Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

When to Initiate Therapy in Antiretroviral-Naive Children <mark>(Last updated November 1, 2012; last reviewed November 1, 2012)</mark>

Overview

The decision on when to initiate antiretroviral therapy (ART) in asymptomatic HIV-infected older children, adolescents, and adults continues to generate controversy among HIV experts. Aggressive therapy in the early stages of HIV infection has the potential to control viral replication before the evolution of HIV in that individual into a diverse and potentially more pathogenic quasispecies. Initiation of therapy at higher CD4 T lymphocyte (CD4 cell) counts has been associated with fewer drug resistance mutations at virologic failure in adults.[1] Early therapy also slows immune system destruction and preserves immune function, preventing clinical disease progression.[2] Ongoing viral replication may be associated with persistent inflammation and development of cardiovascular, kidney, and liver disease and malignancy; studies in adults suggest that early control of replication may reduce the occurrence of these non-AIDS complications.[2-8] In addition, data from a large randomized multinational clinical trial of HIV-serodiscordant adults demonstrated that effective ART reduced secondary transmission to an uninfected sexual partner by 96%.[9] 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 because the patient is symptomatic, and reduced or delayed adverse effects of ART. Because therapy in children is initiated at a young age and will likely be lifelong, concerns about adherence and toxicities are particularly important.

The Health and Human Services (HHS) Adult and Adolescent Antiretroviral Guidelines Panel now recommends initiation of therapy for all adults with HIV infection, with the proviso that the strength of the recommendations is dependent on the pre-treatment CD4 cell count.[10] Randomized clinical trials have provided definitive evidence of benefit with initiation of therapy in adults with CD4 cell counts <350 cells/mm^3.[11] Observational cohort data have demonstrated the benefit of treatment in adults with CD4 cell counts between 350 and 500 cells/mm^3 in reducing morbidity and mortality; therefore, adult treatment guidelines recommend initiation of lifelong ART for individuals with CD4 cell counts ≤500 cells/mm^3.[10, 12-15] For adults with CD4 counts >500 cell/mm^3, observational data are less conclusive regarding the potential survival benefit of early treatment.[12, 13, 16] The recommendation for initiation of therapy at CD4 counts >500/mm^3 (BIII evidence) in adults is based on accumulating data that untreated HIV infection may be associated with development of many non-AIDS-defining diseases, the availability of more effective ART regimens with improved tolerability, and evidence that effective ART reduces sexual HIV transmission. However, the Adult Guidelines Panel acknowledges that the amount of data supporting earlier initiation of therapy decreases as the CD4 cell count increases above 500 cells/mm^3, and that concerns remain over the unknown overall benefit, long-term risks, cumulative additional costs, and potential for decreased medication adherence associated with earlier treatment in asymptomatic patients.[10]

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

Panel's Recommendations

- Antiretroviral therapy (ART) should be initiated in all children with AIDS or significant symptoms (Clinical Category C or most Clinical Category B conditions) **(AI*)**.

- ART should be initiated in HIV-infected infants <12 months of age regardless of clinical status, CD4 percentage or viral load (**AI** for infants <12 weeks of age and **AII** for infants ≥12 weeks to 12 months).

- ART should be initiated in HIV-infected children ≥1 year who are asymptomatic or have mild symptoms with the following CD4 values:

  - Age 1 to <3 years
    - with CD4 T lymphocyte (CD4 cell) count <1000 cells/mm^3 or CD4 percentage <25% **(AII)**

  - Age 3 to <5 years
    - with CD4 cell count <750 cells/mm^3 or CD4 percentage <25% **(AII)**

  - Age ≥5 years
    - with CD4 cell count <350 cells/mm^3 **(AI*)**
    - with CD4 cell count 350–500 cells/mm^3 **(BII*)**

- ART should be considered for HIV-infected children ≥1 year who are asymptomatic or have mild symptoms with the following CD4 values:

  - Age 1 to <3 years
    - with CD4 cell count ≥1000 cells/mm^3 or CD4 percentage ≥25% **(BIII)**

  - Age 3 to <5 years
    - with CD4 cell count ≥750 cells/mm^3 or CD4 percentage ≥25% **(BIII)**

  - Age ≥5 years
    - with CD4 cell count >500 cells/mm^3 **(BIII)**

- In children with lower-strength (B level) recommendations for treatment, plasma HIV RNA levels >100,000 copies/mL provide stronger evidence for initiation of treatment **(BII)**.

- Issues associated with adherence should be assessed and discussed with an HIV-infected child's caregivers before initiation of therapy **(AIII)**. 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.

