



## **Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection**

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## Treatment Recommendations (Last updated November 1, 2012; last reviewed November 1, 2012)

### General Considerations

Antiretroviral (ARV) treatment of pediatric HIV infection has steadily improved with the introduction of potent combination drug regimens that effectively suppress viral replication in most patients, resulting in a lower risk of failure due to development of drug resistance. Currently, combination regimens including at least three drugs from at least two drug classes are recommended; such regimens have been associated with enhanced survival, reduction in opportunistic infections and other complications of HIV infection, improved growth and neurocognitive function, and improved quality of life in children.<sup>1-5</sup> In the United States and the United Kingdom, significant declines (81%–93%) in mortality have been reported in HIV-infected children between 1994 and 2006, concomitant with increased use of highly active combination regimens;<sup>6-8</sup> significant declines in HIV-related morbidity and hospitalizations in children have been observed in the United States and Europe over the same time period.<sup>4,7</sup>

The increased survival of HIV-infected children is associated with challenges in selecting successive new ARV drug regimens. Additionally, therapy is associated with short- and long-term toxicities, some of which are only now beginning to be recognized in children.<sup>9-11</sup> (See [Management of Medication Toxicity or Intolerance](#) and [Table 17](#).)

ARV drug-resistant virus can develop during combination antiretroviral therapy (ART) because of poor adherence, a regimen that is not potent, or a combination of these factors which results in incomplete viral suppression. Additionally, primary drug resistance may be seen in ARV-naive children who have become infected with a resistant virus.<sup>12,13</sup> Thus, decisions about when to start therapy and what drugs to choose in ARV-naive children and on how to best treat ARV-experienced children remain complex. Whenever possible, decisions regarding the management of pediatric HIV infection should be directed by or made in consultation with a specialist in pediatric and adolescent HIV infection. Treatment of ARV-naive children (when and what to start), when to change therapy, and treatment of ARV-experienced children will be discussed in separate sections of the guidelines.

Several factors need to be considered in making decisions about initiating and changing ART in children, including:

- severity of HIV disease and risk of disease progression, as determined by age, presence or history of HIV-related or AIDS-defining illnesses (see pediatric clinical staging system for HIV, [Table 6](#)),<sup>14,15</sup> degree of CD4 T lymphocyte (CD4 cell) immunosuppression, and level of HIV plasma viremia;
- availability of appropriate (and palatable) drug formulations and pharmacokinetic (PK) information on appropriate dosing in a child's age group;
- potency, complexity (such as dosing frequency, food and fluid requirements), and potential short- and long-term adverse effects of the ARV regimen;
- effect of initial regimen choice on later therapeutic options;
- a child's ART history;
- presence of ARV drug-resistant virus;
- presence of comorbidity, such as tuberculosis, hepatitis B or C virus infection, or chronic renal or liver disease, that could affect drug choice;
- potential ARV drug interactions with other prescribed, over-the-counter, or complementary/alternative medications taken by a child; and

- the ability of the caregiver and child to adhere to the regimen.

The following recommendations provide general guidance for decisions related to treatment of HIV-infected children, and flexibility should be exercised according to a child's individual circumstances. Guidelines for treatment of HIV-infected children are evolving as new data from clinical trials become available. Although prospective, randomized, controlled clinical trials offer the best evidence for formulation of guidelines, most ARV drugs are approved for use in pediatric patients based on efficacy data from clinical trials in adults, with supporting PK and safety data from Phase I/II trials in children. In addition, efficacy has been defined in most adult trials based on surrogate marker data, as opposed to clinical endpoints. For the development of these guidelines, the Panel reviewed relevant clinical trials published in peer-reviewed journals or in abstract form, with attention to data from pediatric populations when available.

