Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Overview

The Department of Health and Human Services (HHS) Adult and Adolescent Antiretroviral Guidelines Panel (the Panel) has recommended initiation of therapy for all adults with HIV infection (see the Adult and Adolescent Guidelines). In addition to trials demonstrating benefit of therapy in symptomatic adults and those with lower CD4 T lymphocyte (CD4) cell counts, a randomized clinical trial has provided definitive evidence of benefit with initiation of antiretroviral therapy (ART) in asymptomatic adults with CD4 cell counts >500 cells/mm³. The START trial randomized 4,685 antiretroviral (ARV)-naive adults with HIV (median age 36 years) with CD4 cell counts >500 cells/mm³ to immediately initiate ART or defer ART until the CD4 cell count declined to <350 cells/mm³ 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 vs. 1.8% in the immediate treatment arm. Sixty-eight percent of the primary end points occurred in patients with CD4 cell counts >500 cells/mm³. The risk of Grade 4 events or unscheduled hospital admissions was similar in the two groups.2 The Panel’s recommendation for initiation of therapy for all adults with HIV is also based on the availability of effective ART regimens with improved tolerability, and evidence that effective ART reduces secondary sexual HIV transmission.3

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 strength of the recommendation and urgency for immediate initiation varies by age and pretreatment CD4 cell count due to fewer available data in the pediatric population 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 a young age and will likely be life-long. In children under 1 year of age, the benefit of immediate ART has been clearly demonstrated in the CHER trial,4 but data in older children are more equivocal. The PREDICT trial, which enrolled children aged >1 year (median age 6.4 years), found the risk of clinical progression was extremely low in both children initiating immediate versus delayed (CD4-based) ART and no clinical benefit of immediate ART was observed.5 However, in an observational study including over 20,000 children aged 1 to 16 years from 19 cohorts in Europe, Southern African and West Africa, immediate ART was associated with lower mortality and better growth in children aged <10 years compared with delaying ART until CD4 count decreased to <350 cells/mm³.6

Considerations for aggressive therapy in the early stages of HIV infection in both children and adults include the potential to 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.7 Early therapy also preserves immune function, preventing clinical disease progression.8,9 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.8,10-12 Conversely, delaying therapy until later in the course of HIV infection, when clinical or immunologic symptoms appear, 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.

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

<table>
<thead>
<tr>
<th>Age</th>
<th>Criteria</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;12 Months*</td>
<td>Regardless of clinical symptoms, immune status, or viral load</td>
<td>Urgentb treatment (All except Ai for ≥6 weeks to &lt;12 weeks of age)</td>
</tr>
<tr>
<td>1 to &lt;6 Years</td>
<td>CDC Stage 3-defining opportunistic illnessesc</td>
<td>Urgentb treatment (AI*)</td>
</tr>
<tr>
<td></td>
<td>CDC Stage 3 immunodeficiency; CD4 &lt;500 cells/mm³</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Moderate HIV-related symptomsc</td>
<td>Treatc (AIl)</td>
</tr>
<tr>
<td></td>
<td>CD4 cell count; 500–999 cells/mm³</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Asymptomatic or mild symptoms and CD4 cell count ≥1000 cells/mm³</td>
<td>Treatc (BI*)</td>
</tr>
<tr>
<td>≥6 Years*</td>
<td>CDC Stage 3-defining opportunistic illnessesc</td>
<td>Urgent treatment (AI*)</td>
</tr>
<tr>
<td></td>
<td>CDC Stage 3 immunodeficiency; CD4 &lt;200 cells/mm³</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Moderate HIV-related symptomsc</td>
<td>Treatc (AIl)</td>
</tr>
<tr>
<td></td>
<td>CD4 cell count; 200–499 cells/mm³</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Asymptomatic or mild symptoms and CD4 cell count ≥500 cells/mm³</td>
<td>Treatc (BI*)</td>
</tr>
</tbody>
</table>

### 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 with HIV and their caregivers before initiation of therapy (AIII).

