The Changing Face of HIV Infection in Children

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OUR ABILITY TO DRASTICALLY REDUCE MOTHER-TO-CHILD HIV TRANS-mission rates has been heralded as one of the most important break-throughs in the history of HIV research. But try explaining such good fortune to the estimated 10,000-plus children—or their caregivers—in the United States who are already infected with the virus. Yet, as we have been seeing with HIV-positive adults, managing HIV disease progression in our youngest patients has dramatically improved in recent years. Not even ten years ago, a pediatric HIV diagnosis was associated with a dismal prognosis: most infected children would die before their fifth birthday. Today, thanks to early access to care and potent antiretroviral therapy, HIV-infected children can look forward to entering and graduating from high school and beyond. And with more information quickly emerging with respect to how HIV-infected children should be treated, we can expect continued improvements in prognosis.

To explore the issue of pediatric HIV infection, PRN invited Dr. Joseph Cervia, a longtime expert in the research and care of HIV-infected children and adolescents, to speak at a recent PRN meeting. What follows is a detailed overview of the epidemiology, natural history, and treatment of pediatric HIV infection, based on Dr. Cervia's presentation and the Department of Health and Human Services' (DHSS) *Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States* (updated November 2003) and its *Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection* (updated January 2004).

I. Epidemiology of Children with HIV and AIDS

THE INCIDENCE AND PREVALENCE OF HIV AMONG CHILDREN UNDER THE age of 13 can be tied to an interplay of three major factors: the increase in HIV infection rates among women of childbearing age, the availability of antiretrovirals to prevent vertical transmission of the virus, and the changing rates of morbidity and mortality associated with the use of effective antiretroviral therapy and prophylaxis.

In 2002, according to estimates from the Joint United Programme on HIV/AIDS (UNAIDS), an estimated 800,000 children were newly infected with HIV and 610,000 children under the age of 15 died of AIDS, the vast majority of them infected perinatally in developing countries. The fact that nearly 50% of all HIV-positive people in developing nations are women of childbearing years—many of whom do not have access to family planning or HIV testing/counseling services—speaks to the severity of the situation in areas such as Africa and Asia. Fortunately, because efforts to reduce mother-to-child transmission—via increased international and non-government involvement and the corporate donation of both rapid-testing assays (e.g., Abbott's Determine assay) and antiretrovirals (e.g., Boehringer-Ingelheim's Viramune)—the incidence of new infections among children in many parts of the world should improve in the years to come.

In the United States and other developed nations, women of child-bearing age also account for a sizeable percentage of HIV infections. What's more, it appears that an increasing percentage of these women—both knowingly and unknowingly infected with the virus—are becoming pregnant and carrying their pregnancies to term. However, with stepped-up efforts to test pregnant women for HIV and other infectious diseases—along with the widespread use of antiretrovirals during pregnancy, elective cesarean delivery, and avoidance of breastfeeding—rates of mother-to-child transmission are currently estimated to be under 2%. Compounded by the advances made in the areas of caring for and treating children who are infected with the virus, the number of AIDS cases remains at an all-time low. For example, between July 1999 and June 2000, only 224 cases of AIDS in children under 13 were reported to the U.S. Centers for Disease Control—down from a high of 959 cases reported in 1993. When reporting delays are adjusted for, it is estimated that only 155 new cases of pediatric AIDS were diagnosed in 1999.

Even more encouraging, according to data from UNAIDS, fewer than 500 new HIV infections and fewer than 100 AIDS-related deaths were estimated in North American children younger than 15 years of age in 2002. Conversely, in sub-Saharan Africa, approximately 720,000 new HIV infections were diagnosed and 550,000 AIDS-related deaths occurred in children under the age of 15 in the same year.

"What do all these numbers mean to us, here in the United States?" Dr. Cervia asked. "We certainly find ourselves in a much better place than most clinicians caring for children with HIV in many parts of the world. We are also in a much better place than we were in the late 80s and early 90s, when I became the director of the pediatric HIV program at Cornell and we were going to a funeral every month for one of our children. At that time, we cared for approximately 80 children there. When I left the program to take on my current position at Long Island Jewish Medical Center, we cared for approximately 210 children and had only one funeral in the year prior. And this is largely related to the advances resulting from combination antiretroviral therapy."

II. Perinatal Transmission

The Role of Viral Load

THERE ARE THREE BASIC DETERMINANTS OF PERINATAL HIV TRANSMISSION. The first is a low CD4+ cell count, representing advanced disease progression. The second is ruptured membranes for greater than four hours. "The longer the delivery," Dr. Cervia commented, "the greater the risk of transmission." The third determinant is maternal viral load, both before and during delivery.

According to the Department of Health and Human Services, as stated in its R*ecommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States*, the correlation of HIV-

TABLE 1. 1994 Revised Human Immunodeficiency Virus Pediatric Classification System: Immune Categories Based on Age-Specific CD4+ Cell Count and Percentage

Immune category	< 12 mos		1–5 yrs		6–12 yrs	
	No./mm³	(%)	No./mm³	(%)	No./mm³	(%)
Category 1: No suppression	>1,500	(>25%)	>1,000	(>25%)	>500	(>25%)
Category 2: Moderate suppression	750–1,499	(15%–24%)	500–999	(15%–24%)	200–499	(15%–24%)
Category 3: Severe suppression	<750	(<15%)	<500	(<15%)	<200	(<15%)

Source: U.S. Centers for Disease Control and Prevention. 1994 Revised classification system for human immunodeficiency virus infection in children less than 13 years of age. *MMWR* 43 (No. RR-12): 1–10, 1994.

rna levels with risk for disease progression in nonpregnant infected adults suggests that hiv-rna should be monitored during pregnancy at least as often as recommended for persons who are not pregnant (i.e., every three to four months or approximately once each trimester). In addition, hiv-rna levels should be evaluated at 34 to 36 weeks of gestation to allow discussion of options for mode of delivery based on hiv-rna results and clinical circumstances.

