Perspective

Prevention of Mother-to-Child Transmission of HIV in Africa

HIV infection and mortality rates in African children are astoundingly high. Risk factors for mother-to-child transmission of HIV include maternal plasma viral load and breastfeeding. With regard to the latter, current data indicate that mixed feeding (breastfeeding with other oral foods and liquids) is associated with the greatest risk of transmission. Studies are under way to determine if exclusive breastfeeding with rapid early weaning can reduce transmission rates in the absence of exclusive formula feeding for all infants. Perinatal transmission rates have been dramatically reduced with the use of single-dose nevirapine, but this strategy protects only approximately 50% of infants, and more than 75% of women receiving nevirapine develop a major nevirapine resistance mutation. In developed areas of the world, antiretroviral therapy has reduced perinatal transmission by more than 90% compared with 1993 rates. Improved HIV-related care for HIV-infected women in Africa is needed to reduce rates of HIV infection in children and to prevent maternal mortality. This article summarizes a presentation by Sten H. Vermund, MD, PhD, at the International AIDS Society–USA course in Chicago in May 2004.

Since the finding in Pediatric AIDS Clinical Trials Group (PACTG) Study 076 (Connor et al, *New Engl J Med,* 1994) that zidovudine treatment for pregnant women decreased the rate of HIV transmission to the newborn from approximately 25% to 8%, the rate of perinatally acquired HIV infection in the United States has decreased more than 90%, to fewer than 50 per year (Figure 1). However, the situation in Africa and other locales worldwide is quite different. The Joint United Nations Program on HIV/AIDS (UNAIDS) estimates that the ratio of African children to North American children under 15 years of age with new HIV infection in 2002 was 3000 to 1, and the ratio of African children to North American children who died from HIV disease in 2002 was 10,000 to 1. This is in the context of a 2.6 population ratio for Africa and North America.

Risk Factors for Maternal Transmission

Risk factors for mother-to-child transmission include high plasma viral load in the mother; choriodecidual inflammation; obstetric factors, such as vaginal delivery (cesarean delivery is protective) and preterm delivery; and breastfeeding (Mofenson, *Semin Pediatr Infect Dis*, 2003). Mixed feeding (ie, breast milk plus other foods and liquids by mouth) appears to account for substantial transmission risk via this route in the first six months of life (Coutsoudis et al, *Lancet*, 2000).

Maternal Viral Load

The eminent preventability of perinatal transmission is indicated by Figure 2. Rates of transmission are under 2% when the infected mother receives potent antiretroviral therapy or when the mother's plasma HIV RNA level is below assay detection limits, but are as high as 50% in women with high HIV RNA levels who are receiving no antiretroviral therapy (Cooper et al, *J Acquir Immune Defic Syndr*, 2002).

Preterm Delivery and Chorioamnionitis

Data showing markedly increased risk of maternal HIV transmission in infants born very prematurely (Figure 3; European Collaborative Study, *Lancet*, 1992) prompted Dr Robert Goldenberg and colleagues to perform a study in Zambia, Malawi, and Tanzania to determine if simple antibiotic therapy to reduce maternal bacterial infection during gestation might have an impact on reducing HIV transmission rates and perhaps on preventing preterm deliveries. The rationale for the intervention is that chorioamnionitis during pregnancy may result in increased white blood cell recruitment to the site, offering target cells for HIV (Goldenberg et al, *Lancet*, 1998). In this

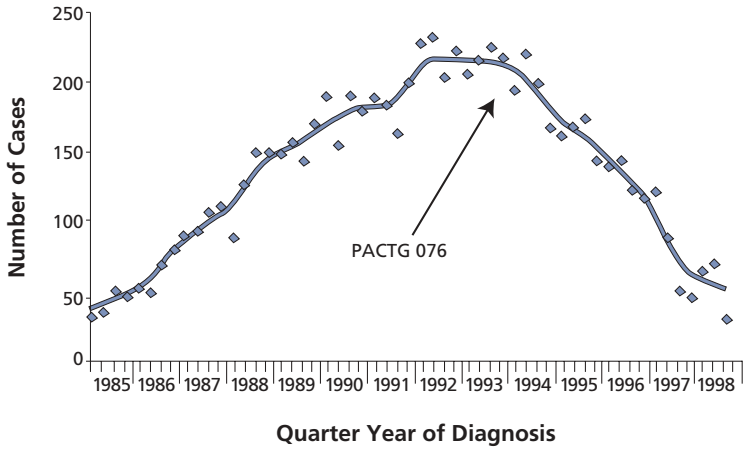

Figure **1.** Perinatally acquired AIDS cases in the United States, by quarter year, from 1985 to 1998. Cases are adjusted for reporting delays and redistribution of "no identified risk" cases into probable risk categories; data were reported through March 1999. Arrow indicates when the Pediatric AIDS Clinical Trials Group study 076 was reported in 1994. Adapted from Centers for Disease Control and Prevention, Pediatric HIV/AIDS surveillance slides at www.cdc.gov.