* Treatment of infants ≤2 weeks is a more complex issue and an area of active investigation. See Specific Issues in Antiretroviral Therapy for Neonates.

* Within 1–2 weeks, including an expedited discussion on adherence

* See Table 6 for definitions

* CD4 cell counts should be confirmed with a second test to meet the treatment criteria before initiation of ART.

* 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.

* For initiation of ART for adolescents aged ≥13 years and sexually maturity ratings or 4 or 5, see the Adult and Adolescent Guidelines.

### Key to Acronyms:
- CD4 = CD4 T lymphocyte
- CDC = Centers for Disease Control and Prevention

### 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 perinatally infected infants with 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 in 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 achieved with...
deferred ART. 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 <12 months regardless of clinical status, CD4 percentage, or viral load (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 younger than 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 infants with HIV; by 12 months, approximately 50% of children develop moderate immune suppression and 20% develop severe immune suppression. In the HIV Paediatric Prognostic Markers Collaborative 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. Unfortunately, although the risk of progression is greatest in the first year of life, the ability to differentiate children at risk of rapid versus slower disease progression by clinical and laboratory parameters is also most limited in young infants. 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 infection, 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 (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 HIV-seronegative; however, a viral reservoir remains present, as demonstrated by viral rebound if ART is stopped. Although there is a single case report of a period of 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 lymphocytes and other cells.

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 3-drug ART regimen at ages 30 hours through 18 months, after which ART was discontinued against medical advice. Intensive follow-up evaluations showed no evidence of virologic rebound for more than 2 years following discontinuation of ART, after which time viremia recurred and ART was restarted. This experience has prompted increasing support for initiation of treatment in the first weeks of life, as soon as the diagnosis is made. However, because of limited safety and pharmacokinetic data and experience with ARV drugs in infants <2 to 4 weeks, particularly among premature infants, drug and dose selection in this age group is challenging (see What to Start and Specific Issues in Antiretroviral Treatment for Neonates). If early treatment is initiated, the Panel does not recommend empiric treatment interruption.

Virologic suppression may take longer to achieve in young children than in older children or adults. Possible reasons for the slower response in infants include higher virologic set points in young infants, inadequate ARV drug levels, 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 at <12 months. In a 5-year follow-up study of 40 children with HIV who initiated treatment at <6 months, 98% had CD4 percentage >25% and 78% had

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undetectable viral load with median follow-up of 5.96 years.8

More rapid viral suppression in young infants may be important in reducing the long-lived HIV reservoir. Several studies comparing children initiating ART before age 12 weeks to those initiating ART at age 12 weeks to 1 to 2 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.37,38 Similarly, the Pediatric HIV/AIDS Cohort Study/Adolescent Master Protocol (a cross-sectional study of 144 youth with perinatal HIV with long-term viral suppression) 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).40

Information on appropriate drug dosing in infants aged <3 to 6 months, and particularly preterm infants, is limited.8 Hepatic and renal functions are immature in newborns 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.41 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 Adherence).

Finally, the possibility of long-term toxicities (e.g., lipodystrophy, dyslipidemia, glucose intolerance, osteopenia, mitochondrial dysfunction) with prolonged therapy is a concern.42 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.15 However, children with CDC Clinical Stage 3-defining OIs (see Revised Surveillance Case Definition for HIV Infection at http://www.cdc.gov/mmwr/pdf/rr/rr6303.pdf 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.43 ART is also recommended for these children, but because of 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 Collaboration44 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.4,45 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 Pediatric Randomised Early versus Deferred Initiation in Cambodia and Thailand (PREDICT) multicenter, open-label trial randomized 300 children with HIV aged >1 year (median 6.4 years) to immediate initiation of ART or deferral until the CD4 percentage was <15%.46 AIDS-free survival at week 144 was 98.7% (95% CI, 94.7–99.7) in the deferred group and 97.9% (CI, 93.7–99.3) in the immediate therapy group (P = 0.6), and immediate ART did not significantly improve neurodevelopmental outcomes.5 However, because of the low event rate, the study was underpowered to detect a difference between the 2 groups. The trial did show better height gain for children who started ART immediately.46 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 limited enrollment of children aged <3 years poses restrictions on its value for recommendations in that age group.

