



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 March 1, 2016; last reviewed March 1, 2016)

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 [Antiretroviral Guidelines for Adults and Adolescents](#)). In addition to trials demonstrating benefit of therapy in symptomatic adults and those with lower CD4 T lymphocyte (CD4) cell counts,¹ 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 HIV-infected adults (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 endpoints 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 HIV-infected adults 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 HIV-Infected Children recommends treatment for all HIV-infected children. However, the strength of the recommendation 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 HIV-infected children than in adults. 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, as demonstrated by the lack of clinical benefit of immediate ART observed in the PREDICT trial, which enrolled children aged >1 year (median age 6.4 years), and the risk of progression was extremely low in both groups.⁵ Concerns about adherence and toxicities become particularly important when therapy in children is initiated at a young age and will likely be life-long.

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 quasispecies. Initiation of therapy at higher CD4 cell counts has been associated with fewer drug resistance mutations at virologic failure in adults.⁶ Early therapy also slows immune system destruction and preserves immune function, preventing clinical disease progression.^{7,8} 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.^{7,9-11} 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.

Treatment Recommendations for Initiation of Therapy in Antiretroviral-Naive, HIV-Infected Infants and Children

Panel Recommendations		
Age	Criteria	Recommendation
<12 Months ^a	Regardless of clinical symptoms, immune status, or viral load	Urgent ^b treatment (All except AI for ≥6 weeks to <12 weeks of age)
1 to <6 Years	CDC Stage 3-defining opportunistic illnesses ^c	Urgent ^b treatment (AI*)
	CDC Stage 3 immunodeficiency: ^d CD4 <500 cells/mm ³	
	Moderate HIV-related symptoms ^c	Treat ^c (AI)
	CD4 cell count ^c 500–999 cells/mm ³	
	Asymptomatic or mild symptoms ^c and CD4 cell count ^c ≥1000 cells/mm ³	Treat ^c (BI*)
≥6 Years	CDC Stage 3-defining opportunistic illnesses ^c	Urgent ^a treatment (AI*)
	CDC Stage 3 immunodeficiency: ^d CD4 <200 cells/mm ³	
	Moderate HIV-related symptoms ^c	Treat ^b (AI)
	CD4 cell count ^d 200–499 cells/mm ³	
	Asymptomatic or mild symptoms ^c and CD4 cell count ^c ≥500 cells/mm ³	Treat ^c (BI*)
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 postpubertal adolescents		

Note: Adherence should be assessed and discussed with HIV-infected children and their caregivers before initiation of therapy (**AI**).

^a For infants ≤2 weeks, see [Specific Issues in Antiretroviral Therapy for Neonates](#)

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

^c Table 6

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

^e 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.

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 percentage (>25%) resulted in a 75% reduction in early mortality, compared with delaying treatment until the infants met clinical or immune criteria.⁴ 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.¹² 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 initiating therapy for all infants <12 months regardless of clinical status, CD4 percentage, or viral load ([Box Recommendations](#)). Before therapy is initiated, it is important to fully assess, discuss, and address issues associated with adherence with an HIV-infected infant's caregivers. However, given the high risk of disease progression and mortality in young HIV-infected infants, it is important to expedite this assessment in infants younger than 12 months.

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 infected infants; by 12 months, approximately 50% of children develop moderate immune suppression and 20% develop severe immune suppression.¹³ 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.¹⁴ 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.¹⁴

Identification of HIV infection during the first few months of life permits clinicians to initiate ART during the initial phases of primary infection. Data from a number of observational studies in the United States and Europe suggest that infants who receive early treatment are less likely to progress to AIDS or death than those who start therapy later.^{7,15,16} A study of 195 South African children initiating ART aged <24 months found that infants treated by 6 months achieved target growth milestones more rapidly than children who initiated therapy between 12 and 24 months.¹⁷ Several small studies have demonstrated that, despite the very high levels of viral replication in perinatally infected infants, early initiation of treatment can result in durable viral suppression and normalization of immunologic responses to non-HIV antigens in some infants.^{18,19} In infants with sustained control of plasma viremia, failure to detect extra-chromosomal replication intermediates suggests near-complete control of viral replication.²⁰ Some of these infants have become HIV seronegative. Although there is a single case report of a period of remission in an HIV-infected child, discussed below, current ART has not been shown to eradicate HIV infection in perinatally infected infants because of persistence of HIV in CD4 lymphocytes and other cells.²¹⁻²³

