

# When to Initiate Therapy in Antiretroviral-Naive Children

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Panel's Recommendations
<ul style="list-style-type: none"><li>Antiretroviral therapy (ART) should be initiated in all infants and children with HIV infection (<b>AI</b> for children aged &lt;3 months, <b>AI*</b> for older children).<ul style="list-style-type: none"><li>Rapid ART initiation (defined as initiating ART immediately or within days of HIV diagnosis), accompanied by a discussion of the importance of adherence and provision of subsequent adherence support, is recommended for all children with HIV.</li></ul></li><li>If a child with HIV has not initiated ART, health care providers should closely monitor the virologic, immunologic, and clinical status at least every 3 to 4 months (<b>AIII</b>).</li></ul>
<p><b>Rating of Recommendations:</b> A = Strong; B = Moderate; C = Optional</p> <p><b>Rating of Evidence:</b> 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</p> <p><sup>†</sup>Studies that include children or children/adolescents, but not studies limited to postpubertal adolescents</p>

## Overview

The Panel on Antiretroviral Therapy and Medical Management of Children Living With HIV (the Panel) recommends initiating treatment for all children with HIV **as soon as is feasible after diagnosis**. Multiple studies have shown a benefit to early antiretroviral therapy (ART) initiation,<sup>1-3</sup> and that ART initiation within the first year of life is associated with reduced size of viral reservoirs.<sup>4</sup> Treatment initiation in young infants with HIV during the early stages of infection may control viral replication before HIV can evolve into diverse and potentially more pathogenic quasi-species.<sup>5</sup> Initiation of therapy at higher CD4 T lymphocyte (CD4) counts has been associated with the presence of fewer drug-resistant mutations at virologic failure in adults.<sup>6</sup> Early therapy **has also been shown to preserve immune function and prevent clinical disease progression in perinatal infection<sup>7-9</sup> and may prevent or reduce persistent inflammation, a precipitant of cardiovascular, kidney, and liver disease and malignancy.<sup>10,11</sup>**

Rapid treatment initiation, defined as therapy initiated immediately or within days of HIV diagnosis, is recommended except **in children with cryptococcal meningitis, disseminated *Mycobacterium avium* complex disease, or *Mycobacterium tuberculosis***. Due to concerns regarding the risk of immune reconstitution inflammatory syndrome, ART initiation may be deferred until the optimal timing relative to treatment of the opportunistic infection (see [Guidelines for the Prevention and Treatment of Opportunistic Infections in Children With and Exposed to HIV](#) and [WHO Updated Recommendations on HIV Prevention, Infant Diagnosis, Antiretroviral Initiation and Monitoring, March 2021](#)). Timing of ART initiation in these cases should be discussed with a pediatric HIV specialist.

Although rapid initiation of ART is recommended in all children with HIV, individual clinical and/or psychosocial factors may lead patients, caregivers, and providers to make a collaborative decision to defer ART initiation. When making the decision to defer ART, medical factors—such as the opportunity to limit seeding of the viral reservoir in newborns, the child’s HIV disease stage,<sup>12</sup> and the presence of HIV-related signs and symptoms<sup>13</sup>—need to be balanced against any potential barriers to rapid ART initiation. If ART is deferred, the health care provider should continue to educate and work with the family to overcome barriers to treatment, as well as closely monitor the child’s virologic, immunologic, and clinical status at least every 3 to 4 months (AIII) (see [Clinical and Laboratory Monitoring of Pediatric HIV Infection](#)). Clinicians should initiate ART in children with HIV for whom treatment has been deferred when at least one of the following conditions occur:

- HIV RNA levels increase,
- CD4 count or percentage values decline (e.g., approaching Centers for Disease Control and Prevention Stage 2 or 3),<sup>12</sup>
- The child develops new HIV-related clinical symptoms,<sup>13</sup>
- The ability of a caregiver and child to adhere to the prescribed regimen improves.

### ***Survival and Health Benefits Associated With Early Initiation of Antiretroviral Therapy***

The Children with HIV Early Antiretroviral Therapy (CHER) trial was a randomized clinical trial in South Africa that initiated ART in infants with HIV who were aged 6 to 12 weeks and were asymptomatic with normal CD4 percentages (>25%). Immediate initiation of ART resulted in a 75% reduction in early mortality among these infants, compared with delayed treatment until the infants met clinical or immune criteria according to standard of care at the time of the study.<sup>2</sup> Consistent with the CHER trial, data from a number of observational studies in the United States, Europe, and South Africa demonstrated that infants who received early treatment were less likely to progress to AIDS or death, and they also had improved growth compared with those who started treatment later.<sup>14-17</sup>

