WHEN TO INITIATE ANTIRETROVIRAL TREATMENT IN CHILDREN WITH HIV INFECTION

Updated: September 30, 2025
Reviewed: September 30, 2025

Panel's Recommendations
• Antiretroviral therapy (ART) should be initiated in all infants and children with HIV infection (**AI** for children aged <3 months, **AI*** for older children). o 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 **(AI*).** o However, in ART-naive children and adolescents with cryptococcal meningitis, tuberculous meningitis, and disseminated *Mycobacterium avium* complex disease, the Panel on Antiretroviral Therapy and Medical Management of Children Living With HIV recommends initiation of treatment for the opportunistic infection first, before ART initiation (see Guidelines for the Prevention and Treatment of Opportunistic Infections in Children With and Exposed to HIV) **(AII).** The timing of ART initiation in these cases should be discussed with a pediatric HIV specialist. • 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 **(AIII).** o ART initiation should be discussed and strongly encouraged at every visit **(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*

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[1-3] and that ART initiation within the first year of life is associated with reduced size of viral reservoirs.[4] 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.[5] Initiation of therapy at higher CD4 T lymphocyte (CD4) cell counts has been associated with the presence of fewer drug-resistant mutations at virologic failure in adults.[6] Early therapy has also been shown to preserve immune function and prevent clinical disease progression in perinatal infection[7-9] and may prevent or reduce persistent inflammation, a precipitant of cardiovascular, kidney, and liver disease and malignancy.[10,11]

Rapid treatment initiation, defined as therapy initiated immediately or within days of HIV diagnosis, is recommended except in children with cryptococcal meningitis, tuberculous meningitis, and disseminated *Mycobacterium avium* complex disease. Due to concerns regarding the risk of immune reconstitution inflammatory syndrome, ART initiation may be deferred briefly until the optimal timing relative to treatment of these opportunistic infections. Timing of ART initiation in these cases should be discussed with a pediatric HIV specialist (see Guidelines for the Prevention and Treatment of Opportunistic Infections in Children With and Exposed to HIV). A retrospective review of children and adolescents with HIV in six African countries between 2013 and 2020 showed that there was no mortality difference if ART was initiated <2 weeks (n = 266) versus 2 weeks to 2 months (n = 398) after starting anti-tuberculous therapy for pulmonary tuberculosis (TB).[12] This finding supporting ART initiation in children and adolescents with HIV within the first 2 weeks of treatment for TB is consistent with World Health Organization Updated Recommendations on HIV Prevention, Infant Diagnosis, Antiretroviral Initiation and Monitoring, March 2021,[13] which advocate for ART initiation within 2 weeks of TB treatment initiation for infants and children, except when signs and symptoms of meningitis are present. In the case of tuberculous meningitis, the Panel recommends initiating ART within 2 to 8 weeks of TB treatment initiation, depending on clinical considerations and in consultation with a pediatric HIV specialist (see Guidelines for the Prevention and Treatment of Opportunistic Infections in Children With and Exposed to HIV).

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,[14] and the presence of HIV-related signs and symptoms[15]—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; more frequent monitoring may be needed in infants or young children ≤4 years of age given the higher mortality risk in this age group **(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) (see Appendix C. CDC Pediatric HIV CD4 Cell Count/Percentage and HIV-Related Disease Categorization)[14]
- The child develops new HIV-related clinical symptoms (see Appendix C. CDC Pediatric HIV CD4 Cell Count/Percentage and HIV-Related Disease Categorization)[15]
- The ability of a caregiver and child to adhere to the prescribed regimen improves

Survival 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%). Immediately initiating ART resulted in a 75% reduction in early mortality among these infants compared with delaying treatment until the infants met clinical or immune criteria according to the standard of care at the time of the study.[2] 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 these infants also had improved growth and lower morbidity compared with those who started treatment later.[16-20]

Health Benefits Associated With Early Initiation of Antiretroviral Therapy

In general, studies that evaluate later initiation of ART in children have a selection bias: 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, multiple studies have demonstrated the benefits of early ART initiation across several health outcomes.