Initial data regarding the correlation of viral load with risk for perinatal transmission were conflicting, with some studies suggesting an absolute correlation between hiv-rna copy number and risk of transmission (Dickover, 1996). However, although higher hiv-rna levels have been observed among women who transmitted hiv to their infants, the fact is that transmission has been observed across the entire range of hiv-rna levels—including in women with hiv-rna copy number below the limit of detection of the assay—and the predictive value of rna copy number for transmission in an individual woman has been relatively poor (Cao, 1997; Mayaux, 1997, Thea, 1997).

More recent data from larger numbers of zidovudine (Retrovir)-treated infected pregnant women indicate that hiv-rna levels do, in fact, correlate with risk of transmission (European Collaborative Study, 1999; Garcia, 1999; Mofenson, 1999; Shapiro, 1999). "Certainly, control of maternal viremia is an important management goal in pregnancy, in terms of preventing perinatal hiv transmission," Dr. Cervia commented.

PACTG 076 and Beyond

IN A NOVEMBER 1996 ISSUE OF *THE NEW ENGLAND JOURNAL OF MEDICINE,* Dr. Rhoda Sperling and her colleagues presented follow-up data involving all 402 mother/infant pairs enrolled in PACTG 076, by far the most important perinatal hiv transmission clinical trial reported to date (Sperling, 1996). The Kaplan-Meier-estimated hiv transmission rate for infants who received placebo was 22.6%, compared with 7.6% for those who received zidovudine: a 66% reduction in risk for transmission.

It is interesting to note that the mechanism by which zidovudine reduced transmission in PACTG 076 participants is still a matter of debate. According to Dr. Sperling's report, even among women who did not experience significant reductions in hiv-rna while taking zidovudine, the risk of transmission was significantly less than that seen in women receiving placebo. In turn, it is argued that the effect of zidovudine on maternal hiv-rna does not fully account for the observed effectiveness of therapy in reducing transmission. "Not all of the reduction in perinatal transmission risk was explained by viral load and, thus, some experts seem to feel that zidovudine has a special mystique about it and that it

somehow acts in a way that we don't completely understand," Dr. Cervia commented. "However, I don't know if this is true."

As suggested in the perinatal transmission *Guidelines,* one possibility is that zidovudine may serve as preexposure prophylaxis for the fetus. This has led to the argument that transplacental passage of antiretroviral drugs is crucial for the prevention of transmission. Zidovudine does this. What's more, in placental perfusion studies, zidovudine has been shown to metabolize into the active triphosphate within the placenta, which may provide additional protection against *in utero* transmission. This phenomenon may be unique to zidovudine because metabolism to the active triphosphate form within the placenta has not been observed in the other nucleoside analogs that have been evaluated (e.g., didanosine [Videx/Videx EC]).

In PACTG 076, similar rates of congenital abnormalities occurred among infants with and without *in utero* zidovudine exposure. Data from the Antiretroviral Pregnancy Registry also have demonstrated no increased risk for congenital abnormalities among infants born to women who receive zidovudine antenatally compared with the general population. Among uninfected infants from PACTG 076 followed from birth to a median age of 4.2 years, no differences were noted in growth, neurodevelopment, or immunologic status between infants born to mothers who received zidovudine compared with those born to mothers who received placebo (Culnane, 1999). What's more, no malignancies have been observed in short-term—up to six years of age—follow-up of more than 727 infants from PACTG 076 or from a prospective cohort study involving infants with *in utero* zidovudine exposure (Hanson, 1999). However, as is stressed in the DHHS perinatal transmission *Guidelines*, follow-up is too limited to provide a definitive assessment of carcinogenic risk with human exposure. Long-term monitoring continues to be recommended for all infants who have received *in utero* exposure to zidovudine or any of the antiretroviral drugs.

As for combination antiretroviral therapy, at least two studies have suggested that it may further reduce the risk of perinatal hiv transmission. In an open-label, nonrandomized study of 445 pregnant women with hiv infection in France, lamivudine (Epivir) was added at 32 weeks' gestation to standard zidovudine prophylaxis; lamivudine was also given to the infant for six weeks in addition to zidovudine (Mandelbrot, 2001). The transmission rate in the zidovudine/lamivudine group was 1.6%. In a historical control group of women receiving only zidovudine, the risk of transmission was 6.8%. Data are also available from a longitudinal study (PACTG 367) that has been underway in the United States since 1990 (Cooper, 2002). In this study, transmission rates were 20% among women who received no antiretroviral therapy during

pregnancy, 10.4% among women who received zidovudine monotherapy, 3.8% among women who received a combination of drugs that did not include a protease inhibitor, and 1.2% among women who received a protease inhibitor-based regimen. "Indeed, the transmission rate of less than 2% among women receiving protease inhibitor-based regimens was the goal we set at the Pediatric AIDS Clinical Trials Group," Dr. Cervia added. "We were all very happy to see that we achieved this goal in many areas of the country."

