Perspective

Review of Recent Guidelines for Antiretroviral Treatment of HIV-Infected Children

Antiretroviral treatment of HIV infection in children requires consideration of a number of factors specific to this population, including differences in drug pharmacokinetics and in virologic and immunologic markers compared with older patients, as well as age-related adherence issues. Recommendations for treatment of pediatric HIV disease have been finalized by the François-Xavier Bagnoud Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children. Working Group recommendations included when to initiate treatment, which regimens to use in initial treatment, and considerations in switching regimens. This article, which summarizes this guideline update, is drawn from a presentation by James M. Oleske, MD, MPH, given at the June 2003 International AIDS Society–USA-sponsored 6th Annual Ryan White CARE Act Clinical Conference in Orlando, Florida.

Recent scares to society such as smallpox, severe acute respiratory syndrome (SARS), and monkey pox produced public health responses reflecting considerable investment of time, effort, and resources. This is as it should be. However, for some of us at least, there is constant incredulity over how easily it appears that some segments of society are distracted from the current suffering caused by and the ubiquitous threat posed by HIV disease—a disease that may claim the lives of one fourth of the world's population. This abandonment is perhaps greatest in regard to HIV-infected children who depend on adults to bring them safely through childhood. The burden of disease in places such as Chennai, India, where virtually all HIV-infected children also have cavitary tuberculosis and where many live in orphanages, is particularly alarming. This is not to say that response to HIV disease has been or is optimal in the United States. Our American dream continues to be plagued by disparities in treatment, quality of care, and outcomes among different demographic groups.

The recommendations for treatment of pediatric HIV disease recently finalized by the Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Infants and Children are intended for the United States, which has the resources to ensure their implementation. However, for many other locations around the world, including those with the greatest burden of disease, these US recommendations are far beyond available health care resources. Specific recommendations for the use of antiretroviral drugs in resource-poor areas of the world have recently been developed (WHO guidelines, 2003, www.who.int/3by5/publications/guidelines/en/arv_guidelines.pdf).

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Special Considerations in Antiretroviral Therapy

Treating HIV-infected children involves special considerations in the areas of diagnosis, age-related differences in pharmacokinetics, age-related differences in disease natural history—including differences in virologic and immunologic markers of disease—and adherence to treatment. Diagnostic testing of HIV-exposed infants should be performed with HIV DNA polymerase chain reaction testing or HIV culture within 48 hours of birth, at 14 days (optimal), at 1 to 2 months, and at 3 to 6 months. With regard to the pharmacokinetics of antiretroviral and other drugs used in treating HIV disease and opportunistic illnesses, differences between children and adults in body composition, renal excretion, liver metabolism, and gastrointestinal function are associated with potential differences in drug distribution, metabolism, and clearance, and thus potential differences in drug dosing requirements and adverse effects.

Special considerations in the natural history of disease include recognition that growth failure and central nervous system (CNS) disease in children may require specific attention to the use of antiretroviral drugs that sufficiently penetrate the CNS. Further, young children have higher normal CD4+ cell counts than adults, with levels slowly declining to adult levels by about 6 years of age. If CD4+ cell count is to be used in treatment decisions, age-appropriate cell counts should be used. CD4+ cell percentage is likely a better marker for HIV disease progression than CD4+ cell count in children. As in adults, plasma HIV RNA level is the best indicator of risk for disease progression in children and is used to help determine when to initiate and change antiretroviral therapy in pediatric patients. Plasma HIV RNA level is characteristically very high in HIV-infected newborns and young children. For purposes of treatment decisions, changes in plasma HIV RNA level should be considered significant only if they are greater than 5-fold (0.7 $\log_{10}$ RNA copies/mL) in infants aged 2 years or younger and greater than 3-fold (0.5 $\log_{10}$ RNA copies/mL) in children older than 2 years. Special considerations in adherence will be discussed throughout this article. The importance of maintaining strict adherence (>85%) with antiretroviral schedules has become increasingly relevant.

Factors in Decisions Regarding Initiation of Treatment

As in adults, factors involved in decisions on initiation of antiretroviral treatment in children include severity of disease and risk of progression as assessed by CD4+ cell count or percentage and

plasma HIV RNA level, and as indicated by the presence or history of severe opportunistic illness. Other factors to be considered include the availability of appropriate, palatable drugs (liquid preparations are required in many cases), the complexity of regimens, and expected adverse effects in these patients, who are still growing and developing. Decisions regarding initial treatment also need to take into account the effect of the initial choice on later treatment options, a problem heightened by the length of time that these patients conceivably will require treatment. Finally, the presence of co-morbidities and the potential drug interactions of antiretrovirals with other required medications need to be considered.

Adherence to antiretroviral regimens is crucial to successful treatment, and the ability of the child and caregiver(s) to adhere to regimens is thus a central consideration in the decision to initiate treatment. Antiretroviral treatment is most effective in treatment-naive patients, and poor adherence enhances the emergence of viral resistance. To maximize the benefit to be derived from initial treatment, it is thus essential that adherence issues are assessed, discussed, and addressed, and that all potential problems with adherence are resolved prior to initiating therapy.