Growth Outcomes

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 gain in height among children who started ART immediately was reported.[21] Similarly, other studies have reported an association between younger age at initiation of ART and more rapid growth reconstitution.[17,22-24] Studies[16-20,25] conducted in and outside the United States have reported an association between delayed ART initiation and delay of pubertal development and menarche.[26]

Immune Outcomes

A proteomics study of children who initiated ART early (within 12 weeks of birth) versus later (12–50 weeks after birth) identified a protein signature among later initiators associated with a proinflammatory state. This proinflammatory state 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.[10] A longitudinal study found that early ART initiation (≤6 months of age) compared with later ART initiation (>6 months and <2 years of age) was associated with decreased inflammatory cytokines and chemokines 12.5 years after ART initiation, despite both groups achieving and maintaining virologic suppression (HIV RNA <50 copies/mL) for at least 5 years at study enrollment.[27]

Cardiopulmonary Outcomes

A cross-sectional study from Mozambique found that earlier age at ART initiation was independently associated with improved large artery elasticity in childhood, as measured by pulse wave velocity, independent of the effect of elevated visceral fat, lipids, and insulin resistance.[11] Regarding lung health, although multiple studies have demonstrated poor pulmonary function among children with perinatal HIV infection,[28-30] a longitudinal study in South Africa found that among 122 children with HIV who were promptly initiated on ART (median age 4.0 months), lung function trajectories throughout childhood demonstrated similar spirometry to children without HIV who were not HIV-exposed (n = 80), highlighting that early ART can mitigate the loss of lung function in children with perinatal HIV. Plethysmography, however, demonstrated increased air trapping in children with HIV, suggesting that there remains a concern for small airway disease in this group.[31]

Neurodevelopmental Outcomes

Early infant initiation of ART has been associated with improved neurodevelopmental outcomes compared with later initiation of ART. Examples include a CHER trial substudy in which infants who

initiated ART early had significantly better gross motor and neurodevelopmental profiles than those whose therapy was deferred.[32] Additionally, 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 ages 3 to 12 months.[33] Among Kenyan children with HIV who initiated ART within 1 year of birth (early ART; n = 54) versus 1.5 to 6 years after birth (late ART; n = 27) between 2007 and 2009 and were prospectively assessed for neurocognitive outcomes at a median age of 6.9 years, the children with later ART initiation had significantly higher odds of impairment in global cognition, short-term memory, visuospatial processing, learning, planning, nonverbal test performance, and motor skills (adjusted odds ratios 2.87–16.22; *P* values ≤ 0.05).[34] Lastly, a study of South African infants with perinatally acquired HIV (PHIV) who initiated ART within 21 days of life (median 6 days) found that neurodevelopmental scores at approximately 11.5 months of age were within the normal range for age in the domains of locomotor, personal–social, hearing and language, and visual–motor.[35]

Other Health Outcomes

Although research on epigenetic aging among adolescents with HIV has been limited, a longitudinal study of 40 children from the Pediatric HIV/AIDS Cohort Study (PHACS) —including 32 children with PHIV and 8 children without HIV who had perinatal HIV exposure—evaluated epigenetic aging (via DNA methylation) compared to chronologic aging over time. Children with PHIV experienced an increased rate of epigenetic aging compared with children without HIV. In those with PHIV, higher viral load and lower CD4 count were associated with accelerated epigenetic aging, emphasizing the importance of early and sustained suppressive treatment for children with PHIV.[36]

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-naive T cells, and retention of innate effector frequencies, resulting in greater immune reconstitution than that achieved in infants who received deferred ART.[9] The IMPAACT 1115 Phase 1/2 proof-of-concept study of very early ART initiation began treatment of 54 infants within 10 days of birth. CD4 counts were ≥1,500 cells/mm^3, and CD4 percentages were ≥25% among 84% of infants at 24 weeks after treatment initiation and among 80% of infants at 48 weeks after treatment initiation.[37] 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.[38] Available data suggest that both children and adults who initiate treatment with a higher CD4 percentage or CD4 count have better immune recovery than individuals who initiate treatment with lower CD4 percentages or CD4 counts.[23,39-41] Among 1,236 children with PHIV 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%.[42] Finally, earlier age at ART initiation results in higher rates of CD4:CD8 ratio normalization and improved immunogenicity of childhood vaccines.[43-45]

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.[46-51]

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.[52] 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.[53-55] 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 both younger age and viral load at the time of ART initiation associated with lower reservoir levels.[56] In the CHER study, early ART initiation and longer duration of ART were associated with lower proviral DNA levels at 5 years of age.[57] Among adolescents with PHIV in Cameroon, lower HIV proviral DNA levels were associated with ART initiation before 1 year of age.[58] In the Early Infant Treatment Study in Botswana, 40 infants initiated ART at a median 2 days of life, with 2 infants dying within 12 to 24 weeks of treatment initiation. Low HIV reservoirs were noted among the 38 who survived to 96 weeks, even though most infants experienced periods of detectable HIV-1 RNA between 24 to 96 weeks. Low pre-ART reservoir size was predictive of preserved CD4 count and low viral reservoirs.[59] A meta-analysis of 49 studies (including some of those highlighted above) from 17 countries, which included 2,356 children and adolescents with PHIV infection, found that initiating ART before 2 months of age limited viral reservoir size as measured by HIV-1 DNA ($P = 0.054$).[60]

