Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Overview

The Department of Health and Human Services (HHS) Panel on Antiretroviral Guidelines for Adults and Adolescents recommends initiation of therapy for all adults and adolescents with HIV (see the Adult and Adolescent Guidelines). In addition to trials demonstrating the benefits of therapy in symptomatic adults and those with lower CD4 T lymphocyte (CD4) cell counts, a randomized clinical trial has shown definitive benefit 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) with CD4 cell counts >500 cells/mm$^3$ to immediately initiate ART or defer ART until their CD4 cell counts declined to <350 cells/mm$^3$ or until the development of any condition that dictated use of ART. There were 42 primary endpoints (AIDS, serious non-AIDS events, or death) among those enrolled in the study’s early treatment group, compared with 96 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 the primary endpoint was low: 3.7% in the deferred arm versus 1.8% 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 in the two groups.

A second analysis of 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 23% greater) than suggested by the intention-to-treat analysis. 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 immediately initiating treatment versus those deferring ART. The recommendation to initiate therapy in all adults and adolescents with HIV is also based on the availability of effective ART regimens with improved tolerability, as well as evidence that effective ART reduces secondary sexual HIV transmission.

The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) also recommends treatment for all children with HIV. However, the urgency for immediate initiation varies by age and pretreatment CD4 cell count, due to fewer 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 in children is initiated at an early age and will likely be life-long. In children aged <1 year, the benefit of immediate ART has been clearly demonstrated in the CHER trial. In addition, Shiau et al. reported that among two cohorts of infants with HIV in Johannesburg, South Africa, infants who initiated ART aged <6 months had better sustained viral control after achieving suppression than infants starting therapy between the ages of 6 and 24 months. Data in older children are equivocal. The PREDICT trial, which enrolled children 1 to 12 years of age (median age: 6.4 years), found that the risk of clinical progression was extremely low in both children receiving immediate ART and delayed (CD4-based) ART; additionally, no clinical benefit of immediate ART was observed. In contrast, in an observational study including over 20,000 children ages 1 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 count decreased to <350 cells/mm$^3$. In children aged >10 years at enrollment, there was no difference in mortality or growth associated with immediate ART initiation.

Immediate therapy 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 fewer drug resistance mutations at virologic failure in adults. Early therapy also preserves immune function, preventing clinical disease progression. Ongoing viral replication may be associated with persistent inflammation and development of cardiovascular,
kidney, and liver disease and malignancy; studies in adults also suggest that early control of replication may reduce the occurrence of these non-AIDS complications. Conversely, delaying therapy until later in the course of HIV infection may result in reduced evolution of drug-resistant virus due to a lack of drug selection pressure, improved adherence to the therapeutic regimen due to perceived need when the patient becomes symptomatic, and reduced or delayed adverse effects of ART.

### Treatment Recommendations for Initiation of Therapy in Antiretroviral-Naive Infants and Children with HIV

<table>
<thead>
<tr>
<th>Panel's Recommendations</th>
<th>Aged</th>
<th>Criteria</th>
<th>Recommendation</th>
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<tbody>
<tr>
<td></td>
<td>&lt;12 Months</td>
<td>Regardless of clinical symptoms, immune status, or viral load</td>
<td>Urgent&lt;sup&gt;b&lt;/sup&gt; treatment (&lt;sup&gt;AI&lt;/sup&gt; I except &lt;sup&gt;AI&lt;/sup&gt; I for children aged ≥6 weeks to &lt;12 weeks)</td>
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<tr>
<td></td>
<td>1 to &lt;6 Years</td>
<td>CDC Stage 3-defining opportunistic illnesses&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Urgent&lt;sup&gt;b&lt;/sup&gt; treatment (&lt;sup&gt;AI&lt;/sup&gt;*)</td>
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<td></td>
<td>1 to &lt;6 Years</td>
<td>CDC Stage 3 immunodeficiency: CD4 &lt;500 cells/mm&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Treat&lt;sup&gt;e&lt;/sup&gt; (&lt;sup&gt;AI&lt;/sup&gt;)</td>
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<td>1 to &lt;6 Years</td>
<td>Moderate HIV-related symptoms&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Treat&lt;sup&gt;e&lt;/sup&gt; (&lt;sup&gt;AI&lt;/sup&gt;*)</td>
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<td></td>
<td>1 to &lt;6 Years</td>
<td>CD4 cell count: 500–999 cells/mm&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Treat&lt;sup&gt;e&lt;/sup&gt; (&lt;sup&gt;AI&lt;/sup&gt;*)</td>
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<td>1 to &lt;6 Years</td>
<td>Asymptomatic or mild symptoms&lt;sup&gt;c&lt;/sup&gt; and CD4 cell count ≥1000 cells/mm&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Treat&lt;sup&gt;e&lt;/sup&gt; (&lt;sup&gt;AI&lt;/sup&gt;*)</td>
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<tr>
<td></td>
<td>≥6 Years</td>
<td>CDC Stage 3-defining opportunistic illnesses&lt;sup&gt;c&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>≥6 Years</td>
<td>CDC Stage 3 immunodeficiency: CD4 &lt;200 cells/mm&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Treat&lt;sup&gt;e&lt;/sup&gt; (&lt;sup&gt;AI&lt;/sup&gt;)</td>
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<td></td>
<td>≥6 Years</td>
<td>CD4 cell count: 200–499 cells/mm&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Treat&lt;sup&gt;e&lt;/sup&gt; (&lt;sup&gt;AI&lt;/sup&gt;*)</td>
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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

