Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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When to Initiate Therapy in Antiretroviral-Naive Children (Last updated April 16, 2019; last reviewed April 16, 2019)

Panel's Recommendations

- Antiretroviral therapy (ART) should be initiated in all antiretroviral-naive infants and children with HIV infection **(AI**, **AI*** or **AII**; see Table A for details**)**.
  - Rapid ART initiation (within 1-2 weeks of diagnosis) including an expeditated discussion of adherence is recommended for all children <12 months and those with CDC Stage 3-defining conditions.
  - In other situations, sufficient time to fully assess and address issues associated with adherence should be allowed prior to ART initiation.
- Every 3 to 4 months, health care providers should closely monitor the virologic, immunologic, and clinical status of any child with HIV who has not initiated ART **(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 Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents recommends initiating antiretroviral therapy (ART) in all adults and adolescents with HIV (see the Adult and Adolescent Antiretroviral Guidelines). In addition to trials demonstrating the benefits of therapy in symptomatic adults and those with lower CD4 T lymphocyte (CD4) cell counts,[1] a randomized clinical trial has shown definitive benefits to initiating ART in asymptomatic adults with CD4 cell counts >500 cells/mm^3. The START trial randomized 4,685 antiretroviral (ARV)-naive adults with HIV (median age: 36 years) who had CD4 cell counts >500 cells/mm^3 to immediately initiate ART or to defer ART until their CD4 cell counts declined to <350 cells/mm^3 or until they developed any condition that dictated the use of ART. Forty-two patients in the early treatment group met the primary composite endpoint for the study (which included AIDS, serious non-AIDS events, or death) compared with 96 patients who met the primary endpoint in the deferred treatment group, for an overall 57% reduction in risk of serious illness or death with early treatment ($P < 0.001$). It should be noted that the absolute risk for meeting the primary endpoint was low: 3.7% of patients in the deferred arm versus 1.8% of patients in the immediate treatment arm. Sixty-eight percent of the primary endpoints occurred in patients with CD4 cell counts >500 cells/mm^3. The risks of Grade 4 events or unscheduled hospital admissions were similar between the two groups.[2]

A second analysis of the data from this study provided additional support for immediate ART initiation. Complementing the original intention-to-treat analysis, a per-protocol analysis showed that 30% of participants assigned to deferred initiation actually started ART earlier than specified by the protocol, so that the per-protocol risk of serious illness or death was 66% lower with immediate ART (or the benefit was 23% greater) than suggested by the intention-to-treat analysis.[3] Finally, when quality of life was assessed in START Trial participants using validated self-assessment tools, there were modest but significant improvements in reported quality of life among those who immediately initiated treatment versus those who deferred ART.[4] The recommendation to initiate therapy in all adults and adolescents with HIV is also based on the availability of effective ART regimens that are well tolerated, as well as evidence that effective ART reduces secondary sexual HIV transmission.[5]

The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) also recommends initiating treatment for all children with HIV, as do the European pediatric HIV experts in

the 2016 Pediatric European Network for Treatment of AIDS Treatment Guidelines.[6] However, the urgency for immediate initiation varies by age and pretreatment CD4 cell count, due to less available data regarding benefits and risks of immediate therapy in asymptomatic children with HIV than in adults. Concerns about adherence and toxicities become particularly important when therapy is initiated at an early age and will likely continue throughout the patient's life. In children aged <1 year, the health and survival benefit of immediate ART initiation has been clearly demonstrated in the CHER trial.[7] In addition, Shiau et al. reported that, 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 months and 24 months.[8] Several studies have identified that treatment initiation within the first year of life is also associated with reduced size of viral reservoirs.[9-12] Data in older children are equivocal. The PREDICT trial, which enrolled children aged 1 year to 12 years (median age: 6.4 years), found that the risk of clinical progression was extremely low in both children receiving immediate ART and children receiving delayed ART (initiation was determined by CD4 cell count); additionally, no clinical benefit of immediate ART was observed.[13] In contrast, in an observational study that included more than 20,000 children aged 1 year to 16 years from 19 cohorts in Europe, Southern Africa, and West Africa, immediate ART was associated with lower mortality and better growth in children aged <10 years when compared with ART that was delayed until CD4 cell count decreased to <350 cells/mm^3. In children aged >10 years at enrollment, immediate ART initiation had no observable effect on mortality or growth.[14]

