When to Initiate Therapy in Antiretroviral-Naive Children

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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).
  - Rapid ART initiation (defined as initiating ART immediately or within days of 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)**.

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 post-pubertal 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. Multiple studies have shown a benefit to early antiretroviral therapy (ART) initiation. In children aged <1 year, the health and survival benefit of immediate ART initiation has been clearly demonstrated in the Children with HIV Early Antiretroviral Therapy (CHER) trial.[1] In addition, in a study of two cohorts of infants with HIV in Johannesburg, South Africa, infants who initiated ART at ages <6 months had better sustained viral control after achieving suppression than infants who started therapy between the ages of 6 and 24 months.[2] Several studies have reported that treatment initiation within the first year of life also is associated with reduced size of viral reservoirs.[3–7] An observational study of more than 20,000 children aged 1 year to 16 years from 19 cohorts in Europe, Southern Africa, and West Africa[8] found that immediate ART was associated with lower mortality and better growth in children aged <10 years when compared with ART that was delayed until CD4 T lymphocyte (CD4) cell count decreased to <350 cells/mm³. Ongoing viral replication may be associated with persistent inflammation and the development of cardiovascular, kidney, and liver disease and malignancy; studies in adults also suggest that early control of 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 diagnosis, treatment initiation in young infants with HIV during the early stages of HIV 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-resistance 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 Treatment Initiation

The 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.[1] Most of the infant deaths in the delayed treatment arm occurred during the first 6 months after study entry. Consistent with the CHER trial, data from a number of observational studies in the United States, Europe, and South Africa demonstrated that infants who receive

early treatment are less likely to progress to AIDS or death, and they also have improved growth compared with those who start therapy later.[19–22]

Older children with the Centers for Disease Control and Prevention (CDC) Clinical Stage 3–defining opportunistic infections (OIs) (see Revised Surveillance Case Definition for HIV Infection and Table 6) are at high risk of disease progression and death. 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; 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.[8] 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 among those who delayed treatment until their CD4 counts decreased to <350 cells/mm^3. 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 therapy 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]

Neurodevelopmental Benefits Associated with Early Treatment Initiation

A CHER trial substudy found that infants who initiated treatment early had significantly better gross motor and neurodevelopmental profiles than those whose therapy was deferred.[31] In a study of Kenyan infants with HIV who initiated treatment before 6 months of age and who were on treatment for at least 6 months, infants with an effective response to treatment had better gross motor and language attainment than infants who did not meet the parameters for effective treatment response.[32] In this study, an effective response to treatment was defined as HIV RNA <1,000 copies/mL, CD4 percentages ≥25%, and weight-for-age z-scores ≥−2 at 9 months of age. In a cohort from Thailand, the prevalence of global developmental impairment was 22% (95% 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 treatment within 21 days of life (median 6 days) found that early neurodevelopmental scores for these infants were within the normal range.[34]

Immune Benefits Associated with Early Treatment Initiation

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.[6] Shiau et al. reported that, 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 therapy between 6 and 24 months.[2] 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 treatment 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 Treatment Initiation