Note: Adherence should be assessed and discussed with children who have HIV and their caregivers before initiation of therapy (<sup>AI</sup>III).

<sup>a</sup> Treatment of infants aged ≤2 weeks is complex and an area of active investigation. See Antiretroviral Management of Newborns with Perinatal HIV

<sup>b</sup> Within 1–2 weeks, including an expedited discussion on adherence.

<sup>c</sup> See Table 6 for definitions.

<sup>d</sup> CD4 cell count should be confirmed with a second test to meet the treatment criteria before initiation of ART.

<sup>e</sup> More time can be taken to fully assess and address issues associated with adherence with the caregivers and the child prior to initiating therapy. Patients/caregivers may choose to postpone therapy, and on a case-by-case basis, providers may elect to defer therapy based on clinical and/or psychosocial factors, with close patient monitoring.

<sup>f</sup> For initiation of ART for adolescents aged ≥13 years and SMR of 4 or 5, see the Adult and Adolescent Guidelines.

**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, a randomized clinical trial in South Africa, demonstrated that initiating triple-drug ART at ages 6 to 12 weeks in asymptomatic infants with perinatally acquired HIV who had normal CD4 percentages (>25%) resulted in a 75% reduction in early mortality, compared with delaying treatment until the infants met clinical or immune criteria. Most of the deaths of the infants in the delayed treatment arm occurred in the first 6 months after study entry. A substudy of this trial also found that infants treated early had significantly better gross motor and neurodevelopmental profiles than those in whom therapy was deferred. Additionally, infants 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 with deferred ART. Shiau et al. reported that, among two cohorts of South African infants with HIV, those who initiated ART aged <6 months had better sustained viral control after achieving suppression than did infants starting therapy between 6 and 24 months. A 2011 surveillance study followed infants with recently diagnosed HIV 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 diagnosed with HIV during a symptomatic hospital admission. Because the risk of rapid progression is so high in young infants, and based on the data in young infants from the CHER study, the Panel recommends urgent initiation of therapy (within 1–2 weeks) for all infants aged <12 months regardless of clinical status, CD4 percentage, or viral load (see Box Recommendations). Before therapy is initiated, it is important to assess, discuss, and address 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 increased, intensive follow-up in the first few weeks to support the caregiver. The risk of disease progression is inversely correlated with the age of a child, with the youngest infants at greatest risk of rapid disease progression. Progression to moderate or severe immune suppression is also frequent in older, untreated infants with HIV; by 12 months, approximately 50% of children develop moderate immune suppression and 20% develop severe immune suppression. 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 level of CD4 percentage, particularly for infants younger than 12 months. Although the risk of progression is greatest during the first year of life, 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.

Identification of 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 have improved growth compared to those who start therapy later. Several small studies have demonstrated that, despite the very high levels of viral replication in infants with perinatally acquired HIV, early initiation of treatment can result in durable viral suppression and normalization of immunologic responses to non-HIV antigens in some infants. In infants with sustained control of plasma viremia, failure to detect extra-chromosomal replication intermediates suggests near-complete control of viral replication can be achieved. Early initiation of suppressive ART (i.e., aged <6 months) results in a significant proportion of infants with HIV who clear maternally-acquired antibodies to HIV but fail to produce their own HIV-specific antibody, thus testing reveals them to be HIV-seronegative; however, viral reservoirs remain, as demonstrated by viral rebound if ART is stopped. Although there is a single case report of a 27-month remission in a child with HIV infection (discussed below), current ART has not been shown to eradicate HIV infection in infants with perinatally acquired HIV because of persistence of HIV in CD4 and other long-lived cells. For these reasons, the Panel does not recommend empiric treatment interruption.