III. Natural History of Pediatric HIV Infection

THE NATURAL HISTORY OF HIV DISEASE IN CHILDREN DIFFERS FROM adults. Untreated HIV infection in children is generally associated with shorter overall survival, and a sizeable percentage of children—approximately 20%—are rapid progressors, characterized by CDC clinical stage category C within the first year of life. Like adults, the two most important prognostic factors to consider are the CD4+ cell count and viral load. However, with children, there are significant differences in the interpretation of these laboratory values.

Immunologic Parameters

AGE IS AN EXTREMELY IMPORTANT FACTOR TO CONSIDER WHEN INTERpreting CD4+ cell counts in HIV-positive children. In healthy children not infected with HIV, the CD4+ cell count is considerably higher and slowly declines to adult values by six years of age. In turn, a pediatric immunologic staging system for HIV infection has been developed by the CDC—most recently revised in 1994—that includes age-related definitions of immune suppression (see Table 1 on previous page).

It's important to note that, while the absolute CD4+ cell count changes with age, the CD4% does not. In turn, many experts argue that the change in the CD4%, not the absolute number, is a better immunologic marker for identifying HIV disease progression in children.

According to the DHHS, CD4+ cell counts and percentages should be obtained as soon as possible after diagnosis and every three months thereafter. Increased frequency of evaluations may be needed for children experiencing immunologic or clinical deterioration or to confirm an abnormal value. Infected infants who have a lymphocyte profile indicative of thymic defect—for example, a CD4+ count below 1,900 cells/mm³ and a CD8+ count of 850 cells/mm³ or less—during the first six months of life tend to experience more rapid HIV disease progression than infants who do not have this profile (Kourtis, 1996).

In a recent study published in *The Lancet*, Dr. David Dunn and his colleagues with the HIV Pediatric Prognostic Markers Collaborative Study Group evaluated the prognostic value of the CD4% and viral load in a large meta-analysis that incorporated clinical and laboratory data involving 3,941 HIV-positive children enrolled in one of 17 studies (Dunn, 2003). The group evaluated the 12-month risk of developing AIDS or death, based on the child's age, CD4%, and viral load at baseline. As illustrated in Figure 1, the one-year risk of AIDS is less than 10% for children over a year old who have CD4% greater than 25%. However, infants during the first year of life experience a proportionately higher risk. For example, comparing a one-year-old child with CD4% of 25 to a five-year-old child with the same CD4%, there is an approximate fourfold increase in the risk of AIDS—and a sixfold increase in the risk of death—in the one-year-old child. However, all age groups demonstrated rapid increases in risk as the CD4% decreases below 15% to 20%.
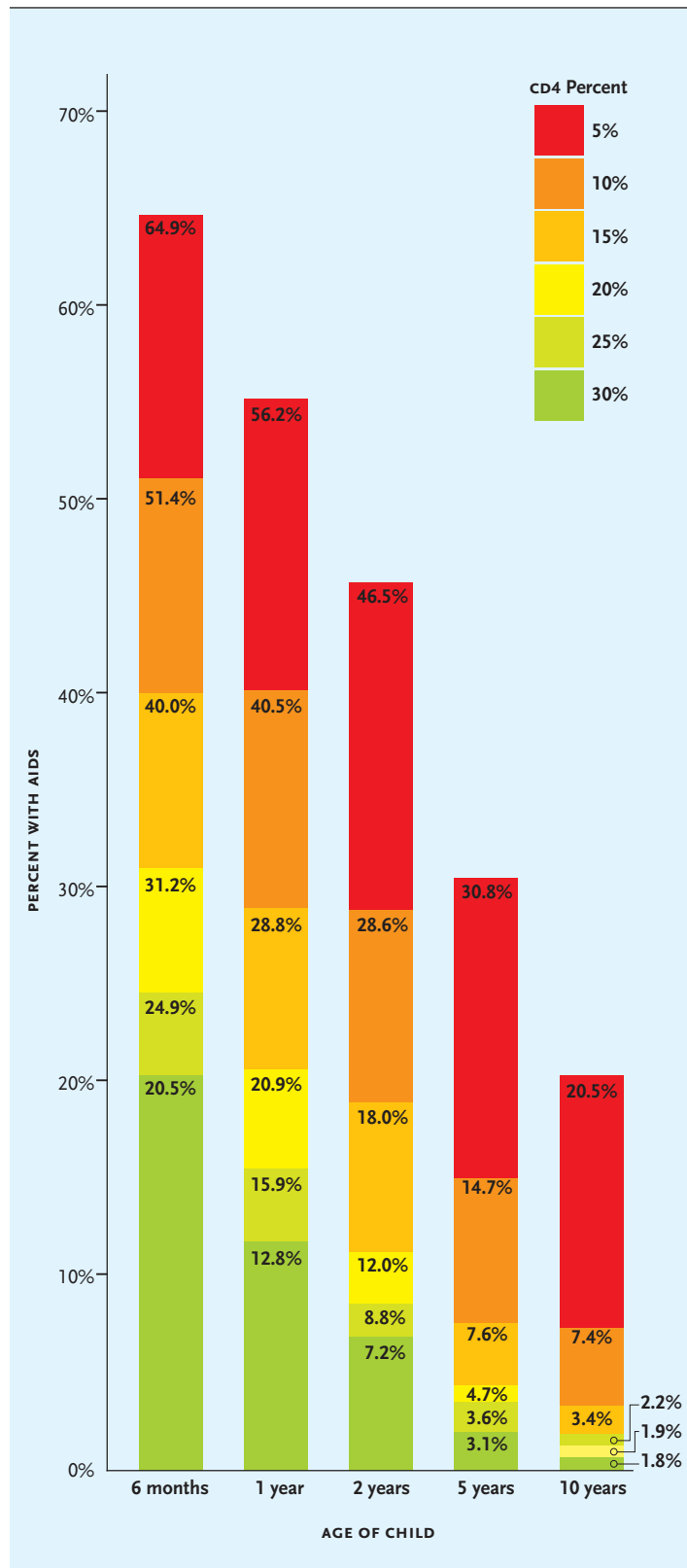

FIGURE 1. **Estimated Probability of Developing AIDS Within 12 Months: CD4 Percentage**

The estimated probability of developing AIDS within 12 months at selected ages by CD4 percentage in HIV-infected children receiving no therapy or zidovudine (Retrovir) monotherapy.