Early initiation of ART within the first 7 days of life, compared to 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, younger age at ART initiation was found to be a predictor of faster virological suppression in a European and Thai cohort of infants with perinatal HIV acquisition and treatment initiation at a median of 2.9 months of age (interquartile range [IQR] 1.4–4.1 months).[48] Several studies have reported that early treatment of infants with perinatally acquired HIV also is associated with reduced size of viral reservoirs.[3,4,6,7,49] Many studies that compared the size of viral reservoirs in children who initiated ART before age 12 weeks to those who initiated ART at ≥12 weeks to ≤2 years of age have 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] Kuhn et al. found that initiating ART at a younger age was associated with lower levels of PBMC-associated HIV DNA. Furthermore, the authors reported that 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 HIV DNA reservoir levels >55 copies/10^6 cells than for infants with HIV DNA reservoir levels ≤55 copies/10^6 cells.[3] Similarly, in a cross-sectional substudy of 144 youth with perinatally acquired HIV and long-term viral suppression in the Pediatric HIV/AIDS Cohort Study (PHACS)/Adolescent Master Protocol (AMP) study, a lower proviral reservoir was found in those who achieved virologic control at <1 year of age than in those who achieved virologic control at 1 to 5 years of age or >5 years of age (4.2 vs. 19.4 vs. 70.7 copies/million PBMCs, respectively).[53]Among 61 children with perinatally acquired HIV in PHACS who achieved viral suppression at ages of <1 year versus ages between 1 and 5 years, the mean half-life of HIV DNA from the time of viral suppression was shorter in the early suppressors—5.9 years versus 18.8 years, respectively.[54] Among children in the European multicenter EPIICAL (Early-treated Perinatally HIV-infected Individuals: Improving Children's Actual Life with Novel Immunotherapeutic Strategies) study who initiated ART at a median of 2.3 [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's being associated with a 13% increase in HIV-1 DNA.[4]

These findings may indicate that initiating treatment 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 likely event for infants with HIV who are destined for life-long treatment. Furthermore, near-complete control of viral replication has been reported in infants who initiated treatment 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 a mother who did not receive antenatal or perinatal ART, 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 continued through age 18 months, and then discontinued against medical advice. Intensive follow-up evaluations showed no evidence of virologic rebound following discontinuation of ART until age 46 months (27 months after the discontinuation of ART), when the plasma viral load rebounded to 16,750 copies/mL; this viral load was confirmed with repeat testing. ART was restarted at that time.[56,57] A second child who was a participant of the CHER study with confirmed HIV-1 DNA PCR at 32 days of life and a 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 antiretroviral treatment, 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.

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 (see What to Start and Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection).[62,63] 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] 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 treatment initiation is associated with immune, growth, and neurodevelopmental benefits. In addition, early treatment 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 diagnosis) for all children who receive an HIV diagnosis. The urgency of rapid treatment 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 the limited data on the PKs 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 therapy 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 treatment 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.[65,66] 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. The need for life-long therapy also can lead to treatment fatigue, which occurs among many children with perinatally acquired HIV during adolescence.[67]

The Panel believes the benefits of early ART initiation outweigh the potential risks and recommends rapid initiation of ART in all children, 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 therapy. When making the decision to defer therapy, medical factors such as the opportunity to limit seeding of the viral reservoir in newborns, the child's HIV disease stage (see Table 5), and the presence of HIV-related signs and symptoms (see Table 6) need to be balanced against any potential barriers to rapid treatment initiation. If therapy is deferred, the health care provider should closely monitor a 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 CDC Stage 2 or 3; see Table 5),
- The child develops new HIV-related clinical symptoms (see Table 6), *or*
- The ability of a caregiver and child to adhere to the prescribed regimen improves.

Table 5. HIV Infection Stage Based on Age-Specific CD4 Count or Percentage

Stage[a]	Aged <1 Year		Aged 1 Year to <6 Years		Aged ≥6 Years	
	Cells/mm³	%	Cells/mm³	%	Cells/mm³	%
1	≥1,500	≥34	≥1,000	≥30	≥500	≥26
2	750–1,499	26–33	500–999	22–29	200–499	14–25
3	<750	<26	<500	<22	<200	<14

[a] The stage is based primarily on the CD4 count; the CD4 count takes precedence over the CD4 percentage, and the percentage is considered only when the count is missing. If a Stage 3-defining condition has been diagnosed (see Table 6), then the stage is 3 regardless of CD4 test results.

Key: CD4 = CD4 T lymphocyte

Source: Centers for Disease Control and Prevention. Revised surveillance case definition for HIV infection—United States, 2014. *MMWR* 2014;63(No. RR-3):1-10.

