General Considerations

Since the introduction of potent combination antiretroviral (ARV) drug regimens in the mid-1990s, the treatment of pediatric HIV has steadily improved. These potent regimens have the ability to suppress viral replication, thus lowering the risk of virologic failure due to the development of drug resistance. Antiretroviral therapy (ART) that includes 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.\(^1\)\(^-\)\(^4\) In the United States and the United Kingdom, significant declines in morbidity, mortality, and hospitalizations have been reported in children living with HIV between 1994 and 2006, concomitant with increased use of highly active combination regimens.\(^5\)\(^-\)\(^7\) As a result, children with perinatal HIV infection are now living into the third and fourth decades of life, and potentially beyond.

The increased survival of children with HIV is associated with challenges in selecting successive new ARV drug regimens. In addition, therapy is associated with short- and long-term toxicities, which can be recognized in childhood or adolescence (see Management of Medication Toxicity or Intolerance).\(^8\)\(^-\)\(^12\)

ARV drug-resistant virus can develop during ART when viral replication occurs in the presence of subtherapeutic ARV concentrations caused by poor adherence, poor absorption, a regimen that is not potent, or a combination of these factors. In addition, primary drug resistance may be seen in ARV-naive children who have contracted a resistant virus.\(^13\)\(^-\)\(^17\) Thus, decisions about which drugs to choose for ARV-naive children (see What to Start) and how to best treat ARV-experienced children remain complex. Whenever possible, decisions regarding the management of pediatric HIV should be directed by or made in consultation with a specialist in pediatric HIV infection. Treatment of ARV-naive children (including information on when to start treatment and which drugs to use), when to change therapy, and treatment of ARV-experienced children are discussed in separate sections of the guidelines. For guidance about treatment of sexually mature adolescents, see the Adult and Adolescent Guidelines.

In addition to trials demonstrating benefits of ART in symptomatic adults and those with lower CD4 T lymphocyte (CD4) cell counts,\(^18\) a randomized clinical trial has provided evidence of benefit with initiation of ART in asymptomatic adults with CD4 cell counts >500 cells/mm\(^3\).\(^19\) Similarly, improved outcomes have been shown with initiation of ART in asymptomatic infants aged 6 to 12 weeks. Although there are fewer available data on the risks and benefits of immediate therapy in asymptomatic children with HIV than in adults, the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) recommends ART for all children with HIV (see When to Start).

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

- **Age** (treatment initiation is urgent for infants aged <12 months)
- Severity of HIV disease and risk of disease progression, as determined by presence (see When to Initiate) or history of HIV-related illnesses, and degree of CD4 immunosuppression, (see Revised Surveillance Case Definition for HIV Infection)

General considerations for choosing specific ARV drugs for ART include (see What to Start):

- Availability of appropriate (and palatable) drug formulations and pharmacokinetic (PK) information on appropriate dosing in a child’s age/weight group;
- Potency, complexity (e.g., dosing frequency, food requirements), and potential short- and long-term adverse effects of the ART 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 decisions about drug choice and the timing of therapy initiation;
• Potential ARV drug interactions with other prescribed, over-the-counter, or complementary/alternative medications taken by a child; and
• The anticipated ability of the caregiver and child to adhere to the regimen.

The following recommendations provide general guidance for treatment of children living with HIV, but a child’s individual circumstances should be considered when making treatment decisions. Guidelines for treatment of children living with HIV are evolving as new data from clinical trials become available. Although prospective, randomized, controlled clinical trials offer the best evidence for creating 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 1/2 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**

Currently available ART has not been shown to eradicate HIV infection in infants with perinatally acquired HIV, due to persistence of HIV in CD4 lymphocytes and other long-lived cells. This was demonstrated when a child with HIV who was treated with ART at 30 hours of age experienced viremic rebound after more than 2 years of undetectable HIV RNA levels while off ART. There are data to suggest that, after viral suppression, the mean half-life of intracellular HIV proviral DNA can be up to almost 16 years. Thus, based on currently available data, HIV causes a chronic infection that likely requires life-long treatment once a child starts therapy. The goals of ART for children living with HIV include:

• Preventing and reducing HIV-related morbidity and mortality;
• 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
• Preventing transmission of HIV to others

Strategies to achieve these goals require a complex balance of potentially competing considerations.

**Use and Selection of Combination Antiretroviral Therapy**

The treatment of choice for children with HIV 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 to Start). The most appropriate regimen for an individual child depends on multiple factors, as noted above. A regimen that is characterized as an alternative choice in the guidelines 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 to Start), thereby sparing three classes of drugs for later use.

Maximizing Adherence

As discussed in Adherence to Antiretroviral Therapy in Children and Adolescents Living with HIV, poor adherence to prescribed regimens can lead to subtherapeutic concentrations of ARV medications, which increases the risk of developing drug resistance and the likelihood of virologic failure. Outside of the very young age group (<1 year) and children with significant immunologic impairment or clinical HIV symptoms (where therapy should be initiated within 1–2 weeks of diagnosis, with an expedited discussion on adherence and close follow-up), the risk of rapid disease progression is low. This provides adequate time to fully assess, identify, discuss, and address issues associated with potential adherence problems with the caregivers and the child (when age-appropriate) prior to initiating therapy. Participation by the caregiver and child in the decision-making process is crucial. 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 and possible viral resistance and to consider measuring serum drug concentrations before making changes to the ART regimen.

References