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.[46,61,62]

The report of prolonged remission in a child with PHIV in Mississippi generated discussion about early initiation of ART as presumptive treatment in newborns at high risk of HIV acquisition.[63,64] Five additional 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.[65] A French child was treated with ART from 3 months of age through approximately 6 years of age; in 2016, at 18.6 years of age and still off ART, HIV RNA had remained below 50 copies/mL with stable CD4 counts.[66] In the IMPAACT P1115 clinical trial, 54 children with *in utero* HIV infection initiated preemptive ART or three-drug ART prophylaxis within 48 hours of birth. Of those who maintained sustained HIV viral suppression beyond 48 weeks of ART, six met criteria to undergo analytical treatment interruption (ATI) at a median age of 5.5 years; one achieved prolonged aviremia through 80 weeks of ATI before viral rebound, and three remained virologically suppressed during ATI at >44 weeks, >48 weeks, and >60 weeks, respectively, at the time of the report.[67] Two children experienced early viral rebound at 3 and 8 weeks, respectively. While these findings hold promise for some early-treated children with HIV, the fact that only 11% of the participants were eligible for ATI highlights the need for further pediatric cure and remission research.

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 PHIV who have undergone treatment interruption, current ART has not

been shown to eradicate HIV infection because HIV persists in CD4 cells and other long-lived cells.[65,66,68,69] 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 data for antiretroviral (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[70,71] (see What to Start and Antiretroviral Management of Infants With *In Utero*, Intrapartum, or Breastfeeding Exposure to HIV). 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.[72,73] When drug concentrations are subtherapeutic—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 an individual's adherence and address potential barriers to adherence during this time (see Adherence to Antiretroviral Therapy in Children and Adolescents With HIV).

Optimizing Antiretroviral Therapy Adherence at Initiation

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 (see Adherence to Antiretroviral Therapy in Children and Adolescents With HIV). The Panel recognizes that achieving consistent adherence in children is often challenging.[74,75] Incomplete adherence leads to loss of viral control and the selection of drug-resistant mutations, but forcibly administrating ARV drugs to younger children may result in treatment aversion, which often persists into adulthood.

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, given the multiple health benefits and potential for minimal HIV viral reservoir size when treatment of initiation occurs within days of birth for infants who are diagnosed with HIV at birth. 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-naive children and adolescents with cryptococcal meningitis, tuberculous meningitis, or disseminated *Mycobacterium avium* complex disease, the Panel recommends initiation of treatment for the opportunistic infection first, before 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.

Finally, readiness for good ART adherence should be considered when preparing to initiate ART, as this is the core requirement for successful virologic control. It is important to assess and discuss issues associated with adherence with caregivers and, when developmentally appropriate, with children (see Adherence to Antiretroviral Therapy in Children and Adolescents With HIV). If it is determined that social or emotional challenges will prevent consistent medication adherence, ART initiation may be briefly delayed to address these barriers. If any 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, and ART initiation should be discussed and strongly encouraged at every visit.

References

1. Schomaker M, Leroy V, Wolfs T, et al. Optimal timing of antiretroviral treatment initiation in HIV-positive children and adolescents: a multiregional analysis from Southern Africa, West Africa and Europe. *Int J Epidemiol*. 2017;46(2):453-465. Available at: https://pubmed.ncbi.nlm.nih.gov/27342220.

2. Violari A, Cotton MF, Gibb DM, et al. Early antiretroviral therapy and mortality among HIV-infected infants. *N Engl J Med*. 2008;359(21):2233-2244. Available at: https://pubmed.ncbi.nlm.nih.gov/19020325.

3. Shiau S, Strehlau R, Technau KG, et al. Early age at start of antiretroviral therapy associated with better virologic control after initial suppression in HIV-infected infants. *AIDS*. 2017;31(3):355-364. Available at: https://pubmed.ncbi.nlm.nih.gov/27828785.

4. Massanella M, Puthanakit T, Leyre L, et al. Continuous prophylactic antiretrovirals/antiretroviral therapy since birth reduces seeding and persistence of the viral reservoir in children vertically infected with human immunodeficiency virus. *Clin Infect Dis*. 2021;73(3):427-438. Available at: https://pubmed.ncbi.nlm.nih.gov/32504081.