The report of a prolonged remission in an HIV-infected child 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 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.^{24,25} 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, 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.^{26,27} 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 HIV-infected infants initiating therapy at <12 months.^{7,28,29} In a 5-year follow-up study of 40 HIV-infected children who initiated treatment at <6 months, 98% had CD4 percentage >25% and 78% had undetectable viral load with median follow-up of 5.96 years.⁷ More rapid viral suppression in young infants may also be important in reducing the long-lived HIV reservoir; a study of 17 HIV-infected infants initiating ritonavir-boosted lopinavir-based ART before 6 months demonstrated that time to the first HIV viral load <400 copies/mL was correlated with the size of the long-lived HIV reservoir (i.e., the resting memory CD4

cell pool).³⁰ In addition, in the Pediatric HIV/AIDS Cohort Study/Adolescent Master Protocol (a cross-sectional study of 144 perinatally infected youth 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 peripheral blood mononuclear cells, respectively).³¹

Information on appropriate drug dosing in infants younger than 3 to 6 months is limited. 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.³² When drug concentrations are subtherapeutic, 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.³³

Children Aged 1 Year and Older

In general, disease progression is less rapid in children aged ≥ 1 year.¹³ However, children with 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.³⁴ In these children, 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 Collaboration³⁵ published a review on the effectiveness of ART in HIV-infected children aged <2 years based on data from published randomized trials of early versus deferred ART.^{4,36} The authors concluded that immediate therapy reduces morbidity and mortality and may improve neurologic outcome, but that data are 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) trial was designed to investigate the impact on AIDS-free survival and neurodevelopment of deferral of ART in children aged >1 year.³⁷ This multicenter, open-label trial randomized 300 HIV-infected children aged >1 year (median 6.4 years) to immediate initiation of ART or deferral until the CD4 percentage was <15%. The median baseline CD4 percentage was 19% (IQR 16% to 22%) and 46% of children in the deferred group started ART during the study. 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 two groups. 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.

In children, the prognostic significance of a specific CD4 percentage or count varies with age.^{14,38} In data from the HIV Paediatric Prognostic Markers Collaborative Study meta-analysis, derived from 3,941 children with 7,297 child-years of follow-up, the risk of mortality or progression to AIDS per 100 child-years is significantly higher for any given CD4 count in children aged 1 to 4 years than in children aged ≥ 5 years (see Figures A and B and Tables A and B in [Appendix C: Supplemental Information](#)). Data from the HIV Paediatric Prognostic Markers Collaborative Study suggest that absolute CD4 cell count is a useful

prognostic marker for disease progression in children aged ≥ 5 years, with risk of progression similar to that observed in adults (see Table B in [Appendix C: Supplemental Information](#)).^{14,39} For children aged 1 to <5 years, a similar increase in risk of AIDS or death is seen when CD4 percentage drops below 25% (see Table A in [Appendix C: Supplemental Information](#)).

Because the CD4 percentage is more consistent than the naturally declining CD4 cell count in the first years of life, it has been used preferentially to monitor immunologic status in children aged <5 years. However, an analysis of more than 21,000 pairs of CD4 measurements from 3,345 children aged <1 to 16 years in the HIV Paediatric Prognostic Markers Collaborative Study found that CD4 cell counts provide greater prognostic value over CD4 percentage for short-term disease progression for children aged <5 years as well as in older children.⁴⁰ For example, the estimated hazard ratio for AIDS or death at the 10th centile of CD4 cell count (compared with the 50th centile) was 2.2 (95% confidence interval [CI] 1.4, 3.0) for children aged 1 to 2 years versus 1.2 (CI 0.8, 1.6) for CD4 percentage. The CDC has issued an updated HIV infection staging classification based on age-specific CD4 values, indicating a preference for CD4 count over CD4 percentage in all ages (see Revised Surveillance Case Definition for HIV Infection at <http://www.cdc.gov/mmwr/pdf/rr/rr6303.pdf> and Table 5).

The level of plasma HIV RNA may provide useful information in terms of risk of progression, although its prognostic significance is weaker than CD4 count.³⁸ Several studies have shown that older children with HIV RNA levels $\geq 100,000$ copies/mL are at high risk of mortality^{41–43} and lower neurocognitive performance;⁴⁴ similar findings have been reported in adults.^{45–47} Similarly, in the HIV Paediatric Prognostic Markers Collaborative Study meta-analysis, the 1-year risk of progression to AIDS or death rose sharply for children aged >1 year when HIV RNA levels were $\geq 100,000$ copies/mL (see Figures D and E and Table A in [Appendix C: Supplemental Information](#)).³⁸ For example, the estimated 1-year risk of death was 2 to 3 times higher in children with plasma HIV RNA 100,000 copies/mL compared with 10,000 copies/mL and 8 to 10 times higher with plasma HIV RNA $>1,000,000$ copies/mL.