## Goals of Antiretroviral Treatment

Current ART does not eradicate HIV infection because of the long half-life of latently infected CD4 cells;<sup>16-18</sup> some data suggest that the half-life of intracellular HIV proviral DNA is even longer in infected children than in adults (median 14 months vs. 5–10 months, respectively).<sup>19</sup> Thus, based on currently available data, HIV causes a chronic infection likely requiring treatment for life once a child starts therapy. The goals of ART for HIV-infected children and adolescents include:

- reducing HIV-related mortality and morbidity;
- restoring and/or preserving immune function as reflected by CD4 cell measures;
- maximally and durably suppressing viral replication;
- preventing emergence of viral drug-resistance mutations;
- minimizing drug-related toxicity;
- maintaining normal physical growth and neurocognitive development;
- improving quality of life; and
- reducing the risk of sexual transmission to discordant partners in adolescents who are sexually active.

Strategies to achieve these goals require complex balancing of sometimes competing considerations.

*Use and selection of ART:* The treatment of choice for HIV-infected children is a regimen containing at least three drugs from at least two classes of ARV drugs. The Panel has recommended several preferred and alternative regimens (see [What Drugs to Start: Initial Combination Therapy for Antiretroviral-Naive Children](#)). The most appropriate regimen for an individual child depends on multiple factors as noted above. A regimen that is characterized as an alternative choice may be a preferred regimen for some patients.

*Drug sequencing and preservation of future treatment options:* The choice of ARV treatment regimens should include consideration of future treatment options, such as the presence of or potential for drug resistance. Multiple changes in ARV drug regimens can rapidly exhaust treatment options and should be avoided. Appropriate sequencing of drugs for use in initial and second-line therapy can preserve future treatment options and is another strategy to maximize long-term benefit from therapy. Current recommendations for initial therapy are to use two classes of drugs (see [What Drugs to Start: Initial Combination Therapy for Antiretroviral-Naive Children](#)), thereby sparing three classes of drugs for later use.

*Maximizing adherence:* As discussed in [Adherence to Antiretroviral Therapy in HIV-Infected Children and Adolescents](#), poor adherence to prescribed regimens can lead to subtherapeutic levels of ARV medications, which enhances the risk of development of drug resistance and likelihood of virologic failure. Issues related to adherence to therapy should be fully assessed, discussed, and addressed with a child's caregiver and the child (when age appropriate) before the decision to initiate therapy is made. **Participation by the caregiver and child**

**in the decision-making process is crucial.** Potential problems should be identified and resolved before starting therapy, even if this delays initiation of therapy. In addition, frequent follow-up is important to assess virologic response to therapy, drug intolerance, viral resistance, and adherence. Finally, in patients who experience virologic failure, it is critical to fully assess adherence before making changes to the ARV regimen.

**Table 6. 1994 Revised HIV Pediatric Classification System: Clinical Categories (page 1 of 2)**

<p><b>Category N: Not Symptomatic</b></p> <p>Children who have no signs or symptoms considered to be the result of HIV infection or who have only one of the conditions listed in Category A.</p>
<p><b>Category A: Mildly Symptomatic</b></p> <p>Children with <b>two</b> or more of the following conditions but none of the conditions listed in Categories B and C:</p> <ul style="list-style-type: none"> <li>• Lymphadenopathy (<math>\geq 0.5</math> cm at more than two sites; bilateral = one site)</li> <li>• Hepatomegaly</li> <li>• Splenomegaly</li> <li>• Dermatitis</li> <li>• Parotitis</li> <li>• Recurrent or persistent upper respiratory infection, sinusitis, or otitis media</li> </ul>
<p><b>Category B: Moderately Symptomatic</b></p> <p>Children who have symptomatic conditions, other than those listed for Category A or Category C, that are attributed to HIV infection. Examples of conditions in Clinical Category B include, but are not limited to, the following:</p> <ul style="list-style-type: none"> <li>• Anemia (<math>&lt; 8</math> g/dL), neutropenia (<math>&lt; 1,000</math> cells/mm<sup>3</sup>), or thrombocytopenia (<math>&lt; 100,000</math> cells/mm<sup>3</sup>) persisting <math>\geq 30</math> days</li> <li>• Bacterial meningitis, pneumonia, or sepsis (single episode)</li> <li>• Candidiasis, oropharyngeal (that is, thrush) persisting for <math>&gt; 2</math> months in children aged <math>&gt; 6</math> months</li> <li>• Cardiomyopathy</li> <li>• Cytomegalovirus infection with onset before age 1 month</li> <li>• Diarrhea, recurrent or chronic</li> <li>• Hepatitis</li> <li>• Herpes simplex virus (HSV) stomatitis, recurrent (that is, more than two episodes within 1 year)</li> <li>• HSV bronchitis, pneumonitis, or esophagitis with onset before age 1 month</li> <li>• Herpes zoster (that is, shingles) involving at least two distinct episodes or more than one dermatome</li> <li>• Leiomyosarcoma</li> <li>• Lymphoid interstitial pneumonia (LIP) or pulmonary lymphoid hyperplasia complex</li> <li>• Nephropathy</li> <li>• Nocardiosis</li> <li>• Fever lasting <math>&gt; 1</math> month</li> <li>• Toxoplasmosis with onset before age 1 month</li> <li>• Varicella, disseminated (that is, complicated chickenpox)</li> </ul>