5. Persaud D, Ray SC, Kajdas J, et al. Slow human immunodeficiency virus type 1 evolution in viral reservoirs in infants treated with effective antiretroviral therapy. *AIDS Res Hum Retroviruses*. 2007;23(3):381-390. Available at: https://pubmed.ncbi.nlm.nih.gov/17411371.

6. Palumbo PJ, Fogel JM, Hudelson SE, et al. HIV drug resistance in adults receiving early vs. delayed antiretroviral therapy: HPTN 052. *J Acquir Immune Defic Syndr*. 2018;77(5):484-491. Available at: https://pubmed.ncbi.nlm.nih.gov/29293156.

7. Rinaldi S, Pallikkuth S, Cameron M, et al. Impact of early antiretroviral therapy initiation on HIV-specific CD4 and CD8 T cell function in perinatally infected children. *J Immunol*. 2020;204(3):540-549. Available at: https://pubmed.ncbi.nlm.nih.gov/31889024.

8. Planchais C, Hocqueloux L, Ibanez C, et al. Early antiretroviral therapy preserves functional follicular helper T and HIV-specific B cells in the gut mucosa of HIV-1-infected individuals. *J Immunol*. 2018;200(10):3519-3529. Available at: https://pubmed.ncbi.nlm.nih.gov/29632141.

9. Azzoni L, Barbour R, Papasavvas E, et al. Early ART results in greater immune reconstitution benefits in HIV-infected infants: working with data missingness in a longitudinal dataset. *PLoS One*. 2015;10(12):e0145320. Available at: https://pubmed.ncbi.nlm.nih.gov/26671450.

10. Tarancon-Diez L, Rull A, Herrero P, et al. Early antiretroviral therapy initiation effect on metabolic profile in vertically HIV-1-infected children. *J Antimicrob Chemother*. 2021;76(11):2993-3001. Available at: https://pubmed.ncbi.nlm.nih.gov/34463735.

11. Dobe IS, Mocumbi AO, Majid N, et al. Earlier antiretroviral initiation is independently associated with better arterial stiffness in children living with perinatally acquired HIV with sustained viral suppression in Mozambique. *South Afr J HIV Med*. 2021;22(1):1282. Available at: https://pubmed.ncbi.nlm.nih.gov/34858652.

12. Kay A, Mendez-Reyes J, Devezin T, et al. Optimal timing of antiretroviral therapy initiation in children and adolescents with human immunodeficiency virus-associated pulmonary tuberculosis. *Clin Infect Dis*. 2023;76(1):10-17. Available at: https://pubmed.ncbi.nlm.nih.gov/36097966.

13. World Health Organization. Updated recommendations on HIV prevention, infant diagnosis, antiretroviral initiation and monitoring. Geneva, Switzerland. 2021. Available at: https://www.who.int/publications/i/item/9789240022232.

14. Centers for Disease Control and Prevention. Revised surveillance case definition for HIV infection—United States, 2014. *MMWR Recomm Rep*. 2014;63(RR-03):1-10. Available at: https://pubmed.ncbi.nlm.nih.gov/24717910.

15. Centers for Disease Control and Prevention. 1994 revised classification system for human immunodeficiency virus infection in children less than 13 years of age. *MMWR*. 1994;43(RR-12):1-10. Available at: https://www.cdc.gov/mmwr/preview/mmwrhtml/00032890.htm.

16. Goetghebuer T, Le Chenadec J, Haelterman E, et al. Short- and long-term immunological and virological outcome in HIV-infected infants according to the age at antiretroviral treatment initiation. *Clin Infect Dis*. 2012;54(6):878-881. Available at: https://pubmed.ncbi.nlm.nih.gov/22198788.

17. Shiau S, Arpadi S, Strehlau R, et al. Initiation of antiretroviral therapy before 6 months of age is associated with faster growth recovery in South African children perinatally infected with human immunodeficiency virus. *J Pediatr*. 2013;162(6):1138-1145 e1132. Available at: https://pubmed.ncbi.nlm.nih.gov/23312691.

18. Iyun V, Technau KG, Eley B, et al. Earlier antiretroviral therapy initiation and decreasing mortality among HIV-infected infants initiating antiretroviral therapy within 3 months of age in South Africa, 2006–2017. *Pediatr Infect Dis J*. 2020;39(2):127-133. Available at: https://pubmed.ncbi.nlm.nih.gov/31725119.

