

A PEER-REVIEWED ARTICLE

## **There is much to be considered when prescribing ARV therapy in HIV+ children**

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The rapidly expanding body of knowledge concerning treatment of adult HIV infection over the past two years, with the introduction of novel antiretroviral (ARV) agents in multiple new classes, certainly benefits all people living with the disease. Treatment of children with perinatally-acquired HIV infection, however, requires additional considerations due to the unique characteristics of the pediatric population—or more accurately, the several distinct populations included in the term “children.” Since perinatal transmission of HIV remains epidemic globally, continuing research on safe and effective ARV therapy for HIV-infected people at the various stages of childhood remains vital.

### **The timing of initiation of ARV therapy**

In most cases, it is recommended that ARV therapy in asymptomatic adults be delayed until clinical and laboratory parameters indicate an increasing risk of eminent progression to severe disease.<sup>1</sup> The issue of when to begin therapy in children is less well defined due to differences in the natural history of perinatally-acquired infection, as well as the toxicity, pharmacology and administration issues involved in giving medicines to small children.

The expected progression of disease differs between adult and pediatric populations. The immature immune function of infants, the high level of immune activation during early childhood, and other factors lead to relatively rapid progression to advanced-stage disease and death in many perinatally-infected children as compared to people infected later in life.<sup>2</sup> Furthermore, CD4 percentage and viral load measures are not as predictive of short-term disease progression in young children as in adults,<sup>3</sup> making the deferral of initiation of therapy based on favorable laboratory values more risky than in adult patients.

Another unique feature of the pediatric population is that most HIV-infected patients under 13 years of age are infected through vertical transmission and their infection status is detected within the first few weeks to months of life. This early diagnosis of HIV infection offers the opportunity to provide aggressive therapy during acute infection. Early control of viral replication using ARV therapy may allow for the normal development of immune function during infancy and early childhood and thereby mitigate the factors of immaturity that seem to influence the rapid progression of perinatal HIV infection. A number of studies have shown that ARV therapy begun within the first 3-6 months of life significantly reduced morbidity and mortality in perinatally-infected infants as compared to infants for whom therapy was delayed until after six months of life.<sup>4,5,6</sup> Some studies of very early aggressive therapy have, in fact, shown such complete control of viral replication that a portion of the infants have converted to HIV seronegative after the loss of maternal antibody acquired by transplacental transfer.<sup>5</sup> -

Unpublished experience within the University of Mississippi pediatric HIV clinic suggests that children who, with aggressive therapy, maintain good control of viral replication throughout infancy but discontinue therapy later may also demonstrate lower viral set points and slower decline of CD4 cell counts than their untreated peers.

Use of early therapy in perinatally-infected infants does not come without significant risks. The short- and long-term toxicities of ARV medications on the rapidly developing organ systems of infants and young children are difficult to predict, making long-term follow up of ARV-exposed children essential. Furthermore, the possibility of encouraging development of viral resistance to multiple drugs early in life for a child who may need a lifetime of treatment is a daunting prospect for any clinician prescribing ARV therapy for infants.

After consideration of all of the issues involved, the Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children recommends initiating treatment for infected infants under 12 months of age regardless of CD4 cell count, viral load, or clinical symptomatology.<sup>7</sup> (It should be noted that European guidelines differ by recommending *consideration* of early therapy for infants.<sup>8</sup>) In the American guidelines, treatment is recommended for children between one and five years of age with immunologic evidence of risk, defined as CD4 <25%, and that treatment be considered for children in that age range with CD4 >25% with viral load >100,000. Current recommendation is deferral of therapy for ARV-naïve children over five years of age until CD4 declines to <350 or viral load is >100,000 copies/mL<sup>7</sup>.

### **Effective antiretroviral regimens for children**

The basic theory of using combinations of at least three active drugs chosen from two different classes mirrors the recommendations for adult therapy. There is additional complexity in the pharmacological treatment of children stemming from a number of characteristics that are inherent in the population. Consideration must be given not only to the effect of developing hepatic, renal, and gastrointestinal function on the metabolism of the drugs but also to the short- and long-term effects of the drugs on maturing neurologic, endocrine, immunologic, cardiovascular, and musculoskeletal systems. Furthermore, even with similar pharmacokinetics, the efficacy of particular ARV regimens may not necessarily parallel that in adults due to differences in the innate immune responses and cellular dynamics between children and adults.

Pharmacokinetic parameters of individual drugs may change several times during the growth and development of an individual through infancy, early childhood, puberty, and late adolescence. In addition, the availability of liquid formulations and small dose pills along with the palatability of the medications both influence the practicality of using many of the medications in small children.

Of the 25 ARV drugs that have been FDA approved for use in adults to date, only 16 have approved indications for any of the pediatric age groups.<sup>7</sup> Fewer still of these drugs have been studied in the youngest children and only ZDV has been well characterized in very-low-birth-weight infants.<sup>9</sup> Ironically, one of the biggest barriers to conducting the necessary clinical trials that would make more therapeutic options available to children is, in fact, the greatest achievement of HIV prevention efforts: the effective prevention of mother-to-child transmission of HIV has limited the number of children available to become study subjects in developed nations. Therefore, for now, ARV regimens in children must be chosen from a smaller repertoire than that available for adult treatment and careful consideration of sequencing of therapy to preserve future options is essential.