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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, after which ART was 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 was confirmed with repeat testing! ART was restarted at that time.\textsuperscript{35,36} This experience has prompted increasing support for initiation of treatment in 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 experience with ARV drugs in infants aged <2 to 4 weeks, particularly among premature infants, drug and dose selection in this age group is challenging (see \textbf{What to Start} and \textbf{Antiretroviral Management of Newborns}).\textsuperscript{37} In a single-center, retrospective review of 22 infants with HIV who started ART in the first month of life (median: 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.\textsuperscript{38}

Virologic suppression may take longer to achieve in young children than in older children or adults.\textsuperscript{39-41} 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 initiating therapy aged <12 months.\textsuperscript{41,42,43} In a 5-year follow-up study of 40 children with HIV who initiated treatment aged <6 months, 98% had CD4 percentage >25% and 78% had undetectable viral load with median follow-up of 5.96 years.\textsuperscript{11}

More rapid viral suppression in young infants may be important in reducing the long-lived HIV reservoirs. Several studies comparing children initiating ART before age 12 weeks to those initiating ART at age 12 weeks to 1 years have found that the size of the viral reservoir (as measured by peripheral blood mononuclear cell [PBMC] HIV-1 DNA levels) after 1 and 4 years of ART significantly correlated with age at ART initiation and age at viral control.\textsuperscript{44-46} Similarly, in a cross-sectional study of 144 youth with perinatally acquired HIV with long-term viral suppression, PHACS/AMP found a lower proviral reservoir in those who achieved virologic control at <1 year versus 1 to 5 years versus >5 years of age (4.2 vs. 19.4 vs. 70.7 copies/ million PBMCs, respectively).\textsuperscript{47} In addition, among 61 children with perinatally acquired HIV in PHACS/AMP who achieved viral suppression aged <1 year versus aged between 1 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.\textsuperscript{48}

Information on appropriate drug dosing in infants aged <3 months, and particularly preterm infants, is limited.\textsuperscript{37} 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.\textsuperscript{49} When drug concentrations are sub-therapeutic, either because of inadequate dosing, poor absorption, or incomplete adherence, ARV drug resistance can develop rapidly, particularly in the setting of high levels of viral replication in young infants. Frequent follow-up for dose optimization during periods of rapid growth and continued assessment and support of adherence are especially important when treating young infants (see \textbf{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.\textsuperscript{50} However, the clear benefit of immediate ART in reducing mortality and morbidity in infants outweighs such potential risks.
Children Aged 1 Year and Older

In general, disease progression is less rapid in children aged ≥1 year. 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 urgent treatment (i.e., within 1–2 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 increased, intensive follow-up in the first few weeks 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. ART is also recommended for these children, but because of the lower risk of rapid disease progression, more time can be taken to fully assess, discuss and address issues associated with adherence with the caregivers and the children prior to initiating therapy.

The Cochrane Collaboration published a review on the effectiveness of ART in children with HIV aged <2 years based on data from published randomized trials of early versus deferred ART. The authors concluded that immediate therapy reduces morbidity and mortality and may improve neurologic outcome, but that data were less compelling in support of universal initiation of treatment between ages 1 and 2 years.

The PREDICT multicenter, open-label trial randomized 300 children with HIV aged 1 to 12 years at enrollment (median: 6.4 years) to immediate initation of ART or deferral until the CD4 percentage was <15%. AIDS-free survival at 144 weeks was 98.7% (95% CI, 94.7–99.7) in the deferred group and 97.9% (95% CI, 93.7–99.3) in the immediate therapy group (P = 0.6), and immediate ART did not significantly improve neurodevelopmental outcomes. However, because of the low event rate, the study was underpowered to detect a difference between the two groups. The trial did show better height gain for children who started ART immediately. This study population likely had a selection bias toward relatively slowly progressive 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 (IQR 18–94) found there was no statistical difference in mortality among children who initiated ART at <18 months of age (7.9%) compared with those who initiated ART after development of symptoms or aged >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 progressive disease who may have died prior to HIV diagnosis and those who presented later may have been slow progressors with a better prognosis.