Source: Department of Health and Human Services. *Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection* [Figure 1]. January 20, 2004. Accessed at: http://www.aidsinfo.nih.gov/guidelines/pediatric/PED_012004.html#tables

Virologic Parameters

THE HIV-RNA PATTERN IN PERINATALLY INFECTED INFANTS DIFFERS FROM that in infected adults. High HIV-RNA copy numbers persist in infected children for prolonged periods. In one prospective study, HIV-RNA levels generally were low at birth (i.e., less than 10,000 copies/mL), increased to high values by age two months—most infants had values greater than 100,000 copies/mL, ranging from undetectable to nearly 10 million copies/mL—and then decreased slowly; the mean HIV-RNA level during the first year of life was 185,000 copies/mL (Shearer, 1997). Additionally, in contrast to the adult pattern, after the first year of life, viral load slowly declines over the next few years of life. This pattern probably reflects the lower efficiency of an immature but developing immune system in containing viral replication and possibly a greater number of HIV-susceptible cells.

The HIV Pediatric Prognostic Markers Collaborative Study Group has also attempted to elucidate the predictive value of HIV-RNA in terms of HIV disease progression (Dunn, 2003). Just like the CD4% analysis discussed above, the study group also looked at age-associated risk in the context of HIV-RNA levels. Similar to data from previous studies, the risk of clinical progression to AIDS or death dramatically increased when viral load exceeded 100,000 copies/mL; at lower values, only older children show much variation in risk (see Figure 2 [Figure 3 in the DHHS *Guidelines*]). However, the relationship between viral load and disease progression risk approached a more linear association—as opposed to a more stepwise association—than for the CD%, resulting in greater difficulty in defining a particular point representing a watershed. At any given level of HIV-RNA, infants under one year of age were at higher risk of progression than older children, although these differences were less striking than observed for the CD4% data.

Clinical Manifestations

A WIDE SPECTRUM OF CLINICAL MANIFESTATIONS OF HIV INFECTION AND AIDS can occur in children. While there are a number of similarities between the manifestations seen in HIV-positive children and adults, there are also a number of significant differences.

Features common to both children and adults with HIV and AIDS include generalized lymphadenopathy, fever, rash, and diarrhea. Children, like adults, can also experience a variety of fungal, viral, protozoal, and bacterial infections. Hematologic complications including anemia, thrombocytopenia, and leukopenia are also common. Clubbing of digits, cardiomyopathy, progressive renal disease, and hepatitis are also reported in both HIV-positive children and adults.

A feature more commonly seen in children is failure to thrive—failure to achieve a normal rate of growth—which affects more than 50% of HIV-infected pediatric patients. A sizeable percentage of children experience lymphoid interstitial pneumonitis (LIP), a chronic condition that can lead to hypoxia and clubbing. Invasive and recurrent bacterial infections—including meningitis, bacteremia, pneumonia, sinusitis, otitis media, deep tissue abscesses, osteomyelitis, and septic arthritis—are more prominent in HIV-positive children than in adults. Inflammation of the parotid gland (parotitis) also appears to be more common in HIV-positive children.