19. Tagarro A, Dominguez Rodriguez S, Violari A, et al. Poor outcome in early treated HIV perinatally infected infants in Africa. Abstract 806. Presented at: Conference on Retroviruses and Opportunistic Infections. 2020. Boston, MA. Available at: https://www.croiconference.org/abstract/poor-outcome-in-early-treated-hiv-perinatally-infected-infants-in-africa.

20. Anderson K, Iyun V, Eley BS, et al. Hospitalization among infants who initiate antiretroviral therapy before 3 months of age. *AIDS*. 2023;37(3):435-445. Available at: https://pubmed.ncbi.nlm.nih.gov/36695356.

21. Puthanakit T, Saphonn V, Ananworanich J, et al. Early versus deferred antiretroviral therapy for children older than 1 year infected with HIV (PREDICT): a multicentre, randomised, open-label trial. *Lancet Infect Dis*. 2012;12(12):933-941. Available at: https://pubmed.ncbi.nlm.nih.gov/23059199.

22. McGrath CJ, Chung MH, Richardson BA, et al. Younger age at HAART initiation is associated with more rapid growth reconstitution. *AIDS*. 2011;25(3):345-355. Available at: https://pubmed.ncbi.nlm.nih.gov/21102302.

23. Simms V, Rylance S, Bandason T, et al. CD4+ cell count recovery following initiation of HIV antiretroviral therapy in older childhood and adolescence. *AIDS*. 2018;32(14):1977-1982. Available at: https://pubmed.ncbi.nlm.nih.gov/29927784.

24. Traisathit P, Urien S, Le Coeur S, et al. Impact of antiretroviral treatment on height evolution of HIV infected children. *BMC Pediatr*. 2019;19(1):287. Available at: https://pubmed.ncbi.nlm.nih.gov/31421667.

25. Williams PL, Jesson J. Growth and pubertal development in HIV-infected adolescents. *Curr Opin HIV AIDS*. 2018;13(3):179-186. Available at: https://pubmed.ncbi.nlm.nih.gov/29432228.

26. Mwambenu B, Ramoloko V, Laubscher R, Feucht U. Growth and the pubertal growth spurt in South African adolescents living with perinatally-acquired HIV infection. *PLoS One*. 2022;17(1):e0262816. Available at: https://pubmed.ncbi.nlm.nih.gov/35077489.

27. Nguyen AN, Plotkin AL, Odumade OA, et al. Effective early antiretroviral therapy in perinatal-HIV infection reduces subsequent plasma inflammatory profile. *Pediatr Res*. 2023;94(5):1667-1674. Available at: https://pubmed.ncbi.nlm.nih.gov/37308683.

28. Attia EF, Bhatraju PK, Triplette M, et al. Endothelial activation, innate immune activation, and inflammation are associated with postbronchodilator airflow limitation and obstruction among adolescents living with HIV. *J Acquir Immune Defic Syndr*. 2020;83(3):267-277. Available at: https://pubmed.ncbi.nlm.nih.gov/32032277.

29. Githinji LN, Gray DM, Hlengwa S, et al. Longitudinal changes in spirometry in South African adolescents perinatally infected with human immunodeficiency virus who are receiving antiretroviral therapy. *Clin Infect Dis*. 2020;70(3):483-490. Available at: https://pubmed.ncbi.nlm.nih.gov/30938406.

30. Githinji LN, Gray DM, Hlengwa S, et al. Lung function in South African adolescents infected perinatally with HIV and treated long-term with antiretroviral therapy. *Ann Am Thorac Soc*. 2017;14(5):722-729. Available at: https://pubmed.ncbi.nlm.nih.gov/28248548.

31. Gie A, Davies C, Vaida F, et al. Lung function tracking in children with perinatally acquired HIV following early antiretroviral therapy initiation. *Thorax*. 2023;78(12):1233-1239. Available at: https://pubmed.ncbi.nlm.nih.gov/37479478.

32. Laughton B, Cornell M, Grove D, et al. Early antiretroviral therapy improves neurodevelopmental outcomes in infants. *AIDS*. 2012;26(13):1685-1690. Available at: https://pubmed.ncbi.nlm.nih.gov/22614886.

33. Jantarabenjakul W, Chonchaiya W, Puthanakit T, et al. Low risk of neurodevelopmental impairment among perinatally acquired HIV-infected preschool children who received early antiretroviral treatment in Thailand. *J Int AIDS Soc*. 2019;22(4):e25278. Available at: https://pubmed.ncbi.nlm.nih.gov/30990969.