Working Group Recommendations for Initiating Antiretroviral Treatment

Children Younger Than 12 Months

Risk of disease progression is inversely correlated with age in younger HIV-infected children. However, the ability to distinguish infants (ie, children younger than 6 months) at risk for rapid progression versus slower progression is very limited at present. There are few clinical trial data on the effects of aggressive antiretroviral therapy in infants. There is potential for underdosing and overdosing of infants due to inadequate information on optimal drug levels, and there is also inadequate information on long-term toxicities in children beginning therapy at this early age.

Under the newly revised guidelines, the Working Group recommends that treatment be initiated for any infant with clinical or immunologic symptoms of HIV disease regardless of plasma HIV RNA level, and that treatment be considered for infants who are asymptomatic and have normal immune function; some experts would treat all infants aged 6 months or younger. The indications for initiating treatment according to clinical status, CD4+ cell percentage, and plasma HIV RNA level are shown in Table 1.

Children 12 Months of Age and Older

Risk of rapid disease progression is lower in children aged 12 months or older than in younger children, and children in this older age group with mild or moderate clinical symptoms (category A or B) or moderate immune suppression (category 2) are at reduced risk of progression compared with children having more severe findings. In children in this age group, plasma HIV RNA levels provide useful information on the risk of disease progression and should be taken into account in decisions regarding initiation of therapy.

The Working Group recommends that treatment be started in children with AIDS (category C) or severe immune suppression (category 3) and that treatment be considered in children with mild-to-moderate clinical symptoms (category A or B), moderate immune suppression (category 2), or confirmed plasma HIV RNA level of 100,000 copies/mL or higher. Factors to consider in deciding whether to initiate therapy in children in this age group include the rate of plasma HIV RNA level increases (and how close the value is to 100,000 copies/mL), the rate of CD4+ cell count or percentage declines and how close they are to that associated with severe immune suppression, and the presence of clinical symptoms. In addition, the ability of the child and caregiver(s) to adhere to the treatment regimen should have an effect on the decision whether to start treatment. Indications for antiretroviral treatment in this age group according to clinical status, CD4+ cell percentage, and plasma HIV RNA level are shown in Table 2.

Choice of Initial Antiretroviral Therapy

The goals of antiretroviral therapy are to achieve maximal suppression of viral replication to below assay detection limits for as long as possible and to preserve or restore immune function. The goal of viral load suppression to below detection limits is not always achievable in children, who may have very high plasma HIV RNA levels. It is recommended that treatment be initiated with triple-drug combinations, since such combinations have been shown to slow disease progression, improve survival, produce a more sustained virologic

Table **1.** Indications for Initiation of Antiretroviral Treatment in Children Younger Than 12 Months

Clinical Category		CD4+ Cell Percentage	Plasma HIV RNA Level	Recommendation
Symptomatic (category A, B, or C)	**OR**	≤25% (category 2 or 3)	Any	Treat
Asymptomatic (category N)	**AND**	>25% (category 1)	Any	Consider treatment

Clinical categories: A indicates mild clinical symptoms with usually only nonspecific generalized lymphadenopathy; B, moderate clinical symptoms; C, AIDS; N, asymptomatic. Immunologic categories (CD4+ cell percentage): 1, >25%; 2, 15%-25%; 3, <15%. Adapted from Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection, September 2003.

Table **2.** Indications for Initiation of Antiretroviral Treatment in Children Aged 12 Months or Older

Clinical Category		CD4+ Cell Percentage		Plasma HIV RNA Level	Recommendation
AIDS (category C)	**OR**	<15% (category 3)		Any	Treat
Mild-to-moderate symptoms (category A or B)	**OR**	15%-25% (category 2)	**OR**	≥100,000 copies/mL	Consider treatment
Asymptomatic (category N)	**AND**	>25% (category 1)	**AND**	<100,000 copies/mL	Many experts would defer therapy and closely monitor clinical, immune, and viral parameters

Clinical categories: A indicates mild clinical symptoms with usually only nonspecific generalized lymphadenopathy; B, moderate clinical symptoms; C, AIDS; N, asymptomatic. Immunologic categories (CD4+ cell percentage): 1, >25%; 2, 15%-25%; 3, <15%. Adapted from Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection, September 2003.

response, and delay the emergence of viral resistance. Zidovudine monotherapy is recommended for prophylaxis in perinatally exposed infants with indeterminate infection status during the first 6 weeks of life (with this constituting the only recommended use of antiretroviral monotherapy). It is also recommended that viral resistance testing be considered prior to initiation of treatment in newly diagnosed infants younger than 12 months, particularly if the mother is known or suspected to have drug-resistant virus.

The Working Group recommendations on regimens for use in initial therapy have been formulated with consideration of the following: data on the durability of viral suppression and clinical and immunologic response; data on the types and incidence of toxic effects; availability and palatability of drug formulations for children; dosing frequency and food or fluid needs; and the potential for drug-drug interactions.