Rapid initiation of therapy, defined as therapy that is initiated within 1 or 2 weeks of diagnosis, in the early stages of HIV infection in both children and adults could potentially control viral replication before HIV can evolve into diverse and potentially more pathogenic quasi-species. Initiation of therapy at higher CD4 cell counts has been associated with the presence of fewer drug-resistance mutations at virologic failure in adults.[15] Early therapy also preserves immune function, preventing clinical disease progression.[16,17] 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.[16,18-20]

Table A. Treatment Recommendations for Initiation of Antiretroviral Therapy in Antiretroviral-Naive Infants and Children with HIV

Age	Criteria	Recommendation
<12 Months[a]	Regardless of clinical symptoms, immune status, or viral load	Rapid initiation[b] of treatment **(AII**, but **AI** for children aged ≥6 weeks to <12 weeks**)**
1 Year to <6 Years	CDC Stage 3-defining conditions[c]	Rapid initiation[b] of treatment **(AI*)**
	CDC Stage 3 immunodeficiency:[d] CD4 cell count <500 cells/mm^3	
	Moderate HIV-related symptoms[c]	Treat[e] **(AII)**
	CD4 cell count[c] 500–999 cells/mm^3	
	Asymptomatic or mild symptoms[c] **and** CD4 cell count[c] ≥1,000 cells/mm^3	Treat[e,f] **(AI*)**
≥6 Years[g]	CDC Stage 3-defining conditions[c]	Rapid initiation[b,] of treatment **(AI*)**
	CDC Stage 3 immunodeficiency:[d] CD4 cell count <200 cells/mm^3	
	Moderate HIV-related symptoms[c]	Treat[e] **(AII)**
	CD4 cell count[d] 200–499 cells/mm^3	
	Asymptomatic or mild symptoms[c] **and** CD4 cell count ≥500 cells/mm^3	Treat[e,f,g] **(AI*)**

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 and adolescents but not studies limited to post-pubertal adolescents

[a] Treatment of infants aged ≤2 weeks is complex, and it is an area of active investigation. See Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV.

[b] Within 1 week–2 weeks, including an expedited discussion on adherence.

[c] See Table 6 for definitions.

[d] CD4 cell counts should be confirmed with a second test to meet the treatment criteria before initiating ART.

[e] Allow sufficient time to fully assess and address issues associated with adherence prior to initiating therapy.

[f] Patients and caregivers, together with their health care providers, may (on a case-by-case basis) decide to defer therapy due to clinical and/or psychosocial factors. Patients should be monitored closely in these cases.

[g] For adolescents aged ≥13 years with SMRs of 4 or 5, see the Adult and Adolescent Antiretroviral Guidelines.

Note: Potential barriers to adherence should be assessed and discussed with children who have HIV and their caregivers before initiation of therapy **(AIII)**.

Key to Acronyms: ART = antiretroviral therapy; CD4 = CD4 T lymphocyte; CDC = Centers for Disease Control and Prevention; SMR = sexual maturity rating

Infants Younger Than 12 Months

The CHER trial was a randomized clinical trial in South Africa that initiated triple-drug ART in asymptomatic infants aged 6 weeks to 12 weeks who had 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.[7] Most of the infant deaths in the delayed treatment arm occurred during the first 6 months after study entry. A substudy of this trial also found that infants who were treated early had significantly better gross motor and neurodevelopmental profiles than those who had their therapy deferred.[21] In a study conducted among

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, defined as HIV viral suppression <1,000 copies/mL, CD4 percentages ≥25%, and weight-for-age z-scores ≥-2 at 9 months of age, had better gross motor and language attainment than infants who did not meet the parameters for effective treatment response. These findings highlight the importance of early, efficacious treatment.[22]

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.[23] 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 months and 24 months.[8] A 2011 surveillance study followed infants who had recently received a diagnosis of HIV and who were aged <24 months (N = 272, median age: 6.1 months) from five inpatient or outpatient settings in Johannesburg, South Africa. By 6 months post-enrollment, 53 infants (19.5%) had died and 73 infants (27%) were lost to follow-up. Despite these discouraging results, there was a 71% reduction in the 6-month risk of death among the children who initiated ART, and infants identified through routine prevention of perinatal transmission or immunization clinics were five times less likely to die than those who received an HIV diagnosis during a symptomatic hospital admission.[8,24]

Finally, several studies have reported that early treatment of infants with perinatally acquired HIV is also associated with reduced size of viral reservoirs.[9-12] Kuhn et al. found that initiating ART at a younger age was associated with lower levels of peripheral blood mononuclear cell (PBMC)-associated HIV DNA. Furthermore, the authors reported that the risk of viral rebound to >50 copies/mL was two-fold 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.[10] This finding 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 destined for life-long treatment.