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.^{48–52} A secondary analysis of PENPACT-1 (Pediatric AIDS Clinical Trials Group 390/Paediatric European Network for Treatment of AIDS 9) evaluated population-level impacts of ART initiation at different CD4 percentages and age thresholds on CD4 percentage recovery.⁵³ PENPACT-1 was a multicenter, Phase 2/3 randomized, open-label trial enrolling ART-naïve children aged >30 days to <18 years from Europe, North America, and South America. The primary aims were to compare a protease inhibitor- or non-nucleoside reverse transcriptase inhibitor-based ART regimen for initial therapy and evaluate viral load thresholds for switching from first-line to second-line ART. Because no significant differences were found among randomized arms, participants were pooled across arms to study CD4 responses. Two hundred and sixty-six children were enrolled, and 162 had at least “mild” immunosuppression at enrollment using World Health Organization (WHO) 2007 criteria; this group was evaluated for CD4 percentage recovery to $\geq 10\%$ for age within 4 years of initiating ART. CD4 percentage recovery was significantly associated with WHO-staged baseline CD4 percentage, with 97% (95% CI: 85%–99%) of those with “mild” immunodeficiency ($n = 31$) and 87% (95% CI: 62%–87%) of those with “advanced” immunodeficiency ($n = 40$) ever having a normal CD4 value within 4 years of ART initiation vs. 60% (95% CI 48–68%) among those with “severe” immunodeficiency ($n = 91$) ($P < 0.001$). When baseline CD4 percentage and age effects were combined, $>90\%$ 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 perinatally infected children 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.⁵⁴ Younger age at initiation of therapy has been associated with improved immune response and with more rapid growth reconstitution.^{17,54,55} Older age at ART initiation (median age 9.4 years; range 5.2–17.6 years) was associated with delayed onset of puberty and all Tanner stages ($P < 0.05$) and menarche ($P = 0.02$) in Ugandan and Zimbabwean HIV-infected children in the ARROW trial.⁵⁶

Finally, the PREDICT Study demonstrated improved height z-scores in the early treatment arm compared with no improvement in the deferred arm.³⁷ These combined data suggest that initiation of ART at higher CD4 values and younger ages maximizes the potential benefit for immunologic recovery.

Given that disease progression in children aged ≥ 5 years is similar to that in adults,³⁹ and the START clinical trial demonstrated reduction in morbidity and mortality with initiation of ART when the CD4 cell count is >500 cells/mm³ (INSIGHT START),^{57,58} most experts feel that recommendations for asymptomatic children in this age range should be similar to those for adults. While the DHHS Adult Treatment Guidelines Panel has moved to endorse initiating ART in all HIV-infected adults regardless of CD4 cell count,⁵⁹ one component of their rationale is the compelling data demonstrating that ART is effective in preventing secondary transmission of HIV. However, prevention of sexual transmission of HIV is not a significant consideration for children aged <13 years. 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, e.g., bone, cardiac, mitochondrial and/or other metabolic toxicities, are not yet available. Some studies have shown that a small proportion of perinatally infected children may be long-term nonprogressors, with no immunologic or clinical progression by age 10 years despite receiving no ART.⁶⁰⁻⁶² Medication adherence is the core requirement for successful virologic control, but achieving consistent adherence in childhood is often challenging.⁶³ 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 perinatally infected children during adolescence.⁶⁴ The relative benefits of initiating ART in asymptomatic children with low viral burdens and high CD4 cell counts in general outweigh these potential risks.

The Panel has used these data to formulate recommendations on 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

Stage	Age on Date of CD4 Test					
	<1 Year	%	1 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 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.

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

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

Mild HIV-Related Symptoms
Children with two 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 [$<1.0 \times 10^9/L$]), and/or thrombocytopenia (platelet count <100 × 10³/μL [$<100 \times 10^9/L$]) persisting for ≥30 days • Bacterial meningitis, pneumonia, or sepsis (single episode) • Candidiasis, oropharyngeal (thrush), persisting (>2 months) in children older than age 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)

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 • <i>Mycobacterium avium</i> complex or <i>Mycobacterium kansasii</i>, disseminated or extrapulmonary • <i>Mycobacterium tuberculosis</i> of any site, pulmonary, disseminated, or extrapulmonary • <i>Mycobacterium</i>, other species or unidentified species, disseminated or extrapulmonary • <i>Pneumocystis jirovecii</i> (previously known as <i>Pneumocystis carinii</i>) 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).

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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