34. Benki-Nugent S, Tamasha N, Mueni A, et al. Early antiretroviral therapy reduces severity but does not eliminate neurodevelopmental compromise in children with HIV. *J Acquir Immune Defic Syndr*. 2023;93(1):7-14. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36693138.

35. Laughton B, Naidoo S, Dobbels E, et al. Neurodevelopment at 11 months after starting antiretroviral therapy within 3 weeks of life. *South Afr J HIV Med*. 2019;20(1):1008. Available at: https://pubmed.ncbi.nlm.nih.gov/31745434.

36. Shiau S, Brummel SS, Kennedy EM, et al. Longitudinal changes in epigenetic age in youth with perinatally acquired HIV and youth who are perinatally HIV-exposed uninfected. *AIDS*. 2021;35(5):811-819. Available at: https://pubmed.ncbi.nlm.nih.gov/33587437.

37. Nelson BS, Tierney C, Persaud D, et al. Infants receiving very early antiretroviral therapy have high CD4 counts in the first year of life. *Clin Infect Dis*. 2023;76(3):e744-e747. Available at: https://pubmed.ncbi.nlm.nih.gov/36031390.

38. Garcia-Broncano P, Maddali S, Einkauf KB, et al. Early antiretroviral therapy in neonates with HIV-1 infection restricts viral reservoir size and induces a distinct innate immune profile. *Sci Transl Med*. 2019;11(520). Available at: https://pubmed.ncbi.nlm.nih.gov/31776292.

39. Picat MQ, Lewis J, Musiime V, et al. Predicting patterns of long-term CD4 reconstitution in HIV-infected children starting antiretroviral therapy in sub-Saharan Africa: a cohort-based modelling study. *PLoS Med*. 2013;10(10):e1001542. Available at: https://pubmed.ncbi.nlm.nih.gov/24204216.

40. Le T, Wright EJ, Smith DM, et al. Enhanced CD4+ T-cell recovery with earlier HIV-1 antiretroviral therapy. *N Engl J Med*. 2013;368(3):218-230. Available at: https://pubmed.ncbi.nlm.nih.gov/23323898.

41. Desmonde S, Dicko F, Koueta F, et al. Association between age at antiretroviral therapy initiation and 24-month immune response in West-African HIV-infected children. *AIDS*. 2014;28(11):1645-1655. Available at: https://pubmed.ncbi.nlm.nih.gov/24804858.

42. Patel K, Hernan MA, Williams PL, et al. Long-term effectiveness of highly active antiretroviral therapy on the survival of children and adolescents with HIV infection: a 10-year follow-up study. *Clin Infect Dis*. 2008;46(4):507-515. Available at: https://pubmed.ncbi.nlm.nih.gov/18199042.

43. Seers T, Vassallo P, Pollock K, et al. CD4:CD8 ratio in children with perinatally acquired HIV-1 infection. *HIV Med*. 2018;19(9):668-672. Available at: https://pubmed.ncbi.nlm.nih.gov/30084150.

44. Moonsamy S, Suchard M, Madhi SA. Effect of HIV-exposure and timing of anti-retroviral treatment on immunogenicity of trivalent live-attenuated polio vaccine in infants. *PLoS One*. 2019;14(4):e0215079. Available at: https://pubmed.ncbi.nlm.nih.gov/31002702.

45. Pensieroso S, Cagigi A, Palma P, et al. Timing of HAART defines the integrity of memory B cells and the longevity of humoral responses in HIV-1 vertically-infected children. *Proc Natl Acad Sci U S A*. 2009;106(19):7939-7944. Available at: https://pubmed.ncbi.nlm.nih.gov/19416836.

46. Ananworanich J, Puthanakit T, Suntarattiwong P, et al. Reduced markers of HIV persistence and restricted HIV-specific immune responses after early antiretroviral therapy in children. *AIDS*. 2014;28(7):1015-1020. Available at: https://pubmed.ncbi.nlm.nih.gov/24384692.

47. Payne H, Mkhize N, Otwombe K, et al. Reactivity of routine HIV antibody tests in children who initiated antiretroviral therapy in early infancy as part of the children with HIV early antiretroviral therapy (CHER) trial: a retrospective analysis. *Lancet Infect Dis*. 2015;15(7):803-809. Available at: https://pubmed.ncbi.nlm.nih.gov/26043884.

48. Kuhn L, Schramm DB, Shiau S, et al. Young age at start of antiretroviral therapy and negative HIV antibody results in HIV-infected children when suppressed. *AIDS*. 2015;29(9):1053-1060. Available at: https://pubmed.ncbi.nlm.nih.gov/25870988.