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

Infants Younger than 12 Months of Age

The Children with HIV Early Antiretroviral Therapy (CHER) Trial, a randomized clinical trial in South Africa, demonstrated that initiating triple-drug, antiretroviral therapy (ART) before age 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.[17] Most of the deaths in the infants in the delayed treatment arm occurred in the first 6 months after study entry. 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 age <12 months regardless of clinical status, CD4 percentage, or viral load (Table 7). 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 <12 months of age.

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 age 12 months, approximately 50% of children develop moderate immune suppression and 20% develop severe immune suppression.[18] 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 <12 months of age.[19] 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 cellcounts.[19]

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.[2, 20-23] 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.[24, 25] In infants with sustained control of plasma viremia, failure to detect extra-chromosomal replication intermediates suggests near-complete control of viral replication. Some of these infants have become HIV seronegative. Therapy is not curative, however, as proviral HIV-1 DNA continues to be detectable in peripheral blood lymphocytes and viral replication resumes if therapy is discontinued.[26, 27]

However, virologic suppression may take longer to achieve in young children than in older children or adults.[28, 29] Possible reasons for the poor response in infants include higher virologic set points in young infants, inadequate antiretroviral (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 of age.[2, 30, 31] In a 5-year follow-up study of 40 HIV-infected children who initiated treatment at <6 months of age, 98% had CD4 percentage >25% and 78% had undetectable viral load with median follow-up of 5.96 years.[2]

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 and continued assessment and support of adherence are especially important when treating young infants (see Adherence to Antiretroviral Therapy in HIV-Infected Children and Adolescents).

Finally, the possibility of toxicities—such as lipodystrophy, dyslipidemia, glucose intolerance, osteopenia,

and mitochondrial dysfunction—with prolonged therapy is a concern.[33] A clinical trial in South Africa is assessing whether it may be possible to stop therapy begun in infancy after a defined duration of treatment that protects a child during the period of greatest risk of HIV disease progression and mortality (such as 1 to 2 years) and then restart therapy when a child meets standard age-related criteria.

Children 1 Year of Age and Older

Disease progression is less rapid in children aged ≥1 year.[18] Children with clinical AIDS or significant symptoms (Clinical Category C or B—Table 6)[34] are at high risk of disease progression and death. The Panel recommends treatment for all such children, regardless of immunologic or virologic status. However, children aged ≥1 year who have mild clinical symptoms (Clinical Category A) or who are asymptomatic (Clinical Category N) are at lower risk of disease progression than children with more severe clinical symptoms.[35] It should also be noted that some Clinical Category B conditions, such as a single episode of serious bacterial infection, may be less prognostic of the risk of disease progression. Consideration of CD4 cell count and viral load may be useful in determining the need for therapy in children with these conditions.

In adults, the strength of recommendations to initiate ART in asymptomatic individuals is based primarily on risk of disease progression, as determined by baseline CD4 cell count.[10] In adults, both clinical trial and observational data support initiation of treatment in individuals with CD4 cell counts <350 cells/mm³. In HIV-infected adults in Haiti, a randomized clinical trial found significant reductions in mortality and morbidity with initiation of treatment when CD4 cell counts fell to <350 cells/mm³, compared with deferring treatment until CD4 cell counts fell to <200 cells/mm³.[11] In observational data in adults, a collaborative analysis of data from 12 adult cohorts in North America and Europe on 20,379 adults starting treatment between 1995 and 2003, the risk of AIDS or death was significantly less in adults who started treatment with CD4 cell counts of 200 to 350 cells/mm³ compared with those who started therapy at CD4 cell counts <200 cells/mm³.[36]

No randomized trial data exist to address the comparative efficacy of starting versus deferring treatment at higher CD4 thresholds in HIV-infected adults or children. Two observational studies in adults—the ART Cohort Collaboration (ART-CC) and North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD)—suggest a higher rate of progression to AIDS or death in patients deferring treatment until CD4 count is <350 cells/mm³ compared with patients starting ART at CD4 cell counts of 351 to 500 cells/mm³.[12, 13] The NA-ACCORD study demonstrated a benefit of starting treatment at CD4 cell counts >500 cell/mm³ compared with starting ART at CD4 cell counts below this threshold;[12] however the ART-CC cohort found no additional benefit for patients starting ART with CD4 cell counts >450 cells/mm³.[13] In a third observational study of 5,162 patients with CD4 cell counts between 500 to 799 cells/mm³, patients who started ART immediately did not experience a significant reduction in progression to AIDS or death (HR: 1.10, 95% CI: 0.67 to 1.79) or death alone (HR: 1.02, 95% CI: 0.49 to 2.12), compared with those who deferred therapy.[15] There are no similar observational data analyses for HIV-infected children.

