

When to Initiate Therapy in Antiretroviral-Naive Children

Updated: Apr. 11, 2022

Reviewed: Apr. 11, 2022

Panel's Recommendations
<ul style="list-style-type: none">• Antiretroviral therapy (ART) should be initiated in all infants and children with HIV infection (AI for children aged <3 months, AI* for older children).<ul style="list-style-type: none">○ 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.• 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).
<p>Rating of Recommendations: A = Strong; B = Moderate; C = Optional</p> <p>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</p> <p>[†]Studies that include children or children/adolescents, but not studies limited to post-pubertal 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. 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.⁴⁻⁸ Ongoing viral replication may be associated with persistent inflammation and the development of cardiovascular, kidney, and liver disease and malignancy; studies in adults suggest that early control of viral replication may reduce the risk of these non-AIDS complications.⁹⁻¹³

In addition to the health benefits of rapid treatment initiation, which is defined as therapy that is initiated immediately or within days of HIV diagnosis, 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.¹⁴ Initiation of therapy at higher CD4 counts has been associated with the presence of fewer drug-resistant mutations at virologic failure in adults.¹⁵ Early therapy also preserves immune function and prevents clinical disease progression.¹⁶⁻¹⁸

Survival and Health Benefits Associated with Early Initiation of ART

The Children with **HIV** Early Antiretroviral Therapy (CHER) trial was a randomized clinical trial in South Africa that initiated triple-drug ART in asymptomatic infants aged 6 to 12 weeks with perinatally acquired HIV and normal CD4 percentages (>25%). Immediate initiation of ART resulted in a 75% reduction in early mortality among these infants, compared with delaying treatment until the infants met clinical or immune criteria.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 they also had improved growth compared with those who started treatment later.¹⁹⁻²²

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, a general trend toward lower mortality and better growth with earlier ART initiation was reported in an evaluation of observational data from 20,756 ART-naive children aged 1 year to 16 years at enrollment from 19 cohorts in Europe, Southern Africa, and West Africa.¹ Children aged <10 years at enrollment had lower mortality and higher mean height-for-age z score after 5 years of follow-up among participants who initiated ART immediately than those who delayed treatment until their CD4 counts decreased to <350 cells/mm³. The multicenter, open-label Pediatric Randomised Early versus Deferred Initiation in Cambodia and Thailand (PREDICT) trial 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%; the study reported better height gain among children who started ART immediately.²³ Similarly, other studies have reported an association between younger age at initiation of ART and more rapid growth reconstitution.^{20,24-26} Studies conducted in and outside the United States have reported an association between delayed ART initiation and delay of pubertal development and menarche.²⁷⁻²⁹ In a study of Zimbabwean children (median age 11 years), earlier ART initiation and improved nutrition were positively associated with improved lung function.³⁰ 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.³¹

Neurodevelopmental Benefits Associated with Early Initiation of ART

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.³² 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.³³ 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.³⁴

Immune Benefits Associated with Early Initiation of ART

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.¹⁸ 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.⁷ Among two cohorts of South African infants with HIV, those who initiated ART at ages <6 months had better sustained viral control after achieving suppression than infants who started ART between 6 and 24 months.³ 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.^{25,35-37} 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%.³⁸ Finally, earlier age at ART initiation results in higher rates of CD4:CD8 ratio normalization and improved immunogenicity of childhood vaccines.³⁹⁻⁴¹