49. Butler KM, Gavin P, Coughlan S, et al. Rapid viral rebound after 4 years of suppressive therapy in a seronegative HIV-1 infected infant treated from birth. *Pediatr Infect Dis J*. 2015;34(3):e48-51. Available at: https://pubmed.ncbi.nlm.nih.gov/25742088.

50. Wamalwa D, Benki-Nugent S, Langat A, et al. Treatment interruption after 2-year antiretroviral treatment initiated during acute/early HIV in infancy. *AIDS*. 2016;30(15):2303-2313. Available at: https://pubmed.ncbi.nlm.nih.gov/27177316.

51. Veldsman KA, Laughton B, Janse van Rensburg A, et al. Viral suppression is associated with HIV-antibody level and HIV-1 DNA detectability in early treated children at 2 years of age. *AIDS*. 2021;35(8):1247-1252. Available at: https://pubmed.ncbi.nlm.nih.gov/34076614.

52. Dominguez-Rodriguez S, Tagarro A, Palma P, et al. Reduced time to suppression among neonates with HIV initiating antiretroviral therapy within 7 days after birth. *J Acquir Immune Defic Syndr*. 2019;82(5):483-490. Available at: https://pubmed.ncbi.nlm.nih.gov/31714427.

53. McManus M, Mick E, Hudson R, et al. Early combination antiretroviral therapy limits exposure to HIV-1 replication and cell-associated HIV-1 DNA levels in infants. *PLoS One*. 2016;11(4):e0154391. Available at: https://pubmed.ncbi.nlm.nih.gov/27104621.

54. Martinez-Bonet M, Puertas MC, Fortuny C, et al. Establishment and replenishment of the viral reservoir in perinatally HIV-1-infected children initiating very early antiretroviral therapy. *Clin Infect Dis*. 2015;61(7):1169-1178. Available at: https://pubmed.ncbi.nlm.nih.gov/26063721.

55. van Zyl GU, Bedison MA, van Rensburg AJ, et al. Early antiretroviral therapy in South African children reduces HIV-1-infected cells and cell-associated HIV-1 RNA in blood mononuclear cells. *J Infect Dis*. 2015;212(1):39-43. Available at: https://pubmed.ncbi.nlm.nih.gov/25538273.

56. Foster C, Dominguez-Rodriguez S, Tagarro A, et al. The CARMA study: early infant antiretroviral therapy-timing impacts on total HIV-1 DNA quantitation 12 years later. *J Pediatric Infect Dis Soc*. 2021;10(3):295-301. Available at: https://pubmed.ncbi.nlm.nih.gov/32678875.

57. Payne H, Chan MK, Watters SA, et al. Early ART-initiation and longer ART duration reduces HIV-1 proviral DNA levels in children from the CHER trial. *AIDS Res Ther*. 2021;18(1):63. Available at: https://pubmed.ncbi.nlm.nih.gov/34587974.

58. Ka'e AC, Santoro MM, Duca L, et al. Evaluation of HIV-1 DNA levels among adolescents living with perinatally acquired HIV-1 in Yaounde, Cameroon: a contribution to paediatric HIV cure research in Sub-Saharan Africa. *J Virus Erad*. 2024;10(1):100367. Available at: https://pubmed.ncbi.nlm.nih.gov/38601701.

59. Ajibola G, Maswabi K, Hughes MD, et al. Brief report: long-term clinical, immunologic, and virologic outcomes among early-treated children with HIV in Botswana: a nonrandomized controlled clinical trial. *J Acquir Immune Defic Syndr*. 2023;92(5):393-398. Available at: https://pubmed.ncbi.nlm.nih.gov/36729692.

60. Ka'e AC, Santoro MM, Nanfack A, et al. Characterization of HIV-1 reservoirs in children and adolescents: a systematic review and meta-analysis toward pediatric HIV cure. *J Pediatr*. 2024;267:113919. Available at: https://pubmed.ncbi.nlm.nih.gov/38237889.

61. Bitnun A, Samson L, Chun TW, et al. Early initiation of combination antiretroviral therapy in HIV-1-infected newborns can achieve sustained virologic suppression with low frequency of CD4+ T cells carrying HIV in peripheral blood. *Clin Infect Dis*. 2014;59(7):1012-1019. Available at: https://pubmed.ncbi.nlm.nih.gov/24917662.