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 to 16 years at enrollment from 19 cohorts in Europe, Southern Africa, and West Africa. After 5 years of follow-up, there was lower mortality and higher mean height-for-age z-score with immediate ART initiation versus delaying until CD4 count decreased to <350 cells/mm³ in children aged <10 years at enrollment. The best outcomes were observed in European children, who attained growth outcomes comparable to children without HIV. However, in those aged >10 years at enrollment, neither benefit nor harm was observed with immediate ART.

As with data in adults, data from pediatric studies suggest that improvement in immunologic parameters is better in children when treatment is initiated at higher CD4 percentage/count levels. In the PENACT-1 clinical trial, >90% of children recovered a normal CD4 cell count when ART was initiated during “mild” immunosuppression at any age, or with “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 percentage <15% achieved CD4 percentage >25% after 5 years of therapy, compared with 59% of children starting with CD4 percentages of 15% to 24%. Younger age at initiation of therapy has been associated with improved immune response and with more rapid growth reconstitution.
Additionally, delaying ART initiation to older childhood was found to substantially delay pubertal development and menarche, independent of immune suppression, in Ugandan and Zimbabwean children with HIV in the ARROW trial.\textsuperscript{63} Finally, the PREDICT study demonstrated improved height z-scores in the early treatment arm compared with no improvement in the deferred arm.\textsuperscript{54} These combined data suggest that initiation of ART at higher CD4 values and younger ages maximizes the potential benefit for immunologic recovery and normalization of growth.

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 to address 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, with no immunologic or clinical progression by age 10 years despite receiving no ART.\textsuperscript{64-66} Medication adherence is the core requirement for successful virologic control, but achieving consistent adherence in childhood is often challenging.\textsuperscript{67} Incomplete adherence leads to the selection of viral resistance mutations, but forced administration of ARV drugs to children may result in treatment aversion or fatigue, which occurs among many children with perinatally acquired HIV during adolescence.\textsuperscript{68}

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,\textsuperscript{9} 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 potential risks, and recommends initiation of ART for all children regardless of clinical, immunologic, or virologic status.

Similar recommendations have been made by European pediatric HIV experts in the 2016 Pediatric European Network for Treatment of AIDS Treatment Guidelines.\textsuperscript{69} The Panel has formulated recommendations related to the urgency of ART initiation based on age, clinical status, and CD4 cell count (see Box Recommendations). The Panel has also rated the available evidence. In general, ART should be started urgently (i.e., within 1–2 weeks of HIV diagnosis) in infants aged <12 months and in children with advanced HIV infection. For other children initiating therapy, ART may be delayed long enough to educate caregivers (and children, as appropriate) about regimen adherence and to anticipate and resolve any barriers that might diminish adherence. This is particularly true for children aged ≥5 years, given their lower risk of disease progression.

On a case-by-case basis, patients, caregivers, and providers may collaboratively elect to defer therapy based on 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 (see Clinical and Laboratory Monitoring). Factors to consider in deciding when to initiate therapy in children in whom treatment was deferred include:

- Increasing HIV RNA levels;
- Declining CD4 cell count or percentage values (e.g., approaching CDC Stage 3);
- Development of new clinical symptoms; and
- The ability of caregiver and child to adhere to the prescribed regimen.
Table 5. HIV Infection Stage\textsuperscript{a} Based on Age-Specific CD4 Cell Count or Percentage

<table>
<thead>
<tr>
<th>Stage</th>
<th>&lt;1 Year &lt;1,500</th>
<th>1 to &lt;6 Years 1,000</th>
<th>≥6 Years 500</th>
<th>%</th>
<th>%</th>
<th>%</th>
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<tbody>
<tr>
<td>1</td>
<td>≥34</td>
<td>≥30</td>
<td>≥26</td>
<td></td>
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<tr>
<td>2</td>
<td>26–33</td>
<td>22–29</td>
<td>14–25</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>&lt;26</td>
<td>&lt;22</td>
<td>&lt;14</td>
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\textsuperscript{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 if the count is missing. If a Stage 3-defining opportunistic illness has been diagnosed (Table 6), then the stage is 3 regardless of CD4 test results.