In general, cancers in children differ from those in adults. Non-Hodgkin's lymphoma is the most common malignancy, usually involving the gastrointestinal tract. The second most commonly reported malignancy is leiomyosarcoma, a disease that is extraordinarily rare in adults. Kaposi's sarcoma is very rare in children in developed countries.
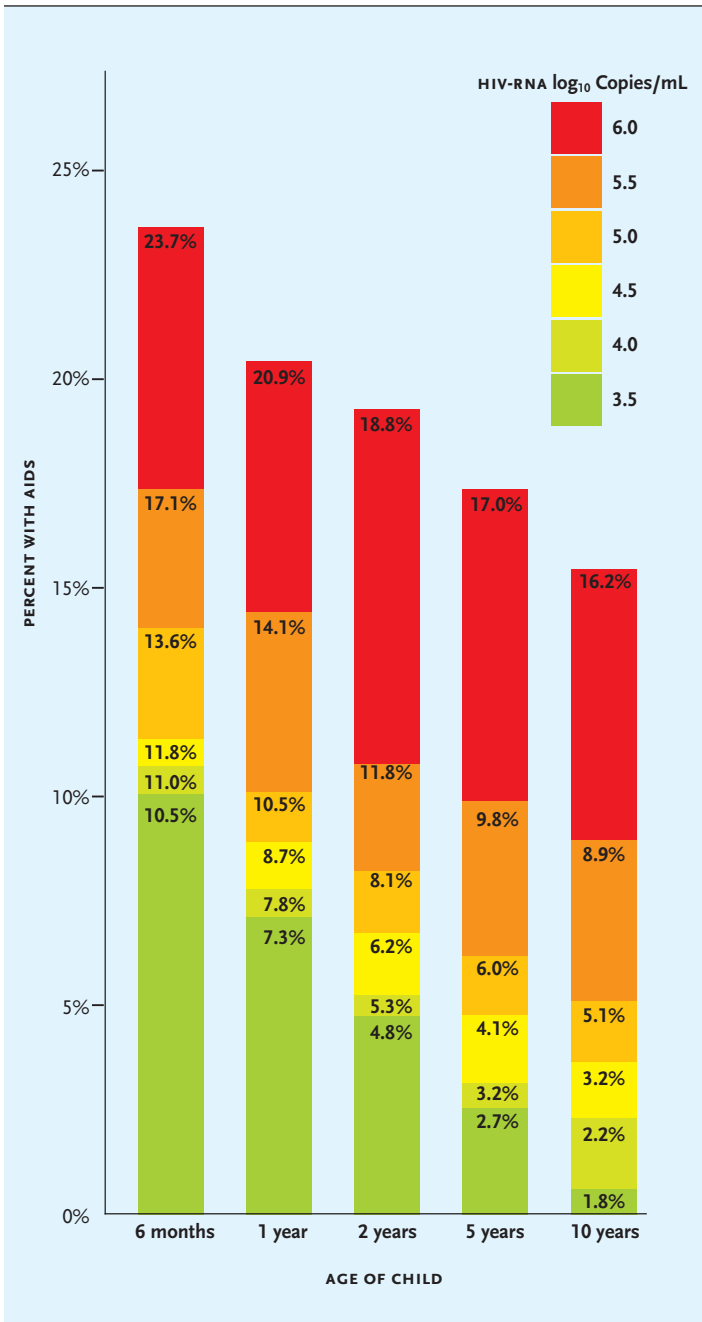

FIGURE 2. **Estimated Probability of Developing AIDS Within 12 Months: Viral Load**

Estimated probability of developing AIDS within 12 months at selected ages by HIV-RNA copy number in HIV-infected children receiving no therapy or zidovudine monotherapy.

Source: Department of Health and Human Services. *Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection* [Figure 3]. January 20, 2004. Accessed at: http://www.aidsinfo.nih.gov/guidelines/pediatric/PED_012004.html#tables

These risk profiles form the rationale for recommendations on when to initiate therapy in a treatment-naive HIV-positive child. A website using the meta-analysis data from the HIV Pediatric Prognostic Markers Collaborative Study Group is available to estimate the short-term risk of progression to AIDS or death according to age and the most recent CD4% and viral load in children who are not taking antiretroviral therapy (http://www.pentatrials.org/hppmcs).

TABLE 2. Indications for Initiation of Antiretroviral Therapy in Children <12 Months of Age Infected with HIV

Clinical Category		CD4+ Cell Percentage	Plasma HIV-RNA Copy Number*	Recommendation
Symptomatic (Clinical category A, B, or C)	OR	< 25% (Immune category 2 or 3)	Any Value	Treat
Asymptomatic (Clinical category N)	AND	> 25% (Immune category 1)	Any Value	Consider Treatment**

* Plasma HIV-RNA levels are higher in HIV-infected infants than in older infected children and adults, and may be difficult to interpret in infants < 12 months of age because overall HIV-RNA levels are high and there is overlap in HIV-RNA levels between infants who have and those who do not have rapid disease progression.

** Because HIV infection progresses more rapidly in infants than in older children or adults, some experts would treat all HIV-infected infants < 6 months or < 12 months of age, regardless of clinical, immunologic or virologic parameters.

This table provides general guidance rather than absolute recommendations for an individual patient. Factors to be considered in decisions about initiation of therapy include the risk of disease progression as determined by CD4+percentage; the potential benefits and risks of therapy; and the ability of the caregiver to adhere to administration of the therapeutic regimen. Issues associated with adherence should be fully assessed, discussed and addressed with the caregivers for the HIV-infected infant before the decision to initiate therapy is made.

Source: Department of Health and Human Services. *Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection* [Table 6]. January 20, 2004.
Accessed at: http://www.aidsinfo.nih.gov/guidelines/pediatric/PED_012004.html#tables

IV. Antiretroviral Therapy

THE DHHS HAS PUBLISHED RECOMMENDATIONS MEANT TO PROVIDE general guidance for decisions related to the treatment of HIV-infected children. For clinicians in New York State, the Department of Health's Committee for the Care of Children and Adolescents with HIV Infection—of which Dr. Cervia is Chair—has drafted its own set of guidelines, which can be accessed through a website maintained by the AIDS Institute (http://www.hivguidelines.org).

Guidelines for when to start antiretroviral therapy and the choice of drug regimens are evolving. Treatment with antiretroviral therapy has had a dramatic impact on the health of HIV-infected children. However, attainment of these benefits requires rigorous adherence to demanding treatment schedules. Additionally, therapy is associated with short- and long-term toxicities, some of which are only now beginning to be appreciated in children. The DHHS *Guidelines* stress that,

whenever possible, decisions regarding the management of pediatric HIV infection should be made by, or in consultation with, a specialist in pediatric and adolescent HIV infection.

Although prospective, randomized, controlled clinical trials offer the best evidence for formulation of guidelines, most antiretroviral drugs are approved for use in pediatric patients based on efficacy data from clinical trials in adults, with supporting pharmacokinetic and safety data from phase I/II trials in children.

When To Start Antiretroviral Therapy

BECAUSE HIV DISEASE PROGRESSION IN CHILDREN IS MORE RAPID THAN in adults, and laboratory parameters are less predictive of risk for disease progression, particularly for young infants, treatment recommendations have been more aggressive in children than in adults.