Given the risk of rapid HIV disease progression and mortality in young infants, and taking into account the findings from multiple studies, including the CHER trial, that demonstrate immune, growth, and neurodevelopmental benefits associated with early treatment initiation among infants with perinatally acquired HIV, the Panel recommends rapid initiation of therapy (within 1 week–2 weeks) for all infants aged <12 months, regardless of clinical status, CD4 percentage, or viral load. Before therapy is initiated, it is important to assess and discuss issues associated with adherence with an infant's caregivers. However, given the high risk of disease progression and mortality in young infants with HIV, it is important to expedite this assessment in infants aged <12 months, and provide intensive follow-up during the first few weeks to months to support the caregiver. The risk of disease progression is inversely correlated with the age of a child, with the youngest infants at the greatest risk of rapid disease progression. Progression to moderate or severe immune suppression also occurs frequently in older, untreated infants with HIV; by 12 months, approximately 50% of children develop moderate immune suppression and 20% develop severe immune suppression.[25] In the HPPMC study meta-analysis, the 1-year risk of AIDS or death was substantially higher in younger children than in older children at any given CD4 percentage, particularly for infants younger than 12 months.[26] Furthermore, clinical and laboratory parameters are limited in their ability to determine which young infants are at risk of rapid disease progression. No specific "at-risk" viral or immunologic threshold can be easily identified, and progression of HIV disease and opportunistic infections (OIs) can occur in young infants with normal CD4 cell counts.[26]

Identifying HIV infection during the first few months of life permits clinicians to initiate ART during the initial phases of primary infection. Consistent with the CHER trial, data from a number of observational studies in the United States and Europe demonstrate that infants who receive early treatment are less likely to progress to AIDS or death, and they have improved growth compared to those who start therapy later.[16,27-29]

Several small studies have demonstrated that, despite the very high levels of viral replication in infants with perinatally acquired HIV, initiating treatment early can result in durable viral suppression and normalization of immunologic responses to non-HIV antigens in some infants.[30,31] In infants with sustained control of plasma viremia, failure to detect extra-chromosomal replication intermediates suggests that near-complete control of viral replication can be achieved.[32,33] Early initiation of suppressive ART (i.e., in infants aged <6 months) results in a significant proportion of infants with HIV who clear maternally-acquired antibodies to HIV but who fail to produce their own HIV-specific antibody. These infants appear to be HIV seronegative when tested; however, viral reservoirs remain, and viral rebound will occur if ART is stopped.[32,34-37] Although there are a limited number of case reports of lengthy remissions in children with perinatally acquired HIV, current ART has not been shown to eradicate HIV infection in infants with perinatally acquired HIV because HIV persists in CD4 cells and other long-lived cells.[38-42] For these reasons, the Panel **does not recommend** empiric treatment interruption.

The report of a prolonged remission in a child with perinatally acquired HIV in Mississippi generated discussion about early initiation of ART in newborn infants with high-risk HIV exposure. This newborn, born to a mother who did not receive antenatal or perinatal ART, was treated with a three-drug ART regimen at age 30 hours through age 18 months. ART was 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.[43,44] This experience has prompted increasing support for initiation of treatment during the first weeks of life, as soon as the diagnosis is made. However, managing neonates with HIV is complex from both a medical and social perspective. Because of limited safety and pharmacokinetic data and limited experience with the use of ARV drugs in infants aged <2 weeks to 4 weeks, particularly among premature infants, drug and dose selection in this age group is challenging (see What to Start and Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV).[45] In a single-center, retrospective review of 22 infants with HIV who started ART during the first month of life (median age at initiation: 13.5 days) in Cape Town, South Africa, only half remained in care at a mean age of 2.1 years, and only two had viral suppression <50 copies/mL when last measured.[46]