Drug combinations recommended for use in children consist of the following: 1) a protease inhibitor (PI) plus 2 nucleoside analogue reverse transcriptase inhibitors (nRTIs); and 2) a nonnucleoside reverse transcriptase inhibitor (NNRTI) plus 2 nRTIs. Recommendations for specific PI-based, NNRTI-based, and nRTI-based regimens are shown in Table 3. An advantage of PI-based regimens is high potency, and disadvantages include a high pill burden and difficulty with palatability. Advantages of NNRTI-based regimens include effectiveness and palatability, and disadvantages include rapid emergence of viral resistance when viral suppression is not optimal. An advantage of nRTI-based regimens is the sparing of other drug classes for future use; however, these regimens have been shown to be less potent than PI- and NNRTI-based combinations in adult clinical trials. Of note, children at a number of treatment sites have received long-term treatment with double-nRTI therapy (ie, largely treatment beginning prior to the potent antiretroviral therapy era) and have maintained good clinical status and immunologic function. Thus, dual-nRTI therapy can be used in special circumstances. *Not recommended* for use in initial therapy are monotherapy (except for zidovudine prophylaxis, as described above), certain dual-nRTI combinations, such as zidovudine and stavudine, and the saquinavir hard-gel capsule formulation.

Currently, there are *insufficient data to recommend the following:* dual-nRTIs; delavirdine; dual PIs (except for the lopinavir/ritonavir co-formulation); three-class combinations (eg, PI plus NNRTI plus nRTI); tenofovir-containing regimens; and enfuvirtide-containing regimens.

Considerations in Changing Regimens

The primary indications for changing an antiretroviral regimen are treatment failure based on clinical, virologic, or immunologic parameters, toxicity or intolerance of the current regimen, and new findings demonstrating that a new regimen is superior to the current regimen. Guiding principles in cases in which the antiretroviral regimen is to be changed because of toxicity or intolerance include the following:

1) Choose drugs with toxicity profiles different from those in the current regimen.
2) Changing a single drug is permissible.
3) If the dose of a drug is reduced, do not reduce the dose below the lower end of the therapeutic range for that particular drug.

Guiding principles in cases in which the antiretroviral regimen must be changed because of disease progression include the following:

1) Assess and review adherence.
2) Never change only 1 drug at a time—a new regimen must contain at least 2 drugs different from those in the current regimen.
3) Consider overlap of resistance patterns of drugs in the new regimen.
4) Consider potential drug interactions with other medications.
5) Discuss quality-of-life issues for patients with advanced HIV disease.

Adherence and Other Special Considerations for Children and Adolescents

There are a number of issues in adherence to antiretroviral treatment specific to pediatric patients that must be addressed to ensure maximum benefit of treatment. Drugs must be available in a palatable liquid or mixable formulation for infants and younger children. Requirements for administering drugs with or without food can be difficult to meet in younger children because of eating schedules. Further, the reluctance

Table 3. Recommended Initial Antiretroviral Therapy for Children

Protease Inhibitor-Based Regimens	
Strongly recommended	2 nRTIs *plus* lopinavir/ritonavir *or* nelfinavir *or* ritonavir
Alternative recommendation	2 nRTIs *plus* indinavir *or* amprenavir (children ≥4 years old)
Use in special circumstances	2 nRTIs *plus* saquinavir soft gel capsule
Nonnucleoside Reverse Transcriptase Inhibitor-Based Regimens	
Strongly recommended	Children >3 years old: 2 nRTIs *plus* efavirenz
	Children ≤3 years old or who cannot swallow capsules: 2 nRTIs *plus* nevirapine
Alternative recommendation	2 nRTIs *plus* nevirapine
Nucleoside Reverse Transcriptase Inhibitor-Based Regimens	
Strongly recommended	None
Alternative recommendation	Zidovudine *plus* lamivudine *plus* abacavir
Use in special circumstances	2 nRTIs

nRTI indicates nucleoside reverse transcriptase inhibitor. Adapted from Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection, September 2003.

of families to disclose the child's HIV diagnosis may interfere with medication administration during day care or school hours. A child's developmental level influences his or her ability and willingness to take medications; this should be taken into account when enlisting the child's cooperation. Finally, the child is dependent on the caregiver(s) for medication administration, and commitment and vigilance on the part of the caregiver(s) is necessary.

For adolescents in particular, there may be psychosocial needs that have to be addressed to maximize the chances of adherence to treatment. Developmental issues that have to be confronted in patients in this group include those surrounding their characteristic concrete thought processes and their desire to be like their peers (ie, those who do not have to take medications). Homelessness and lack of family support are formidable barriers to adherence in many infected adolescents. Treatment adherence is a responsibility for everyone involved with the patient, including the patient him- or herself, the family, the social worker, the nurse, and the physician.

Other issues arise for patients with advanced disease who have extensive prior antiretroviral experience. How does one approach the very sick long-term survivor who must still continue to take numerous medications? What is the best course when there are limited remaining treatment options? What happens when all treatment options are exhausted?

No matter what the status of our patients, caring *about* them matters. We cannot always provide an intervention that dramatically improves their condition. What we can always do is pay attention to the little things, such as making the medication more palatable and easier to take, relieving pain, and making and keeping regular appointments with patients. As Aesop said, "No act of kindness, no matter how small, is ever wasted."

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Suggested Reading

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