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.⁴²⁻⁴⁶

Viral Suppression and Viral Reservoirs with Early Initiation of ART

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.⁴⁷ Similarly, in a European and Thai cohort of infants with perinatal HIV acquisition and treatment initiation <6 months of age, multivariable analysis showed that younger age at ART initiation (adjusted hazard ratio: 0.84 [95% CI, 0.78–0.91] per month older) was found to be a predictor of faster virological suppression.⁴⁸ Other studies have reported that early treatment of infants with perinatally acquired HIV **is also** associated with reduced size of viral reservoirs.⁴⁹ For example, several 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 (as measured by peripheral blood mononuclear cell [PBMC] HIV DNA levels) after 1 year and 4 years of ART significantly correlated with the age at ART initiation and the age at viral control.⁵⁰⁻⁵² Among children in the Early-treated Perinatally HIV-infected individuals: Improving Children's Actual Life with Novel Immunotherapeutic Strategies (EPIICAL) Consortium who initiated ART at a median of 2.3 (interquartile range [IQR] 1.2–4.1) months of age, earlier initiation was associated with lower viral reservoir size, with a 1-month delay in ART initiation associated with a 13% increase in HIV-1 DNA.⁵ In addition, 27 children (also in the EPIICAL cohort) who initiated ART before 2 years of age and maintained a viral load <50 copies/mL for more than 5 years had reduced total HIV-1 DNA levels measured at a median of 12 years after treatment initiation (IQR 7.3–15.4), with younger age and viral load at the time of ART initiation each associated with lower reservoir levels.⁵³ Finally, among 11 infants in the CHER trial who initiated ART between 2.0 and 11.1 months of age and maintained sustained viral suppression, proviral amplification and sequencing of DNA from PBMCs obtained 6 and 9 years after treatment initiation detected only seven (1%) proviral replication competent sequences among three children who initiated treatment after 2.3 months of age, whereas no replication competent proviral sequences were detected in four children who initiated treatment prior to 2.3 months of age.⁵⁴ A study of 145 early-treated infants from South Africa⁴ found that the risk of viral rebound to >50 copies/mL was twofold higher ($P = 0.0006$) in the first 36 months after treatment initiation for infants with baseline HIV DNA reservoir levels >55 copies/10⁶ cells than for infants with HIV DNA reservoir levels ≤55 copies/10⁶ cells.

These findings may indicate that initiating ART soon after an infant acquires HIV can limit the size of the HIV viral reservoir, and that smaller reservoirs 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, near-complete control of viral replication has been reported in infants who initiated ART early and who had sustained control of plasma viremia.^{42,55}

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. This newborn, born to an ART-naive mother, was treated with a three-drug antiretroviral (ARV) regimen at age 30 hours, which was continued following diagnostic testing that confirmed HIV infection. ART was given through age 18 months when the parent discontinued the child's treatment. Intensive follow-up virologic evaluations were negative until 27 months after ART discontinuation—when the plasma viral load rebounded to 16,750 copies/mL—confirmed with repeat testing. ART was restarted with rapid achievement of viral suppression.^{56,57} A second child from the CHER study with HIV-1 viral load of >750,000 copies/mL at 39 days of life was randomized to ART initiation at 61 days of age for 40 weeks. As of 2019, at the age of 9.5 years, the child remains off ART and HIV-1 is detectable only at very low levels (plasma RNA 6.6 copies/mL), and no replication competent virus is detectable.⁵⁸

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 ARV regimens have not been shown to eradicate HIV infection, because HIV persists in CD4 cells and other long-lived cells.⁵⁸⁻⁶¹ 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^{62,63} (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.^{64,65} 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 Living with HIV](#)).

Summary

Multiple studies have reported that early ART initiation is associated with immune, growth, and neurodevelopmental benefits. In addition, early ART initiation may limit the formation of the viral reservoir. 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. 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, it is worth noting that treatment of full-term infants aged ≤2 weeks and preterm infants is complex due to limited PK data and appropriate dosing of ARV drugs in this age group; this is an area of active investigation (see [Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection](#)).⁶³ In ART-naive children and adolescents with tuberculosis or cryptococcal meningitis, the [Panel recommends initiation of treatment for the opportunistic infection first](#), ahead of ART initiation, with ART initiated within 2 to 8 weeks thereafter. However, appropriate timing of ART initiation in these cases should be discussed with a pediatric HIV specialist.

While ART is being initiated, 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.^{66,67} 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. The need for lifelong therapy also can lead to treatment fatigue, which occurs during adolescence among many children with perinatally acquired HIV.⁶⁸

The Panel believes the benefits of early ART initiation outweigh the potential risks and recommends rapid initiation of ART in all children with HIV, regardless of clinical, immunologic, or virologic status. However, individual clinical and/or psychosocial factors may lead patients, caregivers, and providers to make a collaborative decision to defer ART. 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,⁶⁹ and the presence of HIV-related signs and symptoms⁷⁰—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 in whom treatment has been deferred when—

- HIV RNA levels increase,
- CD4 count or percentage values decline (e.g., approaching Centers for Disease Control and Prevention Stage 2 or 3),⁶⁹
- The child develops new HIV-related clinical symptoms,⁷⁰ or
- The ability of a caregiver and child to adhere to the prescribed regimen improves.