**Table 6. 1994 Revised HIV Pediatric Classification System: Clinical Categories (page 2 of 2)**

### **Category C: Severely Symptomatic**

Children who have any condition listed in the 1987 surveillance case definition for AIDS (below), with the exception of LIP, which is a Category B condition:

- Serious bacterial infections, multiple or recurrent (that is, any combination of at least two culture-confirmed infections within a 2-year period), of the following types: septicemia, pneumonia, meningitis, bone or joint infection, or abscess of an internal organ or body cavity (excluding otitis media, superficial skin or mucosal abscesses, and indwelling catheter-related infections)
- Candidiasis, esophageal or pulmonary (bronchi, trachea, lungs)
- Coccidioidomycosis, disseminated (at site other than or in addition to lungs or cervical or hilar lymph nodes)
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis or isosporiasis with diarrhea persisting >1 month
- Cytomegalovirus disease with onset of symptoms at age >1 month (at a site other than liver, spleen, or lymph nodes)
- Encephalopathy (at least one of the following progressive findings present for at least 2 months in the absence of a concurrent illness other than HIV infection that could explain the findings): a) failure to attain or loss of developmental milestones or loss of intellectual ability, verified by standard developmental scale or neuropsychological tests; b) impaired brain growth or acquired microcephaly demonstrated by head circumference measurements or brain atrophy demonstrated by computerized tomography or magnetic resonance imaging (serial imaging is required for children aged <2 years); c) acquired symmetric motor deficit manifested by two or more of the following: paresis, pathologic reflexes, ataxia, or gait disturbance
- Herpes simplex virus infection causing a mucocutaneous ulcer that persists for >1 month or bronchitis, pneumonitis, or esophagitis for any duration affecting a child aged >1 month
- Histoplasmosis, disseminated (at a site other than or in addition to lungs or cervical or hilar lymph nodes)
- Kaposi sarcoma
- Lymphoma, primary, in brain
- Lymphoma, small, noncleaved cell (Burkitt), or immunoblastic or large cell lymphoma of B-cell or unknown immunologic phenotype
- Mycobacterium tuberculosis, disseminated or extrapulmonary
- Mycobacterium, other species or unidentified species, disseminated (at a site other than or in addition to lungs, skin, or cervical or hilar lymph nodes)
- *Mycobacterium avium* complex or *Mycobacterium kansasii*, disseminated (at site other than or in addition to lungs, skin, or cervical or hilar lymph nodes)
- *Pneumocystis jirovecii* pneumonia
- Progressive multifocal leukoencephalopathy
- Salmonella (nontyphoid) septicemia, recurrent
- Toxoplasmosis of the brain with onset at age >1 month
- Wasting syndrome in the absence of a concurrent illness other than HIV infection that could explain the following findings: a) persistent weight loss >10% of baseline; OR b) downward crossing of at least two of the following percentile lines on the weight-for-age chart (such as 95th, 75th, 50th, 25th, 5th) in a child  $\geq 1$  year of age; OR c) <5th percentile on weight-for-height chart on two consecutive measurements,  $\geq 30$  days apart **PLUS 1)** chronic diarrhea (that is,  $\geq$  two loose stools per day for >30 days), **OR 2)** documented fever (for  $\geq 30$  days, intermittent or constant)

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