TABLE 3. Indications for Initiation of Antiretroviral Therapy in Children > 1 Year of Age Infected with HIV

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

* Many experts would initiate therapy if CD4+ cell percentage is between 15 to 20%, and defer therapy with increased monitoring frequency in children with CD4+ cell percentage 21% to 25%.

** There is controversy among pediatric HIV experts regarding the plasma HIV-RNA threshold warranting consideration of therapy in children in the absence of clinical or immune abnormalities; some experts would consider initiation of therapy in asymptomatic children if plasma HIV-RNA levels were between 50,000 to 100,000 copies/mL.

This table provides general guidance rather than absolute recommendations for an individual patient. Factors to be considered in decisions about initiation of therapy include the risk of disease progression as determined by CD4+ percentage and plasma HIV-RNA copy number; the potential benefits and risks of therapy; and the ability of the caregiver to adhere to administration of the therapeutic regimen. Issues associated with adherence should be fully assessed, discussed and addressed with the child, if age-appropriate, and caregiver before the decision to initiate therapy is made.

Source: Department of Health and Human Services. *Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection* [Table 7]. January 20, 2004.
Accessed at: http://www.aidsinfo.nih.gov/guidelines/pediatric/PED_012004.html#tables

TABLE 4. Recommended Antiretroviral Regimens for Initial Therapy for HIV in Children

Protease Inhibitor-Based Regimens	
Strongly recommended:	Two NRTIs[1] *plus* lopinavir/ritonavir (Kaletra) or nelfinavir (Viracept) or ritonavir (Norvir)
Alternative recommendation:	Two NRTIs[1] *plus* amprenavir (Agenerase) (children > 4 years old)[2] or indinavir (Crixivan)
Non-Nucleoside Reverse Transcriptase Inhibitor-Based Regimens	
Strongly recommended:	Children > 3 years: two NRTIs[1] plus efavirenz (Sustiva)[3] (with or without nelfinavir)
	Children < 3 years or who can't swallow capsules: two NRTIs[1] plus nevirapine (Viramune)[3]
Alternative recommendation:	Two NRTIs[1] *plus* nevirapine[3] (children > 3 years)
Nucleoside Analogue-Based Regimens	
Strongly recommended:	None
Alternative recommendation:	Zidovudine (Retrovir) *plus* lamivudine (Epivir) plus abacavir (Ziagen)
Use in special circumstances:	Two NRTIs[1]
Regimens that are Not Recommended	Monotherapy[4]
	Certain two NRTI combinations[1]
	Two NRTIs *plus* saquinavir soft gel (Fortovase) or hard gel (Invirase) capsule as a sole protease inhibitor[5]
Insufficient Data to Recommend	Two NRTIs[1] *plus* delavirdine (Rescriptor)
	Dual protease inhibitors, including saquinavir soft or hard gel capsule with low dose ritonavir, with the exception of lopinavir/ritonavir[4]
	NRTI *plus* NNRTI *plus* protease inhibitor[6]
	Tenofovir (Viread)-containing regimens
	Enfuvirtide (Fuzeon)-containing regimens
	Emtricitabine (Emtriva)-containing regimens
	Atazanavir (Reyataz)-containing regimens
	Fosamprenavir (Lexiva)-containing regimens

[1] Dual NRTI combination recommendations:

Strongly Recommended choices: Zidovudine plus didanosine (Videx) or lamivudine; or stavudine (Zerit) plus lamivudine

Alternative choices: Abacavir plus zidovudine or lamivudine; or didanosine plus lamivudine

Use in Special Circumstances: Stavudine plus didanosine; or zalcitabine (Hivid) plus zidovudine

Insufficient Data: Tenofovir- or emtricitabine-containing regimens

Not Recommended: Zalcitabine plus didanosine, stavudine, or lamivudine; or zidovudine plus stavudine

[2] Amprenavir should not be administered to children under age 4 years due to the propylene glycol and vitamin E content of the oral liquid preparation and lack of pharmacokinetic data in this age group.

[3] Efavirenz is currently available only in capsule form, although a liquid formulation is currently under study to determine appropriate dosage in HIV-infected children under age 3 years; nevirapine would be the preferred NNRTI for children under age 3 years or require a liquid formulation.

[4] Except for zidovudine chemoprophylaxis administered to HIV-exposed infants during the first 6 weeks of life to prevent perinatal HIV transmission; if an infant is confirmed as HIV-infected while receiving zidovudine prophylaxis, therapy should either be discontinued or changed to a combination antiretroviral drug regimen.

[5] With the exception of lopinavir/ritonavir, data on the pharmacokinetics and safety of dual protease inhibitor combinations (e.g., low dose ritonavir pharmacologic boosting of saquinavir, indinavir, or nelfinavir) are limited, use of dual protease inhibitors as a component of initial therapy is not recommended, although such regimens may have utility as secondary treatment regimens for children who have failed initial therapy. Saquinavir soft and hard gel capsule require low dose ritonavir boosting to achieve adequate levels in children, but pharmacokinetic data on appropriate dosing not yet available.

[6] With the exception of efavirenz plus nelfinavir plus one or two NRTIs, which has been studied in HIV-infected children and shown to have virologic and immunologic efficacy in a clinical trial.

