ANTIRETROVIRAL TREATMENT INTERRUPTION IN CHILDREN WITH HIV

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Panel's Recommendations
• Outside the context of clinical trials, treatment interruptions of antiretroviral therapy (ART) **are not recommended** for children. • Treatment interruption **is not recommended** as a strategy in clinical settings to confirm diagnosis or to assess remission or cure **(AII).** • Families should receive education and counseling about common causes of temporary unplanned treatment interruptions and ways to prevent them (e.g., automatic refills, mailed prescriptions, planning for the adequate supply of medications when traveling). See Adherence to Antiretroviral Therapy in Children and Adolescents With HIV **(BIII).** • At times, ART may need to be interrupted or changed due to drug-related side effects or toxicity. See Management of Medication Toxicity or Intolerance for guidance **(AIII).**
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 postpubertal adolescents*

Unplanned Treatment Interruptions

Temporary discontinuation of antiretroviral therapy (ART) may be unavoidable in some situations that preclude oral intake, such as serious treatment-related toxicity, acute gastrointestinal illnesses, or planned surgeries. Children might experience interruptions due to antiretroviral (ARV) drugs being out of stock locally or if they run out of ARV drugs during travel or immigration to the United States. Efforts should be made to minimize the duration of these temporary interruptions. Prolonged interruptions of ART also can result from disengagement from care or other social or psychological issues that affect adherence. Routine assessment of adherence and barriers is essential (see Adherence to Antiretroviral Therapy in Children and Adolescents With HIV). Utilizing viral load testing alone to identify treatment interruptions may not be sufficient as some children may restart treatment in the weeks ahead of clinic visits.

Observational studies of children and youth with unplanned or nonprescribed treatment interruptions suggest that interruptions are common and that prolonged interruptions can lead to immunologic decline.[1-4] In a retrospective study of 483 children in a French pediatric cohort from the National Agency for Research on AIDS and Viral Hepatitis, 42% of participants had treatment interruptions of ≥3 months (with a median of 12.1 months). Interruption was associated with lower CD4 T lymphocyte (CD4) cell percentages after 4 years, even in those who restarted therapy.[5] 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 who had continuous treatment.[6] A study from the International epidemiology Databases to Evaluate AIDS Southern Africa, which includes 53,674 children aged <16 years, found that lapses in clinical care of greater than 180 days within the first 6 months of treatment were associated with increased mortality (adjusted hazard ratio [aHR] = 1.52; 95% confidence interval [CI], 1.12–2.04); while lapses in care after the first 6 months were not (aHR = 1.05; 95% CI, 0.77–1.44).[7]

The risk of unplanned ART interruptions can be mitigated by clinicians working closely with families. Providers should provide anticipatory guidance about potential short-term interruptions (e.g., sleepovers). If a child will be away from home for an extended period of time (e.g., tourism, education, summer camp), clinicians should help families plan to ensure continuous access to medications. Some pharmacies are able to dispense up to 90 days of medication for convenience or upcoming travel; however, authorization from the insurance provider may be required. Clinicians should review the duration of current prescriptions and anticipate any dose changes that might be needed due to growth of the child and to determine when the prescribed refills will terminate. For prolonged travel within the United States, providers either can proactively order refills at pharmacies close to their travel destinations to ensure they will be in stock or have medications mailed directly to families at other convenient locations. Alternatively, changing the ART regimen to incorporate ARV drugs available in the locations where families will be traveling would make it easier to address cases of lost medications or unanticipated prolonged travel. For additional information, refer to the Centers for Disease Control and Prevention (CDC) webpage on Traveling Abroad With Medicine | CDC, as well as the guideline section on Adherence to Antiretroviral Therapy in Children and Adolescents With HIV.

Unforeseeable events, such as natural disasters or political instability, may occur and displace children from their primary HIV care programs. See Guidance for Non-HIV-Specialized Providers Caring for People With HIV Who Have Been Displaced by Disasters (Such as a Hurricane) for information about how to care for children with HIV who are in these situations.

Structured Treatment Interruptions

Structured treatment interruptions are scheduled periods of time during which oral ART is not prescribed or administered. This strategy was once considered a method for providing people with time off ART to reduce the risk of toxicity and costs. Randomized clinical trials of adults with HIV have demonstrated that structured treatment interruptions are associated with significantly higher morbidity and mortality than continuous ART[8]; Current U.S. Department of Health and Human Services HIV treatment guidelines recommend against planned, long-term structured treatment interruptions in adults (see Discontinuation or Interruption of Antiretroviral Therapy in the Adult and Adolescent Antiretroviral Guidelines). The introduction of long-acting injectable regimens may reduce the desire for structured treatment interruptions used solely to relieve the burden of daily dosing of oral ART.