62. Persaud D, Bryson Y, Nelson BS, et al. HIV-1 reservoir size after neonatal antiretroviral therapy and the potential to evaluate antiretroviral-therapy-free remission (IMPAACT P1115): a phase 1/2 proof-of-concept study. *Lancet HIV*. 2024;11(1):e20-e30. Available at: https://pubmed.ncbi.nlm.nih.gov/38061376.

63. Persaud D, Gay H, Ziemniak C, et al. Absence of detectable HIV-1 viremia after treatment cessation in an infant. *N Engl J Med*. 2013;369(19):1828-1835. Available at: https://pubmed.ncbi.nlm.nih.gov/24152233.

64. Luzuriaga K, Gay H, Ziemniak C, et al. Viremic relapse after HIV-1 remission in a perinatally infected child. *N Engl J Med*. 2015;372(8):786-788. Available at: https://pubmed.ncbi.nlm.nih.gov/25693029.

65. Violari A, Cotton MF, Kuhn L, et al. A child with perinatal HIV infection and long-term sustained virological control following antiretroviral treatment cessation. *Nat Commun*. 2019;10(1):412. Available at: https://pubmed.ncbi.nlm.nih.gov/30679439.

66. Frange P, Faye A, Avettand-Fenoel V, et al. HIV-1 virological remission lasting more than 12 years after interruption of early antiretroviral therapy in a perinatally infected teenager enrolled in the French ANRS EPF-CO10 paediatric cohort: a case report. *Lancet HIV*. 2016;3(1):e49-54. Available at: https://pubmed.ncbi.nlm.nih.gov/26762993.

67. Persaud D, Coletti A, Nelson BS, et al. ART-free HIV-1 remission in very early treated children: Results from IMPAACT P1115. Presented at: Conference on Retroviruses and Opportunistic Infections. 2024. Denver, CO. Available at: https://www.croiconference.org/abstract/art-free-hiv-1-remission-in-very-early-treated-children-results-from-impaact-p1115.

68. Shiau S, Abrams EJ, Arpadi SM, Kuhn L. Early antiretroviral therapy in HIV-infected infants: can it lead to HIV remission? *Lancet HIV*. 2018;5(5):e250-e258. Available at: https://pubmed.ncbi.nlm.nih.gov/29739699.

69. Koofhethile CK, Moyo S, Kotokwe KP, et al. Undetectable proviral deoxyribonucleic acid in an adolescent perinatally infected with human immunodeficiency virus-1C and on long-term antiretroviral therapy resulted in viral rebound following antiretroviral therapy termination: a case report with implications for clinical care. *Medicine (Baltimore)*. 2019;98(47):e18014. Available at: https://pubmed.ncbi.nlm.nih.gov/31764816.

70. Cotton MF, Holgate S, Nelson A, et al. The last and first frontier—emerging challenges for HIV treatment and prevention in the first week of life with emphasis on premature and low birth weight infants. *J Int AIDS Soc*. 2015;18(Suppl 6):20271. Available at: https://pubmed.ncbi.nlm.nih.gov/26639118.

71. Clarke DF, Penazzato M, Capparelli E, et al. Prevention and treatment of HIV infection in neonates: evidence base for existing WHO dosing recommendations and implementation considerations. *Expert Rev Clin Pharmacol*. 2018;11(1):83-93. Available at: https://pubmed.ncbi.nlm.nih.gov/29039686.

72. Bekker A, Capparelli EV, Violari A, et al. Abacavir dosing in neonates from birth to 3 months of life: a population pharmacokinetic modelling and simulation study. *Lancet HIV*. 2022;9(1):e24-e31. Available at: https://pubmed.ncbi.nlm.nih.gov/34883066.

73. Chadwick EG, Yogev R, Alvero CG, et al. Long-term outcomes for HIV-infected infants less than 6 months of age at initiation of lopinavir/ritonavir combination antiretroviral therapy. *AIDS*. 2011;25(5):643-649. Available at: https://pubmed.ncbi.nlm.nih.gov/21297419.

74. Hazra R, Siberry GK, Mofenson LM. Growing up with HIV: children, adolescents, and young adults with perinatally acquired HIV infection. *Annu Rev Med*. 2010;61:169-185. Available at: https://pubmed.ncbi.nlm.nih.gov/19622036.

75. Simoni JM, Montgomery A, Martin E, et al. Adherence to antiretroviral therapy for pediatric HIV infection: a qualitative systematic review with recommendations for research and clinical management. *Pediatrics*. 2007;119(6):e1371-1383. Available at: https://pubmed.ncbi.nlm.nih.gov/17533177.