

# Antiretroviral Treatment Interruption in Children With HIV

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Panel's Recommendations
<ul style="list-style-type: none"><li>• Outside the context of clinical trials, structured interruptions of antiretroviral therapy are <b>not recommended</b> for children (All).</li><li>• 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, etc. (see <a href="#">Adherence to Antiretroviral Therapy in Children and Adolescents With HIV</a>).</li><li>• At times, ARV therapy may need to be interrupted or changed due to drug-related side effects or toxicity. See <a href="#">Management of Medication Toxicity</a> for guidance.</li></ul>
<p><i>Rating of Recommendations: A = Strong; B = Moderate; C = Optional</i></p> <p><i>Rating of Evidence: I = One or more randomized trials in children<sup>†</sup> 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<sup>†</sup> 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<sup>†</sup> 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<sup>†</sup> from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion</i></p> <p><i><sup>†</sup> Studies that include children or children/adolescents, but not studies limited to postpubertal adolescents</i></p>

## Unplanned Treatment Interruptions

Temporary discontinuation of antiretroviral therapy (ART) may be unavoidable in some situations—such as in cases of serious treatment-related toxicity, acute illnesses, or planned surgeries—that preclude oral intake. Lack of available medication also may result in temporary ART discontinuation. In resource-limited settings, children might experience interruptions due to drugs being out of stock locally. Children with HIV who are immigrating to the United States also may experience gaps in medication availability. Prolonged interruptions of ART also can result from disengagement from care or other social or psychological issues that affect adherence. Some patients, particularly adolescents and young adults, might attempt to conceal long periods of treatment interruption by restarting treatment in the few weeks ahead of clinic visits and viral load testing.

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.<sup>1-4</sup> In a retrospective study of 483 children in a French pediatric cohort from the National Agency for Research on AIDS and Viral Hepatitis (ANRS), 42% of participants had treatment interruptions of  $\geq 3$  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.<sup>5</sup> 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.<sup>6</sup> **A study from the International**

Epidemiology Databases to Evaluate AIDS Southern Africa, which includes 53,674 children <16 years of age, 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% 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).<sup>7</sup>

Whether unplanned interruptions occur by accident or necessity (e.g., because of toxicity), all efforts should be made to minimize their duration. If a child will be traveling for an extended period, clinicians can help prevent treatment interruption by ensuring that the child will have access to the necessary drugs during the trip. If the required drugs will not be available at the destination, pharmacies can be asked to dispense extra medication. Additional guidance on supporting adherence can be found in [Adherence to Antiretroviral Therapy in Children and Adolescents With HIV](#).

## Structured Treatment Interruptions

Structured treatment interruptions are scheduled periods of time during which ART is not prescribed or administered. This strategy was once considered a method for providing patients 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.<sup>8</sup> 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](#)).

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, suggesting that the time off ART provided by this strategy was ultimately limited.<sup>9,10</sup> 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 reinstate treatment based on CD4 decline. The median time to the start of continuous ART after interruption was 3 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.<sup>11,12</sup> A secondary analysis of neurodevelopmental outcomes at age 5 years did not show any significant differences among the children in the different study arms.<sup>13</sup> However, brain magnetic resonance imaging studies in a subset of participants found that children with HIV on interrupted ART (n = 21) had a thicker cortex than uninfected controls in the left frontal and right insular regions, but children with HIV on CT (n = 25) showed no difference from controls; the clinical significance of these differences is not known.<sup>14</sup> In another randomized trial, 12 of 21 infants in the treatment interruption arm met ART restart criteria within 3 months.<sup>15</sup> 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 Newborns With Perinatal HIV Exposure or HIV](#)).<sup>16,17</sup> However, the “Mississippi infant” had documented viral rebound after 28 months off ART,<sup>18</sup> and additional reports have emerged of infants who experienced rebound viremia after stopping ART, despite having undetectable HIV DNA and RNA while on ART.<sup>19–21</sup> 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.<sup>22</sup> Future research might identify treatment strategies and diagnostic tests that enable ART to be safely interrupted in some children. “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 critically evaluated.<sup>23–25</sup>

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.<sup>26</sup> 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<sup>3</sup>. 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.

The BREATHER (PENTA 16) study sought to examine the safety and benefits of SCT with 5 days on and 2 days off ART; PENTA 16 was a noninferiority trial that randomized 199 children and young adults (aged 8–24 years) for SCT or CT.<sup>27,28</sup> To enroll, participants had to be receiving efavirenz (EFV) plus two nucleoside reverse transcriptase inhibitors, and they had to have been virologically suppressed (defined as a viral load <50 copies/mL) for >12 months. By 48 weeks, six participants (6%) in the SCT arm and seven participants (7%) in the CT arm experienced confirmed virologic failure, which was defined as a viral load >50 copies/mL (difference –1.2%; 90% confidence interval, –7.3% to 4.9%). Of the six participants in the SCT arm who experienced virologic failure, five were able to regain virologic suppression. Two participants in the SCT arm and five participants in the CT arm had major mutations related to resistance to non-nucleoside reverse transcriptase inhibitors 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 reported appreciating the option of SCT.<sup>29</sup>

A long-term follow-up study of children from the BREATHER study (which included 194 of the original 199 children) 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%.<sup>30</sup> 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 versus 8 in the CT arm, with the primary difference being rate of hospitalizations); however, the arms experienced comparable rates of the Centers for Disease Control

and Prevention 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. However, the Panel **currently** believes that additional data are needed to decide whether **the BREATHER** strategy would be safe in different patient populations, with different antiretroviral (ARV) regimens, outside of the context of a trial, and over longer periods.

## 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 patients, 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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