Key to Acronyms: CD4 = CD4 T lymphocyte

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

Mild HIV-Related Symptoms:
Children with 2 or more of the conditions listed, but none of the conditions listed in Moderate Symptoms category:

- Lymphadenopathy (≥0.5 cm at more than 2 sites; bilateral at 1 site)
- Hepatomegaly
- Splenomegaly
- Dermatitis
- Parotitis
- Recurrent or persistent upper respiratory tract infection, sinusitis, or otitis media

Moderate HIV-Related Symptoms:

- Anemia (hemoglobin <8 g/dL [<80 g/L]), neutropenia (white blood cell count <1,000/µL [<1.0 × 10\textsuperscript{9}/L]), and/or thrombocytopenia (platelet count <100 × 10\textsuperscript{3}/µL [<100 × 10\textsuperscript{9}/L]) persisting for ≥30 days
- Bacterial meningitis, pneumonia, or sepsis (single episode)
- Candidiasis, oropharyngeal (thrush), persisting (>2 months) in children aged >6 months
- Cardiomyopathy
- Cytomegalovirus infection, with onset before 1 month
- Diarrhea, recurrent or chronic
- Hepatitis
- Herpes simplex virus (HSV) stomatitis, recurrent (>2 episodes within 1 year)
- HSV bronchitis, pneumonitis, or esophagitis with onset before 1 month
- Herpes zoster (shingles) involving at least 2 distinct episodes or more than 1 dermatome
- Leiomyosarcoma
- Lymphoid interstitial pneumonia or pulmonary lymphoid hyperplasia complex
- Nephropathy
- Nocardiosis
- Persistent fever (lasting >1 month)
- Toxoplasmosis, onset before 1 month
- Varicella, disseminated (complicated chickenpox)
### Table 6. HIV-Related Symptoms (page 2 of 2)

<table>
<thead>
<tr>
<th>Stage-3-Defining Opportunistic Illnesses in HIV Infection</th>
</tr>
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<tbody>
<tr>
<td>- Bacterial infections, multiple or recurrent&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>- Candidiasis of bronchi, trachea, or lungs</td>
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<tr>
<td>- Candidiasis of esophagus</td>
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<tr>
<td>- Cervical cancer, invasive&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td>- Coccidioidomycosis, disseminated or extrapulmonary</td>
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<tr>
<td>- Cryptococcosis, extrapulmonary</td>
</tr>
<tr>
<td>- Cryptosporidiosis, chronic intestinal (&gt;1 month duration)</td>
</tr>
<tr>
<td>- Cytomegalovirus disease (other than liver, spleen, or nodes), onset at age &gt;1 month</td>
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<tr>
<td>- Cytomegalovirus retinitis (with loss of vision)</td>
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<tr>
<td>- Encephalopathy attributed to HIV&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>- HSV: chronic ulcers (&gt;1 month duration) or bronchitis, pneumonia, or esophagitis (onset at age &gt;1 month)</td>
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<tr>
<td>- Histoplasmosis, disseminated or extrapulmonary</td>
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<tr>
<td>- Isosporiasis, chronic intestinal (&gt;1 month duration)</td>
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<tr>
<td>- Kaposi sarcoma</td>
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<tr>
<td>- Lymphoma, Burkit (or equivalent term)</td>
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<tr>
<td>- Lymphoma, immunoblastic (or equivalent term)</td>
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<tr>
<td>- Lymphoma, primary, of brain</td>
</tr>
<tr>
<td>- <em>Mycobacterium avium</em> complex or <em>Mycobacterium kansasii</em>, disseminated or extrapulmonary</td>
</tr>
<tr>
<td>- <em>Mycobacterium tuberculosi</em> of any site, pulmonary, disseminated, or extrapulmonary</td>
</tr>
<tr>
<td>- <em>Mycobacterium</em>, other species or unidentified species, disseminated or extrapulmonary</td>
</tr>
<tr>
<td>- <em>Pneumocystis jirovecii</em> (previously known as <em>Pneumocystis carinii</em>) pneumonia</td>
</tr>
<tr>
<td>- Pneumonia, recurrent&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>- Progressive multifocal leukoencephalopathy</td>
</tr>
<tr>
<td>- Salmonella septicemia, recurrent</td>
</tr>
<tr>
<td>- Toxoplasmosis of brain, onset at age &gt;1 month</td>
</tr>
<tr>
<td>- Wasting syndrome attributed to HIV&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Only among children aged <6 years.

<sup>b</sup> Only among adults, adolescents, and children aged ≥6 years.

<sup>c</sup> 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).

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).

### References


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