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://www.ncbi.nlm.nih.gov/pubmed/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: <http://www.ncbi.nlm.nih.gov/pubmed/19020325>.
3. Shiao 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://www.ncbi.nlm.nih.gov/pubmed/27828785>.
4. Kuhn L, Paximadis M, Da Costa Dias B, et al. Age at antiretroviral therapy initiation and cell-associated HIV-1 DNA levels in HIV-1-infected children. *PLoS One*. 2018;13(4):e0195514. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29649264>.
5. Tagarro A, Chan M, Zangari P, et al. Early and highly suppressive antiretroviral therapy are main factors associated with low viral reservoir in European perinatally HIV-infected children. *J Acquir Immune Defic Syndr*. 2018;79(2):269-276. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30211778>.
6. Veldsman KA, Janse van Rensburg A, Isaacs S, et al. HIV-1 DNA decay is faster in children who initiate ART shortly after birth than later. *J Int AIDS Soc*. 2019;22(8):e25368. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31441231>.
7. 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://www.ncbi.nlm.nih.gov/pubmed/31776292>.
8. Massanella M, Puthanakit T, Leyre L, et al. Continuous prophylactic ARV/ART since birth reduces seeding and persistence of the viral reservoir in vertically HIV-infected children. *Clin Infect Dis*. 2020;ciaa718. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32504081>.
9. Longenecker CT, Triant VA. Initiation of antiretroviral therapy at high CD4 cell counts: does it reduce the risk of cardiovascular disease? *Curr Opin HIV AIDS*. 2014;9(1):54-62. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24275676>.
10. Ghislain M, Bastard JP, Meyer L, et al. Late antiretroviral therapy (ART) Initiation is associated with long-term persistence of systemic inflammation and metabolic abnormalities. *PLoS One*. 2015;10(12):e0144317. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26636578>.
11. Achhra AC, Mocroft A, Ross M, et al. Impact of early versus deferred antiretroviral therapy on estimated glomerular filtration rate in HIV-positive individuals in the START trial. *Int J Antimicrob Agents*. 2017;50(3):453-460. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28668686>.

12. Lundgren JD, Borges AH, Neaton JD. Serious non-AIDS conditions in HIV: benefit of early ART. *Curr HIV/AIDS Rep*. 2018;15(2):162-171. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29504063>.
13. Dharan NJ, Neuhaus J, Rockstroh JK, et al. Benefit of early versus deferred antiretroviral therapy on progression of liver fibrosis among people with HIV in the START randomized trial. *Hepatology*. 2019;69(3):1135-1150. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30298608>.
14. 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://www.ncbi.nlm.nih.gov/pubmed/17411371>.
15. 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://www.ncbi.nlm.nih.gov/pubmed/29293156>.
16. 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://www.ncbi.nlm.nih.gov/pubmed/31889024>.
17. 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://www.ncbi.nlm.nih.gov/pubmed/29632141>.
18. Azzoni L, Barbour R, Pappasavvas 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>.
19. 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: <http://www.ncbi.nlm.nih.gov/pubmed/22198788>.
20. Shiao 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: <http://www.ncbi.nlm.nih.gov/pubmed/23312691>.
21. 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://www.ncbi.nlm.nih.gov/pubmed/31725119>.
22. 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, Massachusetts. Available at: <https://www.croiconference.org/abstract/poor-outcome-in-early-treated-hiv-perinatally-infected-infants-in-africa>.