In general, studies that evaluate later initiation of ART in children have a selection bias, because children with perinatal infection and rapidly progressing disease may have died prior to receiving an HIV diagnosis or ART, and children who present later for ART initiation may be slower progressors with a better prognosis. However, in the multicenter, open-label Pediatric Randomised Early versus Deferred Initiation in Cambodia and Thailand (PREDICT) trial, which randomized 300 children with HIV aged 1 year to 12 years at enrollment (median age 6.4 years) to immediately initiate ART or to defer treatment until their CD4 percentage was <15%, better height gain among children who started ART immediately was reported.<sup>18</sup> Similarly, other studies have reported an association between younger age at initiation of ART and more rapid growth reconstitution.<sup>15,19-21</sup> Studies conducted in and outside the United States have reported an association between delayed ART initiation and delay of pubertal development and menarche.<sup>22</sup> Finally, among 32 youths with perinatally acquired HIV from the Pediatric HIV/AIDS Cohort Study (PHACS), DNA methylation evaluating epigenetic aging was compared to chronologic aging over time. Higher viral load and lower CD4 count were associated with epigenetic aging that exceeded chronologic aging, highlighting the value of achieving early viral suppression and maintaining or reconstituting immune function as close to an HIV diagnosis as possible.<sup>23</sup>

A proteomics study of children who initiated ART early (within 12 weeks of birth) versus later (12 to 50 weeks after birth) identified a protein signature among later initiators associated with a

proinflammatory state, which was associated with elevated lipid levels and other metabolites and clinical parameters, suggestive of a higher risk of premature onset of atherosclerotic disease and metabolic disorders in adulthood.<sup>10</sup> Furthermore, a recent cross-sectional study from Mozambique found that earlier age at ART initiation was independently associated with improved large artery stiffness in childhood, as measured by pulse wave velocity, independent of the effect of elevated visceral fat, lipids, and insulin resistance.<sup>11</sup>

### ***Neurodevelopmental Benefits Associated With Early Initiation of Antiretroviral Therapy***

A CHER trial substudy found that infants who initiated ART early had significantly better gross motor and neurodevelopmental profiles than those whose therapy was deferred.<sup>24</sup> In a cohort from Thailand, the prevalence of global developmental impairment was 22% (95% confidence interval [CI], 11% to 27%) among children with HIV who initiated ART within 3 months of birth, compared with 44% (95% CI, 23% to 66%) among children who initiated ART from 3 to 12 months.<sup>25</sup> A study of South African infants with perinatal HIV infection who initiated ART within 21 days of life (median 6 days) found that neurodevelopmental scores at 11 months of age for these infants were within the normal range.<sup>26</sup>

### ***Immune Benefits Associated With Early Initiation of Antiretroviral Therapy***

In the CHER study, infants who were treated early had decreased immune activation, greater recovery of CD4 cells, expanded CD4-naïve T cells, and retention of innate effector frequencies, resulting in greater immune reconstitution than that achieved in infants who received deferred ART.<sup>9</sup> In a small study in Botswana, infants who initiated ART within the first 7 days of life were found to have decreased immune activation, a more polyfunctional HIV-1-specific CD8 cell response, and a markedly reduced HIV latent reservoir, compared with infants who initiated ART later in the first year of life.<sup>27</sup> Available data suggest that both children and adults who initiate treatment with a higher CD4 percentage or CD4 count have better immune recovery than patients who initiate treatment with lower CD4 percentages or CD4 counts.<sup>20,28-30</sup> Among 1,236 children with perinatally acquired HIV in the United States, only 36% of those who started ART with CD4 percentages <15% achieved CD4 percentages >25% after 5 years of therapy, compared with 59% of children who started with CD4 percentages of 15% to 24%.<sup>31</sup> Finally, earlier age at ART initiation results in higher rates of CD4:CD8 ratio normalization and improved immunogenicity of childhood vaccines.<sup>32-34</sup>

Early initiation of suppressive ART (i.e., in infants aged <6 months) results in a significant proportion of infants with HIV who fail to produce their own HIV-specific antibodies. These infants appear to be HIV-seronegative when tested; however, viral reservoirs remain, and viral rebound occurs if ART is stopped.<sup>35-40</sup>

### ***Viral Suppression and Viral Reservoirs With Early Initiation of Antiretroviral Therapy***

Early initiation of ART within the first 7 days of life, compared with initiation between 8 and 28 days of life, resulted in a fourfold faster time to viral suppression among infants in a multinational study.<sup>41</sup> Studies that compared the size of viral reservoirs in children who initiated ART before age 12 weeks with those in children who initiated ART at ≥12 weeks to ≤2 years of age found that viral reservoir size after 1 year and 4 years of ART significantly correlated with younger age at ART initiation and younger age at viral control.<sup>42-44</sup> Among 27 children in the Early-treated Perinatally HIV-infected Individuals: Improving Children's Actual Life with Novel Immunotherapeutic Strategies (EPIICAL)