Table 6. HIV-Related Symptoms and Conditions (page 1 of 2)

Mildly Symptomatic
Children with two or more of the following conditions, but none of the conditions listed in the Moderately Symptomatic category, are considered mildly symptomatic:
• Lymphadenopathy (lymph nodes are ≥0.5 cm at more than two sites and/or bilateral at one site)
• Hepatomegaly
• Splenomegaly
• Dermatitis
• Parotitis
• Recurrent or persistent upper respiratory tract infection, sinusitis, or otitis media
Moderately Symptomatic
• Anemia (hemoglobin <8 g/dL [<80 g/L]), neutropenia (white blood cell count <1,000 per µL [$<1.0 \times 10^9$ per L]), and/or thrombocytopenia (platelet count $<100 \times 10^3$ per µL [$<100 \times 10^9$ per L]) persisting for ≥30 days
• Bacterial meningitis, pneumonia, or sepsis (single episode)
• Candidiasis, oropharyngeal (thrush), persisting for >2 months in children aged >6 months
• Cardiomyopathy
• CMV infection, with onset before age 1 month
• Diarrhea, recurrent or chronic
• Hepatitis
• HSV stomatitis, recurrent (more than two episodes within 1 year)
• HSV bronchitis, pneumonitis, or esophagitis with onset before age 1 month
• Herpes zoster (shingles) involving at least two distinct episodes or more than one dermatome
• Leiomyosarcoma
• Lymphoid interstitial pneumonia or pulmonary lymphoid hyperplasia complex
• Nephropathy
• Nocardiosis
• Persistent fever (lasting >1 month)
• Toxoplasmosis, onset before age 1 month
• Varicella, disseminated (complicated chickenpox)

Table 6. HIV-Related Symptoms and Conditions (page 2 of 2)

AIDS-Defining Conditions
• Bacterial infections, multiple or recurrent[a]
• Candidiasis of bronchi, trachea, or lungs
• Candidiasis of esophagus
• Cervical cancer, invasive
• Coccidioidomycosis, disseminated or extrapulmonary
• Cryptococcosis, extrapulmonary
• Cryptosporidiosis, chronic intestinal (>1 month duration)
• CMV disease (other than liver, spleen, or lymph nodes), onset at age >1 month
• CMV retinitis (with loss of vision)
• Encephalopathy attributed to HIV[b]
• HSV: chronic ulcers (>1 month duration) or bronchitis, pneumonitis, or esophagitis (onset at age >1 month)
• Histoplasmosis, disseminated or extrapulmonary
• Isosporiasis, chronic intestinal (>1 month duration)
• Kaposi sarcoma
• Lymphoma, Burkitt (or equivalent term)
• Lymphoma, immunoblastic (or equivalent term)
• Lymphoma, primary, (of brain)
• *Mycobacterium avium* complex or *Mycobacterium kansasii*, disseminated or extrapulmonary
• *Mycobacterium* tuberculosis of any site, pulmonary, disseminated, or extrapulmonary
• *Mycobacterium*, other species or unidentified species, disseminated or extrapulmonary
• Pneumocystis jirovecii (previously known as Pneumocystis carinii) pneumonia
• Pneumonia, recurrent[c]
• Progressive multifocal leukoencephalopathy
• Salmonella septicemia, recurrent
• Toxoplasmosis of brain, onset at age >1 month
• Wasting syndrome attributed to HIV[b]

[a] Only among children aged <6 years.

[b] Suggested diagnostic criteria for these illnesses, which might be particularly important for HIV encephalopathy and HIV wasting syndrome, are described in the following references:

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(No. RR-12).

Centers for Disease Control and Prevention. 1993 Revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. *MMWR*. 1992;41(No. RR-17).

[c] Only among adults, adolescents, and children aged ≥6 years.

Key: CMV = cytomegalovirus; HSV = herpes simplex virus

Modified from:

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(No. RR-12).

Centers for Disease Control and Prevention: Revised Surveillance Case Definition for HIV Infection—United States, 2014. *MMWR*. 2014;63(No. RR-3):1-10.

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