Few studies have evaluated structured treatment interruption in children. In one trial from Europe and Thailand (PENTA 11), 109 children (median age 9 years) on ART and with virologic suppression were randomized to receive continuous therapy (CT) or to undergo treatment interruption. Although no significant differences in rates of adverse events (AEs) were observed between the two groups at 2 years, 19 of 56 children (34%) in the structured treatment interruption arm met CD4 criteria to restart therapy between 6 and 42 weeks after interruption; thus, the additional time off ART provided by the strategy ultimately was fairly limited.[9,10] The Children with HIV Early Antiretroviral Therapy (CHER) trial in South Africa was designed to determine whether infants who initiated ART early could safely discontinue therapy at either 40 weeks or 96 weeks; infants would reinitiate treatment based on CD4 decline. There was no continued ART group. The median time to the start

of continuous ART after interruption was 33 weeks (interquartile range [IQR] 26–45 weeks) among the infants who discontinued ART after 40 weeks, and 70 weeks (IQR 35–109 weeks) among the infants who discontinued ART after 96 weeks.[11,12] A secondary analysis of neurodevelopmental outcomes at age 5 years did not show any significant differences among the children in the different study arms.[13] In another randomized trial, 12 of 21 infants in the treatment interruption arm met ART restart criteria within 3 months.[14] In summary, although trials of structured treatment interruptions in children have not shown significant short-term morbidity, the gains in time off ART are limited, and the long-term outcomes remain 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 the intensity of ART (e.g., use fewer agents) in some infants (see Antiretroviral Management of Infants With *In Utero*, Intrapartum, or Breastfeeding Exposure to HIV).[15,16] However, the "Mississippi infant" had documented viral rebound after 28 months off ART,[17] and additional reports have emerged of infants who experienced rebound viremia after stopping ART, despite having undetectable HIV DNA and RNA while on ART.[18-20] A South African child aged 9.5 years was reported to have low levels of virus that was not replication competent after receiving ART from approximately 2 to 24 months of age; the factors that led to this outcome remain unknown.[21]

"Analytical" treatment interruptions are currently being incorporated into studies of remission in adults and children, but the potential risks and benefits of strategies need to be continually evaluated.[22-25] In the IMPAACT P1115 study, infants initiated a regimen that included nevirapine plus two nucleoside reverse transcriptase inhibitors (NRTIs) within 48 hours of life with lopinavir/ritonavir added at ≥42 weeks postmenstrual age; among six children with HIV who had analytical treatment interruption (at a median of 5.5 years of age), four achieved ART-free remission through the study-defined endpoint of 48 weeks.[26] Although the results from P1115 are promising, additional research into the predictors of remission and treatment regimens that achieve remission are needed before similar interruptions are employed in clinical settings.

Currently, the Panel on Antiretroviral Therapy and Medical Management of Children Living With HIV (the Panel) **does not recommend** treatment interruption as a strategy in clinical settings to confirm diagnosis or to assess remission or cure in infants who reverted to negative serology, tested negative for HIV DNA, or received an initial diagnosis that was based on a single positive nucleic acid test. The Panel encourages providers to consult an expert on pediatric HIV when they are concerned about the validity of the test results that led to treatment initiation in children with HIV.

Short-Cycle Therapy Strategies

One approach, called short-cycle therapy (SCT), schedules 4-day treatment interruptions rather than waiting to restart ART after CD4 count declines or other AEs occur. In one proof-of-concept study (ATN015), 32 participants (aged 12–24 years) underwent short cycles of 4 days on and 3 days off ART.[27] Participants received protease inhibitor–based ART and had at least 6 months of documented viral suppression (defined as a viral load <400 copies/mL) and CD4 counts above 350 cells/mm^3. Most participants demonstrated good adherence to the schedule, but 12 participants (37.5%) developed confirmed viral load rebounds >400 copies/mL, and 18 participants (56%) left the study. SCT had no impact on CD4 counts.

Other recent trials have shown more promising results. The BREATHER (PENTA 16) study randomized 199 children and young adults (aged 8–24 years) with virologic suppression for >12 months to SCT of 5 days on and 2 days off ART or CT with efavirenz (EFV) plus two NRTIs; the study demonstrated non-inferiority of SCT compared to CT with similar resistance and inflammatory markers.[28,29] Two participants in the SCT arm and five participants in the CT arm had virologic failure

with major mutations related to resistance to non-nucleoside reverse transcriptase inhibitors. Participants generally reported appreciating the option of SCT.[30]

A long-term follow-up study of children from the BREATHER study suggests comparable virologic failure rates between the SCT and CT arms after a median of 3.6 years; both arms had a failure rate of approximately 16%.[31] The participants in the SCT arm experienced a greater number of serious AEs than participants in the CT arm (20 serious AEs in the SCT arm vs. 8 in the CT arm, with the primary difference being rate of hospitalizations); however, the arms experienced comparable rates of the CDC Grade 3 or 4 AEs. The BREATHER trial suggests that SCT with EFV-based ART may be safe in some adolescents and may yield increased patient satisfaction that could lead to better long-term adherence. In a non-inferiority trial, adults randomized to receive SCT (4 days on and 3 days off) had rates of treatment success similar to adults receiving CT (308 of 318 participants [97%]; adjusted difference −1.3%; 95% CI −4.2 to 1.7), with 153 of 258 participants (59%) reporting improvement in daily life satisfaction.[32]

However, the Panel currently believes that additional data are needed to decide whether the BREATHER strategy would be safe in different populations, with different antiretroviral regimens, outside of the context of a trial, and over longer periods. Use of SCT with integrase strand transfer inhibitor–based regimens has not been studied in children.

Conclusion

Cumulative data have demonstrated that treatment interruptions long enough for viremia to recur are generally harmful to children with HIV. Analytic treatment interruptions to assess for remission are employed in research but not recommended in the clinical context. SCT treatment may be safe and increase satisfaction in some people, but the Panel concludes that more data are needed before SCT can be recommended for routine use in pediatric populations. Currently, 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 are warranted.

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