23. 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: <http://www.ncbi.nlm.nih.gov/pubmed/23059199>.
24. McGrath CJ, Chung MH, Richardson BA, Benki-Nugent S, Warui D, John-Stewart GC. Younger age at HAART initiation is associated with more rapid growth reconstitution. *AIDS.* 2011;25(3):345-355. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21102302>.
25. 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://www.ncbi.nlm.nih.gov/pubmed/29927784>.
26. 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://www.ncbi.nlm.nih.gov/pubmed/31421667>.
27. Szubert AJ, Musiime V, Bwakura-Dangarembizi M, et al. Pubertal development in HIV-infected African children on first-line antiretroviral therapy. *AIDS.* 2015;29(5):609-618. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25710288>.
28. Williams PL, Jesson J. Growth and pubertal development in HIV-infected adolescents. *Curr Opin HIV AIDS.* 2018;13(3):179-186. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29432228>.
29. Williams PL, Abzug MJ, Jacobson DL, et al. Pubertal onset in children with perinatal HIV infection in the era of combination antiretroviral treatment. *AIDS.* 2013;27(12):1959-1970. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24145244>.
30. Rylance S, Rylance J, McHugh G, et al. Effect of antiretroviral therapy on longitudinal lung function trends in older children and adolescents with HIV-infection. *PLoS One.* 2019;14(3):e0213556. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30897116>.
31. 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://www.ncbi.nlm.nih.gov/pubmed/33587437>.
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: <http://www.ncbi.nlm.nih.gov/pubmed/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://www.ncbi.nlm.nih.gov/pubmed/30990969>.
34. 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://www.ncbi.nlm.nih.gov/pubmed/31745434>.
35. 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: <http://www.ncbi.nlm.nih.gov/pubmed/24204216>.
36. 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://www.ncbi.nlm.nih.gov/pubmed/23323898>.
 37. 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://www.ncbi.nlm.nih.gov/pubmed/24804858>.
 38. 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: <http://www.ncbi.nlm.nih.gov/pubmed/18199042>.
 39. Seers T, Vassallo P, Pollock K, Thornhill JP, Fidler S, Foster C. CD4:CD8 ratio in children with perinatally acquired HIV-1 infection. *HIV Med.* 2018;19(9):668-672. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30084150>.
 40. 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://www.ncbi.nlm.nih.gov/pubmed/31002702>.
 41. 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: <http://www.ncbi.nlm.nih.gov/pubmed/19416836>.
 42. 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: <http://www.ncbi.nlm.nih.gov/pubmed/24384692>.
 43. Payne H, Mkhize N, Otvombe 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: <http://www.ncbi.nlm.nih.gov/pubmed/26043884>.
 44. Kuhn L, Schramm DB, Shiao 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: <http://www.ncbi.nlm.nih.gov/pubmed/25870988>.
 45. 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: <http://www.ncbi.nlm.nih.gov/pubmed/25742088>.
 46. 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: <http://www.ncbi.nlm.nih.gov/pubmed/27177316>.
 47. 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://www.ncbi.nlm.nih.gov/pubmed/31714427>.
48. European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC), Early-treated Perinatally HIV-infected Individuals: Improving Children's Actual Life with Novel Immunotherapeutic Strategies (EPIICAL) Study Groups. Predictors of faster virological suppression in early treated infants with perinatal HIV from Europe and Thailand. *AIDS.* 2019;33(7):1155-1165. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30741823>.
 49. Persaud D, Patel K, Karalius B, et al. Influence of age at virologic control on peripheral blood human immunodeficiency virus reservoir size and serostatus in perinatally infected adolescents. *JAMA Pediatr.* 2014;168(12):1138-1146. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25286283>.
 50. 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: <http://www.ncbi.nlm.nih.gov/pubmed/27104621>.
 51. 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: <http://www.ncbi.nlm.nih.gov/pubmed/26063721>.
 52. van Zyl GU, Bedison MA, van Rensburg AJ, Laughton B, Cotton MF, Mellors JW. 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: <http://www.ncbi.nlm.nih.gov/pubmed/25538273>.
 53. 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://www.ncbi.nlm.nih.gov/pubmed/32678875>.
 54. Katusiime MG, Halvas EK, Wright I, et al. Intact HIV proviruses persist in children seven to nine years after initiation of antiretroviral therapy in the first year of life. *J Virol.* 2020;94(4). Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31776265>.
 55. 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: <http://www.ncbi.nlm.nih.gov/pubmed/24917662>.
 56. 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: <http://www.ncbi.nlm.nih.gov/pubmed/24152233>.
 57. 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: <http://www.ncbi.nlm.nih.gov/pubmed/25693029>.

58. 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://www.ncbi.nlm.nih.gov/pubmed/30679439>.
59. 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://www.ncbi.nlm.nih.gov/pubmed/26762993>.
60. 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://www.ncbi.nlm.nih.gov/pubmed/29739699>.
61. 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://www.ncbi.nlm.nih.gov/pubmed/31764816>.
62. Cotton MF, Holgate S, Nelson A, Rabie H, Wedderburn C, Mirochnick M. 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: <http://www.ncbi.nlm.nih.gov/pubmed/26639118>.
63. 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://www.ncbi.nlm.nih.gov/pubmed/29039686>.
64. Bekker A, Capparelli EV, Violari A, et al. Abacavir dosing in neonates from birth: a pharmacokinetic analysis. Presented at: Conference on Retroviruses and Opportunistic Infections; 2021. Virtual Conference. Available at: <https://www.croiconference.org/abstract/abacavir-dosing-in-neonates-from-birth-a-pharmacokinetic-analysis>.
65. 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: <http://www.ncbi.nlm.nih.gov/pubmed/21297419>.
66. 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: <http://www.ncbi.nlm.nih.gov/pubmed/19622036>.
67. Simoni JM, Montgomery A, Martin E, New M, Demas PA, Rana S. 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://www.ncbi.nlm.nih.gov/pubmed/17533177>.
68. Kacanek D, Huo Y, Malee K, et al. Nonadherence and unsuppressed viral load across adolescence among U.S. youth with perinatally acquired HIV. *AIDS*. 2019;33(12):1923-1934. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31274538>.

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