Consortium who initiated ART before 2 years of age and maintained a viral load <50 copies/mL for more than 5 years, total HIV-1 DNA levels measured at a median of 12 years after treatment initiation **were reduced** (interquartile range 7.3–15.4), with younger age and viral load at the time of ART initiation each associated with lower reservoir levels.<sup>45</sup> Finally, in the CHER study, early ART initiation and longer duration of ART was associated with lower proviral DNA levels at age 5 years.<sup>46</sup>

These findings suggest that initiating ART soon after an infant acquires HIV can limit the size of the HIV viral reservoir, and smaller reservoirs **may** provide some level of protection against viral rebound in the setting of treatment nonadherence—a frequent event for infants with HIV who are destined for lifelong treatment. Furthermore, **very low levels of markers of HIV persistence** have been reported in infants who initiated ART early and who had sustained control of plasma viremia.<sup>35,47</sup>

The report of a prolonged remission in a child with perinatally acquired HIV in Mississippi generated discussion about early initiation of ART as presumptive treatment in newborns at high risk of HIV acquisition.<sup>48,49</sup> **Two other children have experienced prolonged remission following early ART initiation. A child from the CHER study received ART between 2 and 10 months of age, and in 2019, at the age of 9.5 years, had HIV-1 detectable only at very low levels (plasma RNA 6.6 copies/mL) and no detectable replication competent virus.<sup>50</sup> A French child was treated with ART from 3 months of age through approximately 6 years of age, and in 2016, at 18.6 years of age and still off ART, HIV RNA had remained below 50 copies/mL with stable CD4 cell counts.<sup>51</sup>**

These experiences have prompted increasing support for initiating treatment as soon as the diagnosis is made, and if possible, during the first weeks of life to limit reservoir formation and possibly facilitate ART-free remission. Although a limited number of case reports describe lengthy remissions in children with perinatally acquired HIV who have undergone treatment interruption, current ART regimens have not been shown to eradicate HIV infection, because HIV persists in CD4 cells and other long-lived cells.<sup>50-53</sup> For these reasons, the Panel **does not recommend empiric treatment interruption** outside of a clinical trial setting.

Managing treatment in neonates with HIV is complex from a medical and social perspective. Because of limited safety and pharmacokinetic (PK) data for ARV drugs in full-term infants aged <2 weeks and preterm infants aged ≤4 weeks, drug and dose selection in this age group is challenging<sup>54,55</sup> (see [What to Start](#) and [Antiretroviral Management of Newborns With Perinatal HIV Exposure or HIV Infection](#)). Hepatic and renal function are immature in newborns who are undergoing rapid maturational changes during the first few months of life, which can result in substantial differences in ARV dose requirements between young infants and older children.<sup>56,57</sup> When drug concentrations are subtherapeutic—either because of inadequate dosing, poor absorption, or incomplete adherence—ARV drug resistance can develop rapidly, particularly in young infants who experience high levels of viral replication. Frequent follow-up for dose optimization during periods of rapid growth is especially important when treating young infants. Furthermore, clinicians should continually assess a patient’s adherence and address potential barriers to adherence during this time (see [Adherence to Antiretroviral Therapy in Children and Adolescents With HIV](#)).

## Summary

The Panel recommends rapid initiation of ART (defined as initiating ART immediately or within days of HIV diagnosis) for all children who receive an HIV diagnosis, **regardless of clinical, immunologic, or virologic status**. The urgency of rapid ART initiation is especially critical for children aged <1 year who carry the highest risk of rapid disease progression and mortality.

However, in ART-naïve children and adolescents with cryptococcal meningitis, disseminated *Mycobacterium avium* complex disease, and *Mycobacterium tuberculosis* disease, the Panel recommends initiation of treatment for the opportunistic infection first, ahead of ART initiation (See [Guidelines for the Prevention and Treatment of Opportunistic Infections in Children With and Exposed to HIV](#)). Timing of ART initiation in these cases should be discussed with a pediatric HIV specialist.

In preparation for ART initiation, it is important to assess and discuss issues associated with adherence with caregivers and, when developmentally appropriate, with children. Intensive follow-up during the first few weeks to months after ART initiation is also recommended to support the child and caregiver. Medication adherence is the core requirement for successful virologic control. The Panel recognizes that achieving consistent adherence in children is often challenging.<sup>58,59</sup> Incomplete adherence leads to loss of viral control and the selection of drug-resistant mutations, but forcibly administering ARV drugs to younger children may result in treatment aversion, which often persists into adulthood.

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