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In contrast, mortality and growth was evaluated after ART initiation using 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, showing a general trend toward lower mortality and better growth with earlier treatment initiation. In children aged <10 years at enrollment, by 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. The best outcomes were observed in European children who attained growth outcomes comparable to children who were HIV-uninfected. 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 PENPACT-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% and 59% of those starting with CD4 percentage 15% to 24% achieved CD4 percentage >25% after 5 years of therapy. 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. Finally, the PREDICT Study demonstrated improved height z-scores in the early treatment arm compared with no improvement in the deferred arm. 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. Medication adherence is the core requirement for successful virologic control, but achieving consistent adherence in childhood is often challenging. 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.

However, the Panel considers that with increasing evidence of long-term benefits of early ART including reduced mortality in children aged <10 years along with improved growth and pubertal outcomes, improved immune reconstitution and reduced inflammation in children and adolescents, the benefits of early ART initiation outweigh potential risks, and recommend 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. The Panel has formulated recommendations related to the urgency of initiation of ART based on age, clinical status and CD4 cell count (see Box Recommendation). In general, except in infants younger than age 12 months and children with advanced HIV infection, ART does not need to be started urgently (i.e., within 1–2 weeks). Before initiating therapy, it is important to take time 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.

Patients, caregivers, and providers may collaboratively choose to postpone therapy, and on a case-by-case basis, may 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\(^a\) Based on Age-Specific CD4 Cell Count or Percentage

<table>
<thead>
<tr>
<th>Stage</th>
<th>&lt;1 Year</th>
<th>1 to &lt;6 Years</th>
<th>≥6 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cells/µL</td>
<td>%</td>
<td>Cells/µL</td>
</tr>
<tr>
<td>1</td>
<td>≥1,500</td>
<td>≥34</td>
<td>≥1,000</td>
</tr>
<tr>
<td>2</td>
<td>750–1,499</td>
<td>26–33</td>
<td>500–999</td>
</tr>
<tr>
<td>3</td>
<td>&lt;750</td>
<td>&lt;26</td>
<td>&lt;500</td>
</tr>
</tbody>
</table>

\(^a\) 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.

Table 6: HIV-Related Symptoms

<table>
<thead>
<tr>
<th>Mild HIV-Related Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children with 2 or more of the conditions listed but none of the conditions listed in Moderate Symptoms category</td>
</tr>
<tr>
<td>• Lymphadenopathy (≥0.5 cm at more than 2 sites; bilateral at 1 site)</td>
</tr>
<tr>
<td>• Hepatomegaly</td>
</tr>
<tr>
<td>• Splenomegaly</td>
</tr>
<tr>
<td>• Dermatitis</td>
</tr>
<tr>
<td>• Parotitis</td>
</tr>
<tr>
<td>• Recurrent or persistent upper respiratory tract infection, sinusitis, or otitis media</td>
</tr>
</tbody>
</table>

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

- Bacterial infections, multiple or recurrent\(^a\)  
- Candidiasis of bronchi, trachea, or lungs  
- Candidiasis of esophagus  
- Cervical cancer, invasive\(^b\)  
- Coccidioidomycosis, disseminated or extrapulmonary  
- Cryptococcosis, extrapulmonary  
- Cryptosporidiosis, chronic intestinal (>1 month duration)  
- Cytomegalovirus disease (other than liver, spleen, or nodes), onset at age >1 month  
- Cytomegalovirus 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).  

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


52. Patel K, Hernan MA, Williams PL, et al. Long-term effectiveness of highly active antiretroviral therapy on the survival