The pharmacokinetics of some of the drugs in the NRTI, NNRTI and PI classes have been well studied in children of various age groups.<sup>10</sup> The fusion inhibitor enfuvirtide has also undergone extensive study in older children but its use in children is limited by the need for twice daily injections and the high incidence of local injection site reactions.<sup>11</sup> Clearly safety and efficacy trials of the newer entry inhibitors, integrase

inhibitors, and “second generation” NNRTI drugs are needed in children. There is need for further study of many older drugs to elucidate the pharmacokinetic profile in all ages along with further development of “kid-friendly” formulations of existing medications.

Current recommendations for specific drug combinations to be used for initiation of therapy at various ages can be found in the guidelines developed by the Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children and are summarized in Table 7 of that document.<sup>7</sup>

The introduction of HAART therapy in both developed and developing countries has significantly improved the outlook for perinatally-infected children.<sup>12,13,14</sup> However, more research is needed in this particularly vulnerable population to assure that future HIV medications are efficacious and safe for the youngest members of the population affected by the HIV epidemic.❖

INITIATION OF TREATMENT RECOMMENDATIONS (summarized from Table 6 of the Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection <sup>7</sup> )		
Age	Clinical/laboratory criteria	Recommendation
0-12 months	Symptomatic or asymptomatic with any CD4 and any viral load	Initiate treatment
1-5 years	Symptomatic (Category B or C)	Initiate treatment
	CD4<25%	Initiate treatment
	Viral load >100,000 copies/mL	Consider treatment
	No or mild symptoms with CD4≥25% and viral load <100,000	Defer treatment
≥5 years	Symptomatic (category B or C)	Initiate treatment
	CD4<350 cells/mm <sup>3</sup>	Initiate treatment
	Viral load >100,000 copies/mL	Consider treatment
	No or mild symptoms with CD4≥350 and viral load <100,000	Defer treatment

#### REFERENCES

1. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. January 29, 2008; 1-128. Available at <http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>.
2. European Collaborative Study. Fluctuations in symptoms in human immunodeficiency virus-infected children: the first 10 years of life. *Pediatrics* 2001; 108:116-122.
3. HIV Pediatric Prognostic Markers Collaborative Study Group. Short-term risk of disease progression in HIV-1-infected children receiving no antiretroviral therapy or zidovudine monotherapy: estimates according to CD4 percent, viral load, and age. *Lancet* 2003; 362:1605-1611.
4. Chiappini E, et al. Virologic, immunologic, and clinical benefits from early combined antiretroviral therapy in infants with perinatal HIV-1 infection. *AIDS* 2006; 20:207-215.
5. Luzuriaga K, McManus M, Mofenson L, et al. A trial of three antiretroviral regimens in HIV-1-infected children. *N Engl J Med* 2004; 350:2471-2480.
6. Patel k, Herson MA, Williams PL, et al. Long term effectiveness of highly active antiretroviral therapy on the survival of children and adolescents with HIV infection: 10 year follow up study. *Clin Infect Dis* 2008; 46(4): 507-515.
7. Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children. Guidelines for the use of antiretroviral agents in pediatric HIV infection. Department of Health and Human Services. July 29, 2008; 1-134. Available at <http://www.aidsinfo.nih.gov/ContentFiles/PediatricGuidelines.pdf>.
8. Sharland M, Blanche S, Casteili G, et al. PENTA guidelines for the use of antiretroviral therapy. *British HIV Association HIV Medicine* 2004; 5:61-86

9. Capparelli EV, Mirochnick M, Dankner WM, et al. Pharmacokinetics and tolerance of zidovudine in preterm infants. *J Pediatrics*, 2003 Jan;142(1):47-52
10. Giaquinto C, Rampon O, Penazzato M, et al. Nucleoside and nucleotide reverse transcriptase inhibitors in children. *Clin Drug Investig* 2007;27(8):509-31.
11. Wiznia A, church J, Emmanuel P, et al. Safety and efficacy of enfuvirtide for 48 weeks as part of an optimized antiretroviral regimen in pediatric human immunodeficiency virus 1 infected patients. *Pediatr Infect Dis J* 2007; 26(9):799-805.
12. Gibb DM, Duong T, Tookey PA, et al. National Study of HIV in pregnancy and childhood collaborative HIV paediatric study. Decline in mortality, AIDS, and hospital admissions in perinatally HIV-1 infected children in the United Kingdom and Ireland. *BMJ*, 2003;327(7422):1019.
13. Viani RM, Araneta MR, Deville JG, Spector SA. Decrease in hospitalization and mortality rates among children with perinatally acquired HIV type 1 infection receiving highly active antiretroviral therapy. *Clin Infect Dis*, 2004. 39(3):725-31.
14. Predergast A, Tudor-Williams G, Jeena P, et al. International perspectives, progress, and future challenges of paediatric HIV infection. *Lancet* 2007. 370(9581):68-80.

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