Source: Department of Health and Human Services. *Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection* [Table 11]. January 20, 2004.
Accessed at: http://www.aidsinfo.nih.gov/guidelines/pediatric/PED_012004.html#tables

And because the risk for rapid disease progression is much more pronounced in infants in the first year of life, two sets of guidelines have been published: for HIV-infected infants younger than 12 months of age, and for HIV-infected children 12 months of age and older.

The DHHS *Guidelines* are clear in recommending antiretroviral therapy for infants under 12 months of age who have clinical or immunologic symptoms of HIV disease, regardless of viral load (see Table 2 on page 24 [Table 6 in the DHHS *Guidelines*]). For HIV-infected infants who are asymptomatic and have normal immune parameters, initiating antiretroviral therapy should at least be considered. Because of the high risk for rapid progression of HIV disease, many experts would treat all HIV-infected infants within the first year of life, regardless of clinical, immunologic, or virologic parameters. Other experts would treat all infected infants younger than six months of age, and use clinical and immunologic parameters and assessment of adherence issues for decisions regarding initiation of therapy in infants six to 12 months of age.

For children one year of age or older, the DHHS recommends that treatment should be started in all children with AIDS (Clinical Category C) or severe immune suppression (Immune Category 3), and should at least be considered for children who have mild-to-moderate clinical symptoms (Clinical Categories A or B), moderate immunologic suppression (Immune Category 2), and/or confirmed HIV-RNA levels 100,000 copies/mL or greater (see Table 3 on page 24 [Table 7 in the DHHS *Guidelines*]). The DHHS *Guidelines* also state that many experts would defer treatment in asymptomatic children one year of age and older with normal immune status in situations in which the risk for clinical disease progression is low (e.g., viral load less than 100,000 copies/mL) and when other factors (i.e., concern for adherence, safety, and persistence of antiretroviral response) favor postponing treatment. In such cases, clinicians should closely monitor virologic, immunologic, and clinical status.

Choice of Initial Antiretroviral Therapy

AS WITH HIV-POSITIVE ADULTS, AGGRESSIVE ANTIRETROVIRAL THERAPY with at least three drugs is recommended for initial treatment of infected children. The goal of such therapy is to maximally suppress viral replication, preferably to undetectable levels for as long a time as possible, while preserving and/or restoring immune function and minimizing drug toxicity.

There are currently 19 unique antiretroviral drugs approved for use in HIV-infected adults and adolescents; 12 of these have an approved pediatric treatment indication. As with the adult DHHS *Guidelines*, the pediatric *Guidelines* list specific protease inhibitor- and non-nucleoside reverse transcriptase inhibitor-based regimens as "strongly recommended," along with a number of "alternative" regimen options. These classifications are based on a number of different factors—much like the classification of specific drug combinations in the adult *Guidelines*—including data demonstrating durable viral suppression, immunologic improvement, and clinical improvement with the regimen.

The "strongly recommended" and "alternative" regimen options for HIV-positive children are reviewed in Table 4 on page 25 (Table 11 in the DHHS pediatric *Guidelines*).

When to Switch and What to Switch To

THE REASONS FOR SWITCHING A CHILD'S ANTIRETROVIRAL DRUG REGIMEN are very similar to the reasons for switching an HIV-positive adult's antiretroviral regimen, although some of the basic parameters are different. Generally speaking, changes to an antiretroviral drug regimen may be necessary when there is documented failure of the current regimen with evidence of disease progression based on virologic, immunologic, or clinical parameters; toxicity or intolerance to the current regimen; and/or consideration of new data demonstrating that a drug or regimen is superior to the current regimen.

Virologic considerations for changing therapy in children are very similar to those listed in the adult version of the DHHS *Guidelines*. The first consideration is less than a minimally acceptable virologic response after eight to 12 weeks of therapy. For children receiving antiretroviral therapy, such a response is defined as less than a tenfold (1 log) decrease from baseline HIV-RNA levels. The second consideration is an HIV-RNA level that is not undetectable after four to six months of therapy. Other considerations include repeated detection of HIV-RNA in children who initially had undetectable levels in response to therapy and reproducible increases in HIV-RNA after an initial drop in viral load.

There are also a number of immunologic considerations for changing therapy in children. These include change in immune classification. However, minimal changes in the CD4% that may result in a change in immune category (i.e., from 26% to 24% or from 16% to 14%) may not be as great a concern as a rapid substantial change in the CD4% within the same immune category (i.e., a decrease from 35% to 25%). A change in therapy is also indicated for any child whose CD4% falls to less than 15% or experiences a persistent decline of 5% or more (e.g., from 15% to 10% or from 10% to 5%). Another consideration is a rapid and substantial decrease in the absolute CD4+ cell counts (e.g., a greater than 30% decline in less than six months).

Finally, there are clinical considerations for changing therapy in children. These include progressive neurodevelopmental deterioration (e.g., the presence of two or more of the following findings documented on repeated assessments: impairment in brain growth, decline of cognitive function documented by psychometric testing, or clinical motor dysfunction). In such cases, the new treatment regimen optimally should include at least one antiretroviral drug with substantial central nervous system penetration (e.g., zidovudine or nevirapine [Viramune]). Growth failure—defined as a persistent decline in weight-growth velocity despite adequate nutritional support and without other explanation—is another clinical consideration, as is general disease progression (e.g., advancement from one pediatric clinical category to another).

