Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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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 is recommended; such regimens have been associated with enhanced survival, reduced incidence of opportunistic infections and other complications of HIV infection, improved growth and neurocognitive function, and improved quality of life in children.\textsuperscript{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. The goal of treatment is to optimize immune status and general health to ensure a full and productive adult life\textsuperscript{5-7} As a result, individuals with perinatally acquired HIV infection are now living well into adulthood.

It can be challenging to select successive new ARV drug regimens across the lifetime of a child with perinatally acquired HIV. In addition, therapy is associated with short-term and long-term toxicities, which can be recognized in childhood or adolescence (see Management of Medication Toxicity or Intolerance).\textsuperscript{8-12} Drug-resistant virus can develop during ART when viral replication occurs in the presence of subtherapeutic ARV concentrations, which can be caused by poor adherence, poor absorption, a regimen that is not sufficiently 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.\textsuperscript{13-17} Thus, clinicians must consider a number of factors when deciding which drugs to choose for ARV-naive children (see What to Start) and how to best treat ARV-experienced children remains complex.

Decisions regarding the management of pediatric HIV should be directed by or made in consultation with a specialist in pediatric HIV infection whenever possible. 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 Antiretroviral Guidelines.

In addition to trials that have demonstrated the benefits of ART in symptomatic adults and those with lower CD4 T lymphocyte (CD4) cell counts,\textsuperscript{18} a randomized clinical trial has provided evidence that initiating ART in asymptomatic adults with CD4 cell counts \(>500\) cells/mm\(^3\) is beneficial as well.\textsuperscript{19} Similarly, improved outcomes have been shown with initiation of ART in asymptomatic infants aged 6 weeks to 12 weeks.\textsuperscript{20} 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 Initiate Therapy in Antiretroviral-Naive Children).

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

- Age (see When to Initiate Therapy in Antiretroviral-Naive Children); and
- Severity of HIV disease and risk of disease progression, as determined by the presence of HIV-related illnesses (see When to Initiate Therapy in Antiretroviral-Naive Children) or a history of HIV-related illnesses, and the patient’s 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):

- Presence of drug-resistant virus;
- 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-term 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 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 treating children who are living with HIV, but a child’s individual circumstances should be considered when making treatment decisions. Guidelines for the 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 that were 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 the persistence of HIV in CD4 cells and other long-lived cells. In one case, a child with HIV who was treated with ART between 30 hours and 18 months of age achieved more than 2 years of undetectable HIV RNA levels while off ART. However, the child subsequently experienced viremic rebound. 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 counts;
- Maximally and durably suppressing viral replication;
- Preventing emergence of viral drug-resistance mutations;
- Minimizing drug-related toxicity;
- Optimizing growth, sexual maturation, 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.
Selection of an Antiretroviral Therapy Regimen

The treatment of choice for children with HIV is a regimen that contains 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 in the guidelines may be a preferred regimen for some patients.

Drug Sequencing and Preservation of Future Treatment Options

When choosing an ART regimen, clinicians should consider the need for future treatment options and take into account the presence of or potential for drug resistance. Making multiple changes to an ART regimen can rapidly exhaust treatment options and should be avoided. Choosing an appropriate sequence of drugs for initial and second-line therapy can preserve future treatment options and can help maximize long-term benefit from therapy. The current recommended regimens for initial therapy include 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 (aged <1 year) and children with significant immunologic impairment or clinical HIV symptoms (therapy should be initiated within 1–2 weeks of diagnosis in these children, 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


