schedules brief (four day treatment interruptions), rather than waiting for CD4 decline or other adverse events to restart ART. In one proof-of-concept study (ATN015), 32 participants (aged 12–24 years) underwent short cycles of 4 days on/3 days off ART.[17] Participants were receiving protease inhibitor-based ART, had at least 6 months of documented viral suppression below 400 copies/mL and CD4 count above 350 cells/mm^3. Participants demonstrated good adherence to the schedule, but 12 (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+ T cell counts. A more recent study suggests that shorter cycles off ART may result in better outcomes. BREATHER (PENTA 16) was a non-inferiority trial that randomized 199 children (aged 8 to 24) years to SCT (5 days on/2 days off) or continuous treatment (CT).[18] Participants were virologically suppressed (viral load <50 copies/mL for >12 months) and receiving efavirenz plus 2 nucleoside reverse transcriptase inhibitors at enrollment. By 48 weeks, 6 participants in the SCT arm and 7 in the CT arm had a confirmed viral load >50 copies/mL [difference -1.2%, 90% CI, -7.3% to 4.9%] and 2 in the SCT group and 4 in the CT group had a confirmed viral load >400 copies/mL (difference -2.1%, 90% CI, -6.2% to 1.9%). Of the 6 participants in the SCT arm with a viral load >50 copies/mL, 5 had resuppression, 3 on the same regimen and 2 with a switch; 2 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 week 48 they found no evidence of increased inflammation in the SCT arm. Participants expressed a strong preference for SCT in a qualitative substudy and in pre- and post-trial questionnaires. In summary, the BREATHER trial suggests that short-cycle treatment may be safe in some adolescents, and yield increased satisfaction that could lead to better long-term adherence. However, additional data are needed about 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, yielding minimal potential benefits, particularly given the lower toxicity of current ARV agents to counterbalance the risks and limited long-term follow-up data. 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.

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