Options for children who require a change to their antiretroviral therapy regimen are somewhat similar to those laid out in the adult version of the *Guidelines*. For example, when therapy is changed because of toxicity or intolerance, agents with different toxicity and side-effect profiles should be chosen, when possible. Before changing therapy because of treatment failure, adherence and pharmacokinetic issues (e.g., rapid drug metabolism) to therapy should be assessed to determine what role they played as a potential cause of treatment failure. If adherence and pharmacokinetic issues can be ruled out, drug-resistance testing should be performed before discontinuing the regimen or initiating a new regimen. And upon changing to a new regimen, there should be discussion of treatment adherence issues by the clinician with the patient, when age-appropriate, and caregivers of the infected child. For patients requiring a change of therapy for treatment failure but without treatment options using currently approved drugs, referral to a pediatric HIV specialist for inclusion into a clinical trial should be considered.

Long-Term Outcomes of Antiretroviral Therapy: PACTG 219

WHILE THERE HAVE BEEN A HANDFUL OF STUDIES EVALUATING THE safety and efficacy of protease inhibitor-based regimens in children and adolescents, there has been only limited evidence of reductions in mortality and morbidity. Long-term outcomes data have been needed to provide such evidence which, fortunately, has been addressed by the Pediatric AIDS Clinical Trials Group (PACTG).

To better understand the effects of protease inhibitor-based regimens on survival in HIV-positive children, PACTG investigators—including Dr. Cervia—turned to data being amassed in PACTG 219, a prospective cohort study designed to assess the long-term effects of prenatal and neonatal exposure to antiretroviral drugs in clinical trials and the late effects of antiretroviral treatment in children infected with HIV (Gortmaker, 2001). All children and adolescents enrolled in PACTG perinatal or treatment trials were eligible for enrollment. The study population for this analysis included 1028 children and adolescents infected with HIV who had been enrolled in PACTG 219 before 1996 and could be followed prospectively through 1999.

In 1996—the year that combination therapy including protease inhibitors first became available—the rate of reported use in this cohort was low (7%). The rate increased to 34% in 1997 and to 64% in 1998. By 1999, among the subjects who had not died or been lost to follow-up, the rate was 73%. In 1999, an additional 24% were receiving only nucleoside reverse transcriptase inhibitors, and 3% were receiving combination therapy including non-nucleoside reverse transcriptase inhibitors and nucleoside reverse transcriptase inhibitors.

There was substantial reduction in mortality over time, from 5.3% in 1996 to 2.1% in 1997, 0.9% in 1998, and 0.7% in 1999 (see Figure 3). There was evidence of reductions in mortality in all subgroups defined according to age, sex, CD4%, educational level of the parent or guardian, and race or ethnic group.

A multivariate proportional-hazards regression model showed that the initiation of combination therapy including protease inhibitors was independently associated with a substantial reduction in mortality; the hazard ratio for death was 0.33. There was no evidence of differences in this effect according to sex, age, CD4%, educational level of the parent or guardian, or race or ethnic group. The survival benefit associated with combination therapy including protease inhibitors also persisted after the PACTG team controlled for the declining trend in mortality over time (hazard ratio for death: 0.32).

In a regression analysis in which only the initiation of combination therapy including protease inhibitors was used as a predictor—and no measures of the severity of illness were included—the unadjusted risk of death was 0.73. This attenuation of the benefit of the therapy is a consequence of the lack of control for the severity of illness — in other words, of confounding by indication. In sicker children, combination therapy including protease inhibitors was more likely to be initiated earlier.

"Essentially, when we looked at the uptake in the use of protease inhibitor-based therapy that occurred after 1996, we saw very strong statistical correlations with declines in mortality," Dr. Cervia commented. "And this was true across all age groups. It was also true for both young boys and young girls. And it is true across all racial and ethnic demographics as well. It has basically shown that combination antiretroviral therapy works. It works for children as well as for adults. And it has resulted in substantial declines in HIV-related mortality." *prn*
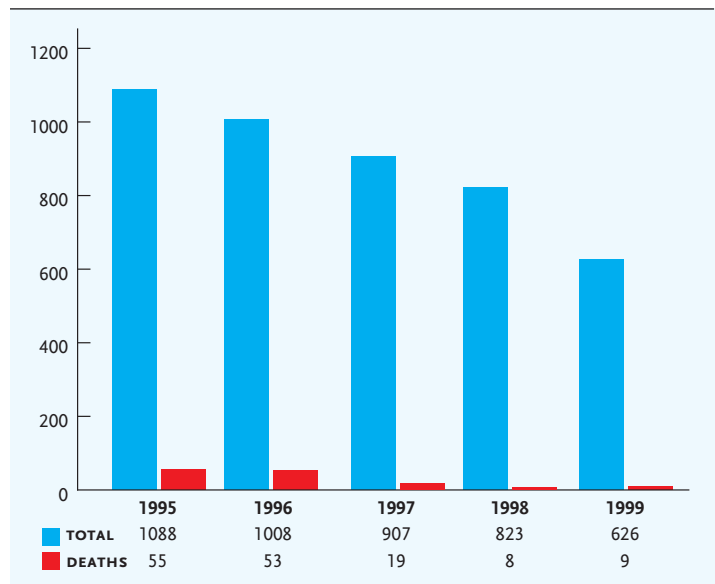

FIGURE 3. Number of HIV-Infected Subjects in PACTG 219: Tabulations by Year

	1995	1996	1997	1998	1999
TOTAL	1088	1008	907	823	626
DEATHS	55	53	19	8	9

Source: Gortmaker SL, Hughes M, Cervia J, et al. *Effect of Combination Therapy Including Protease Inhibitors on Mortality among Children and Adolescents Infected with HIV-1.* N Engl J Med 345(21):1522-8, 2001.

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