Virologic suppression may take longer to achieve in young children than in older children or adults.[47-49] Possible reasons for the slower response in infants include higher virologic set points in young infants, inadequate ARV drug concentrations, and poor adherence because of the difficulties in administering complex regimens to infants. With currently available drug regimens, rates of viral suppression of 70% to 80% have been reported in infants with HIV who initiated therapy at ages of <12 months.[16,50,51] In a 5-year follow-up study of 40 children with HIV who initiated treatment at ages of <6 months, 98% had CD4 percentages >25% and 78% had undetectable viral load with a median follow-up time of 5.96 years.[16]

More rapid viral suppression in young infants may help reduce the size of long-lived HIV reservoirs. Several studies that compared the size of the viral reservoirs in children who initiated ART before age 12 weeks to those who initiated ART at age 12 weeks to 1 to 2 years have found that the size of the viral reservoir (as measured by 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.[52-54] 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).[55] In addition, among 61 children with perinatally acquired HIV in PHACS who achieved viral suppression at ages of <1 year versus ages between 1 year and 5 years, the mean half-life of HIV DNA from viral suppression was shorter in the early suppressors—5.9 years versus 18.8 years, respectively.[56]

Information on the appropriate drug doses for infants aged <3 months, and particularly preterm infants, is limited.[45] Hepatic and renal functions are immature in newborns, who are undergoing rapid maturational changes during the first few months of life. This can result in substantial differences in ARV dose

requirements between young infants and older children.[57] When drug concentrations are sub-therapeutic, 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).

Finally, the possibility of long-term toxicities (e.g., lipodystrophy, dyslipidemia, glucose intolerance, osteopenia, mitochondrial dysfunction) with prolonged therapy is a concern.[58] However, early initiation of ART reduces mortality and morbidity in infants, and this benefit outweighs such potential risks.

Children Aged 1 Year and Older

In general, disease progression is less rapid in children aged ≥1 year.[25] However, children with Centers for Disease Control and Prevention (CDC) Clinical Stage 3-defining OIs (see Revised Surveillance Case Definition for HIV Infection and Table 6) are at high risk of disease progression and death. The Panel recommends rapid treatment initiation (i.e., initiation within 1 week–2 weeks) for all such children with severe HIV disease, regardless of immunologic or virologic status. In these cases, the clinical team should expedite a discussion on adherence and provide intensive follow-up during the first few weeks to months to support the children and families. Children aged ≥1 year who have mild to moderate clinical symptoms (see Table 6) or who are asymptomatic are at lower risk of disease progression than children with more severe clinical symptoms.[59] ART is also recommended for these children, but because the risk of rapid disease progression is lower, more time can be taken to fully assess, discuss, and address issues associated with adherence with the caregivers and children prior to initiating therapy.

The Cochrane Collaboration[60] published a review on the effectiveness of ART in children with HIV aged <2 years based on data from published, randomized trials of early ART versus deferred ART.[7,61] The authors concluded that immediate therapy reduces morbidity and mortality and may improve neurologic outcome, but that these benefits were less pronounced in infants who started ART between ages 1 year and 2 years.

The PREDICT multicenter, open-label 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%.[62] AIDS-free survival at 144 weeks was 98.7% (95% confidence interval [CI], 94.7% to 99.7%) in the deferred group and 97.9% (95% CI, 93.7% to 99.3%) in the immediate therapy group ($P = 0.6$). However, because of the low event rate, the study was underpowered to detect a difference between the two groups. Neurodevelopmental outcomes were similar with immediate versus deferred ART initiation, but both groups performed worse than the children without HIV.[13] The trial did show better height gain for children who started ART immediately.[62] This study likely had a selection bias toward individuals with relatively slowly progressing disease, because it enrolled children who had survived a median of 6 years without ART. The low enrollment of children aged <3 years limits its value in making recommendations in that age group.

A retrospective analysis of 245 Brazilian children with perinatally acquired HIV who initiated ART between 2002 and 2014 at a median of 52 months of age (interquartile range: 18–94 months) found that there was no statistical difference between mortality among children who initiated ART at <18 months of age (7.9%) and those who initiated ART after developing symptoms or reaching an age >18 months (12.4%). However, because the median age of the late presenters was approximately 5 years, the results do not take into consideration children with rapidly progressing disease who may have died prior to HIV diagnosis; those who presented later may have been slow progressors with a better prognosis.[63]

In contrast, 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.[14] In children aged <10 years at enrollment,

there was 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 cell counts decreased to <350 cells/mm^3. The best outcomes were observed in European children, who attained growth outcomes comparable to those of children without HIV. However, immediate ART initiation produced no observable benefits or risks in those aged >10 years at enrollment.

