



Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Considerations About Interruptions in Antiretroviral Therapy (Last updated March 1, 2016, last reviewed March 1, 2016)

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 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 guardian 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.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 percentage at 4 years, even in those who restarted therapy.^{4,5} The case of an infant who initiated ART soon after birth and had a prolonged period without viremia after unplanned interruption is discussed in the [Special Considerations for Neonates](#) section.

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.⁶ Current Department of Health and Human Services guidelines for adults recommend against planned long-term structured treatment interruptions in adults (see the [Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents](#)).

In children, there have been fewer studies of long-term structured treatment interruption. 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.⁷ However, new drug-resistance mutations were detected in three 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 T lymphocyte (CD4)-guided re-initiation of ART.⁸ On average, CD4 values decreased sharply in the first 10 weeks after structured treatment interruption. However, only 34% (19/56) 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% Confidence Interval 0.7–10.4)].⁹

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 reinitiate treatment based on CD4 cell decline. The CHER study in South Africa assessed outcomes in infants randomized to deferred ART (initiation driven by CDC stage and CD4 status), immediate ART with interruption after 40 weeks, or immediate ART with interruption after 96 weeks.^{10,11} 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 ART saved by most children merits the potential risks associated with cessation.

Given the increased availability of medications with less toxicity, the potential benefits of structured treatment interruption may not be justified. Current data do not support use of structured treatment interruption in clinical care of HIV-infected children; additional studies of structured treatment interruption in specific situations for some children may be warranted.

References

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