In children, the prognostic significance of a specific CD4 percentage or count varies with age.[19, 37] 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 (Tables 3–4 and Figures 1–2). 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 age ≥5 years, with risk of progression similar to that observed in adults (Table 4).[19, 38] For children age 1 to <5 years, a similar increase in risk of AIDS or death is seen when CD4 percentage drops below 25% (Table 3).

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 <5 years of age. However,

an analysis of >21,000 pairs of CD4 measurements from 3,345 children <1 to 16 years of age in the HIV Paediatric Prognostic Markers Collaborative Study found that CD4 cell counts and percentages were frequently discordant around established World Health Organization (WHO) and the Pediatric European Network for Treatment of AIDS (PENTA) thresholds for initiation of ART (14% and 21%, respectively).[39] Furthermore, CD4 cell counts were found to provide greater prognostic value over CD4 percentage for short-term disease progression for children <5 years as well as in older children. 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 1 to 2 years of age versus 1.2 (CI 0.8, 1.6) for CD4 percentage. Therefore, the updated pediatric guidelines include CD4 cell count thresholds (which differ for children aged 1 to <3, 3 to 5, and ≥5 years due to age-related changes in absolute CD4 cell count) as well as CD4 percentage thresholds for all children >12 months of age. In the case of discordance between CD4 cell counts and percentages, decisions should be based on the lower value.

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.[37] Several studies have shown that older children with HIV RNA levels ≥100,000 copies/mL are at high risk of mortality[40-42] and lower neurocognitive performance;[43] similar findings have been reported in adults.[44-46] 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 ≥100,000 copies/mL (Table 3 and Figures 4–5).[37] For example, the estimated 1-year risk of death was 2 to 3 times higher in children with plasma HIV RNA of 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.[29, 47-51] In a study of 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.[52] Younger age at initiation of therapy has also been associated with improved immune response and with more rapid growth reconstitution.[47, 52, 53] Given that disease progression in children aged ≥5 years is similar to that in adults,[38] and observational data in adults show decreased risk of mortality with initiation of therapy when CD4 cell count is <500 cells/mm³,[12, 13] most experts feel that recommendations for asymptomatic children in this age range should be similar to those for adults. However, there are no pediatric data to address the optimal CD4 cell count threshold for initiation of therapy in older children; research studies are needed to answer this question in children more definitively. The HHS Adult Treatment Guidelines Committee has moved to endorse initiating ART in all HIV-infected adults regardless of CD4 cell count, using varying strengths of evidence to support different CD4 cell count thresholds[10] and incorporating 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 <13 years of age. Comparative studies on the impact of treatment versus treatment delay at specific higher CD4 cell counts have not been performed in children, and observational adult studies have produced conflicting results.[12, 13, 16] 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 perinatally infected children may be long-term nonprogressors, with no immunologic or clinical progression by 10 years of age despite receiving no ART.[54-56] Medication adherence is the core requirement for successful virologic control, but enforcing consistent adherence in childhood is often challenging.[57] Incomplete adherence leads to the selection of viral resistance mutations but forced administration of ARVs to children may result in treatment aversion or fatigue, which occurs among many perinatally infected children during adolescence.[58] The relative benefits of initiating ART in asymptomatic children with low viral burdens and high CD4 cell counts must be weighed against these potential risks.

The Panel recommends that ART should be initiated in all children who have AIDS or significant HIV-related symptoms (CDC Clinical Categories C and B, except for the following Category B condition: single episode of serious bacterial infection [Table 6]), regardless of CD4 percentage/count or HIV RNA level.

The Panel also generally recommends treatment for all children aged ≥1 year with no or mild symptoms (Clinical Categories N and A, or Clinical Category B disease due to a single episode of bacterial infection [Table 6]), with the strength of recommendation differing based on age and CD4 count/percentage. 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.