Available data suggest that both children and adults who initiate treatment with a higher CD4 percentage or CD4 cell count have better immune recovery than patients who initiate with lower CD4 percentages or CD4 cell counts.[64-68] In the PENPACT-1 clinical trial, >90% of children recovered a normal CD4 cell count when ART was initiated during "mild" immunosuppression at any age, or during "advanced" immunosuppression at <3 years of age. Observational studies in children have reported similar findings. 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%.[69] Younger age at initiation of therapy has been associated with improved immune response and with more rapid growth reconstitution.[29,30,69,70]

Additionally, U.S. and international studies have reported that delaying ART initiation until later in childhood adversely impacts growth and substantially delays pubertal development and menarche, independent of immune suppression.[71-73] Finally, the PREDICT study demonstrated that patients in the early treatment arm had improved height-for-age z-scores compared with the patients in the deferred arm, who showed no improvement.[62] These combined data suggest that initiation of ART at higher CD4 values and younger ages maximizes the potential benefit for immunologic recovery and optimizes growth and sexual maturation.

There are potential concerns regarding starting life-long ART in all children. Drug choices are more limited in children than in adults, and adequate data on the potential long-term toxicities of prolonged ART in a developing child are not yet available. Some studies have shown that a small proportion of children with perinatally acquired HIV may be long-term non-progressors. These children have no immunologic or clinical progression by age 10 years, despite receiving no ART.[74-76] Medication adherence is the core requirement for successful virologic control, but achieving consistent adherence in children is often challenging.[77] Incomplete adherence leads to the selection of drug resistance mutations, but forcibly administrating ARV drugs to children may result in treatment aversion or fatigue, which occurs among many children with perinatally acquired HIV during adolescence.[78]

Despite this, a number of studies have found evidence for the long-term benefits of early ART, including reduced mortality in children aged <10 years,[14] improved growth and pubertal outcomes, improved immune reconstitution, and reduced inflammation in children and adolescents. The Panel believes the benefits of early ART initiation outweigh the potential risks, and recommends initiating ART in all children regardless of clinical, immunologic, or virologic status.

On a case-by-case basis, patients, caregivers, and providers may collaboratively decide to defer therapy due to clinical and/or psychosocial factors. If therapy is deferred, the health care provider should closely monitor a child's virologic, immunologic, and clinical status every 3 to 4 months **(AIII)** (see Clinical and Laboratory Monitoring of Pediatric HIV Infection). Factors to consider when deciding when to initiate therapy in children for whom treatment was deferred include:

- Increasing HIV RNA levels;
- Declining CD4 cell count or percentage values (e.g., approaching CDC Stage 2-3);
- Development of new clinical symptoms; *and*
- The ability of a caregiver and child to adhere to the prescribed regimen.

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

Stage[a]	Age at the Time of the CD4 Test					
	<1 Year		1 Year to <6 Years		≥6 Years	
	Cells/μL	%	Cells/μL	%	Cells/μL	%
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 cell count; the CD4 cell 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.

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.

Key to Acronyms: CD4 = CD4 T lymphocyte

Table 6. HIV-Related Symptoms and Conditions

Mildly Symptomatic
Children with two or more of the conditions listed, but none of the conditions listed in the Moderate Symptoms category:
• 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 × 10^9 per L]), and/or thrombocytopenia (platelet count <100 × 10^3 per μL [<100 × 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
• Cytomegalovirus 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)
AIDS-Defining Conditions
• Bacterial infections, multiple or recurrent[a]
• Candidiasis of bronchi, trachea, or lungs
• Candidiasis of esophagus

Table 6. HIV-Related Symptoms and Conditions, continued

AIDS-Defining Conditions, continued
• Cervical cancer, invasive[b]
• 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[c]
• 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[b]
• Progressive multifocal leukoencephalopathy
• Salmonella septicemia, recurrent
• Toxoplasmosis of brain, onset at age >1 month
• Wasting syndrome attributed to HIV[c]

[a] Only among children aged <6 years.

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

[c] 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).

Key to Acronyms: CDC = Centers for Disease Control and Prevention; 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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