Treatment is strongly recommended regardless of HIV RNA level for children aged 1 to <3 years with CD4 cell counts <1000/mm^3 OR percentage <25%, and for children 3 to <5 years with CD4 cell counts <750 cells/mm^3 OR percentage <25%, based on observational pediatric data.[19] Treatment can also be considered for children aged 1 to <3 years with CD4 cell counts ≥1000/mm^3 and percentage ≥25% and for children 3 to <5 years with CD4 cell counts ≥750 cells/mm^3 and percentage ≥25%, although the strength of the recommendation is lower because of limited data. In these children, plasma HIV RNA levels may be helpful in decision making; plasma HIV RNA >100,000 copies/mL provides higher-rated evidence for treatment, based on pediatric observational data that demonstrate higher mortality risk with high HIV RNA levels.[19, 59]

For children age ≥5 years with no or minimal symptoms, treatment is recommended if CD4 cell counts are ≤500 cells/mm^3, regardless of HIV RNA level. The evidence for this recommendation is strongest for children with CD4 cell counts <350 cells/mm^3. For children with CD4 cell counts 350–500 cells/mm^3, the recommendation is based on observational data in adults and hence the evidence base is not as strong; this recommendation should not prohibit research studies in children designed to answer this question more definitively. Treatment should also be considered for children who are asymptomatic or have mild symptoms with CD4 counts >500 cells/mm^3, although the strength of the recommendation is lower because of limited data. Plasma HIV RNA levels may be helpful in decision making, with plasma HIV RNA >100,000 copies/mL providing higher rated evidence for treatment as noted above.[19, 59]

In general, except in infants and children with advanced HIV infection, ART does not need to be started immediately. Before initiating therapy, it is important to take time to educate caregivers (and older children) 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 and the higher CD4 cell count threshold now recommended for initiating therapy.

If therapy is deferred, the health care provider should closely monitor a child's virologic, immunologic, and clinical status (see Laboratory Monitoring of Pediatric HIV Infection). Factors to consider in deciding when to initiate therapy in children in whom treatment was deferred include:

- Increasing HIV RNA levels (such as HIV RNA levels approaching 100,000 copies/mL);
- CD4 count or percentage values approaching the age-related threshold for treatment;
- Development of clinical symptoms; and
- The ability of caregiver and child to adhere to the prescribed regimen.

Table 7. Indications for Initiation of Antiretroviral Therapy in HIV-Infected Children

Table 7 provides general guidance rather than absolute recommendations for individual patients. Factors to be considered in decisions about initiation of therapy include risk of disease progression as determined by CD4 percentage or count and plasma HIV RNA copy number, the potential benefits and risks of therapy, and the ability of the caregiver to adhere to administration of the therapeutic regimen. Before making the decision to initiate therapy, the provider should fully assess, discuss, and address issues associated with adherence with a child (if age appropriate) and the caregiver. 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.[a]

Age	Criteria	Recommendation
<12 months	• Regardless of clinical symptoms, immune status, or viral load	*Treat (**AI** for <12 weeks of age; **AII** for ≥12 weeks)*
1 to <3 years	• AIDS or significant HIV-related symptoms[b] • CD4 cell count <1000 cells/mm^3 *or* CD4 percentage <25%,[e] • Asymptomatic or mild symptoms[c] and ○ CD4 cell count ≥1000 cells/mm^3 or percentage ≥25%	*Treat (**AI***)* *Treat (**AII**)* *Consider Treatment* [d] *(**BIII**)*
3 to <5 years	• AIDS or significant HIV-related symptoms[b] • CD4 cell count <750 cells/mm^3 *or* CD4 percentage <25%,[e] • Asymptomatic or mild symptoms[c] and ○ CD4 cell count ≥750 cells/mm^3 or percentage ≥25%	*Treat (**AI***)* *Treat (**AII**)* *Consider Treatment* [d] *(**BIII**)*
≥5 years	• AIDS or significant HIV-related symptoms[b] • CD4 cell count ≤500 cells/mm^3,[e] • Asymptomatic or mild symptoms[c] and ○ CD4 cell count >500 cells/mm^3	*Treat (**AI***)* *Treat (**AI*** for CD4 cell count <350 cells/mm^3 and **BII*** for CD4 cell count 350–500 cells/mm^3)* *Consider Treatment* [d] *(**BIII**)*

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

[a] Children in whom ART is deferred need close follow-up. Factors to consider in deciding when to initiate therapy in children in whom treatment was deferred include:
  • Increasing HIV RNA levels (such as HIV RNA levels approaching 100,000 copies/mL);
  • CD4 cell count or percentage values approaching the age-related threshold for treatment;
  • Development of clinical symptoms; and
  • The ability of caregiver and child to adhere to the prescribed regimen.

[b] CDC Clinical Categories C and B (except for the following Category B condition: single episode of serious bacterial infection)

[c] CDC Clinical Category A or N or the following Category B condition: single episode of serious bacterial infection

[d] The rating of the evidence is stronger for treatment in this group of patients if plasma HIV RNA level is >100,000 copies/mL (BII)

[e] Laboratory data should be confirmed with a second test to meet the treatment criteria before initiation of ART.

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