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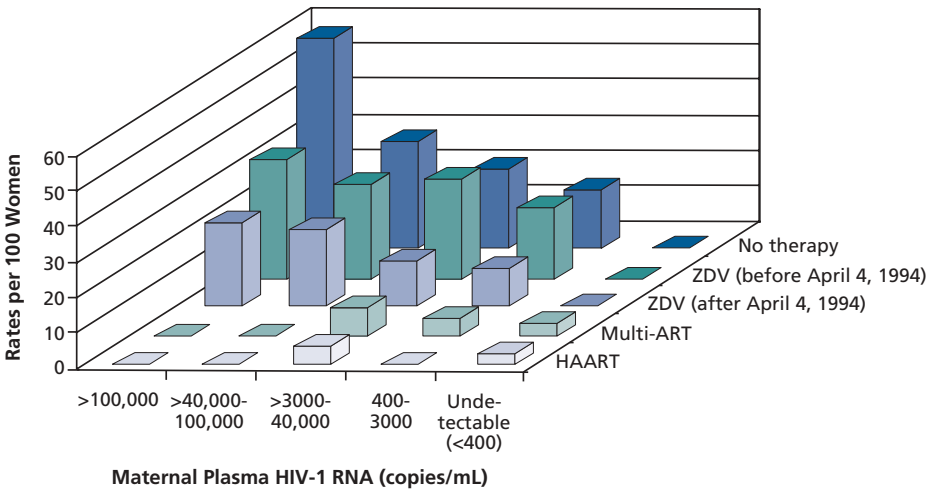

Figure **2.** Rates of perinatal HIV transmission according to maternal plasma viral load at delivery and type of antiretroviral treatment: No therapy, zidovudine monotherapy (ZDV) prior to or after reporting of Pediatric AIDS Clinical Trials Group study 076 in April 1994, combination antiretroviral therapy (multi-ART), or highly active antiretroviral therapy (HAART). Adapted from Cooper et al, *J Acquir Immune Defic Syndr*, 2002; and Mofenson of the National Institute of Child Health and Human Development.

study, HIV-infected pregnant women were randomized either to metronidazole and erythromycin during the second trimester and metronidazole and ampicillin at delivery, or to placebo. Interim analysis of data from the first approximately 1500 women suggests that antibiotic treatment of chorioamnionitis is not likely to be an effective intervention factor in this setting (Taha Taha and Goldenberg, unpublished data), and reemphasizes the need for improved antiretroviral coverage to prevent perinatal transmission.

Breastfeeding

In a study of infants born to HIV-infected women in South Africa, Coutsoudis and colleagues (*Lancet*, 1999; *Lancet,* 2000; XIIIth Int AIDS Conference, 2000) found that HIV infection was detected at 6 months in identical proportions of exclusively breastfed infants (19%) and never-breastfed infants (19%), and that infants who received mixed feeding had a higher rate of infection (26%; Figure 4). By 15 months, the infection rate was higher in exclusively breastfed children than in never-breastfed children, and the rate remained highest in children who received mixed feeding. The explanation for this finding may be the infant's immune response to novel foods, which results in recruitment of white blood cells into the gastrointestinal tract, providing additional targets for HIV infection. A strategy of feeding all infants born to HIV-infected mothers exclusively formula is, sadly, untenable in much of Africa and in other areas of the world, because the daily cost of formula exceeds the daily income of most individuals. Availability of safe drinking water to prepare infant formula is also a limiting factor. Approximately 20% of the human race lives on $1 per person per day and 50% lives on less than $2 per person per day. In this context, Donald Thea and colleagues currently are performing a study in Zambia assessing a strategy of exclusive breastfeeding with rapid weaning at 4 to 6 months versus normal weaning. The target population is 1600 HIV-infected mothers and their infants. Study outcomes include HIV infection status and growth of the child at 24 months, maternal satisfaction with and community acceptance of the rapid weaning approach (which is completely novel in this locale), and maternal morbidity and mortality (Thea et al, *Control Clin Trials*, 2004).

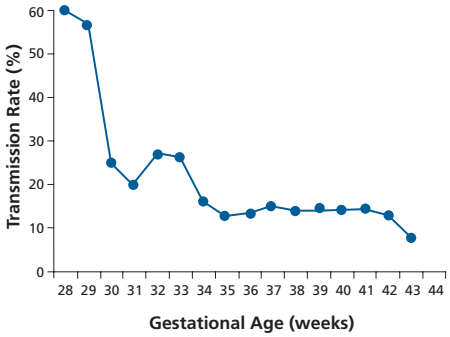

Figure **3.** Perinatal transmission by gestational age at delivery. Adapted from the European Collaborative Study, *Lancet*, 1992.

What About the Mothers?

A coherent public health approach must include upgrading maternal health in parallel with saving infants' lives. The good news in this regard is that there are a number of initiatives under way to improve pre- and postpartum HIV-related care for women, including Mother-to-Child Transmission (MTCT)-Plus, based at Columbia University in New York; the President's Emergency Plan for AIDS Relief (PEPFAR), which represents up to $15 billion over five years, $9 billion of it being new funding; and the Global Fund to Fight AIDS, Tuberculosis, and Malaria.

Efforts to bring adequate antiretroviral therapy to African nations are beginning to bear fruit. Figure 5 shows the decrease in cost of antiretroviral agents over the past several years (Vermund, *Clin Infect Dis*, 2003). Currently, US drugs can be obtained for as little as $600 per person per year, and generic drugs from India and elsewhere can be obtained for as little as $239 (zidovudine, lamivudine, nevirapine) or $132 (stavudine, lamivudine, nevirapine) per person per year when secured through the William Jefferson Clinton Presidential Foundation purchasing agreements (William R. Rodriguez, personal communication, December 2, 2004). However, tests for monitoring effects of antiretroviral therapy remain costly. One potential option for low-cost monitoring is indicated by findings among infected individuals in Tamil Nadu, India, showing a good correlation between increases in CD4+ cell counts and total lymphocyte counts in patients receiving antiretroviral therapy; decreases in CD4+ cell counts correlated less well with total lymphocyte counts (Figure 6; Kumarasamy, *J Acquir Immune Defic Syndr*, 2002; Kumarasamy et al, *Lancet Infect Dis*, 2002; Mahajan et al, *J Acquir Immune Defic Syndr*, 2004). Measurement of the total lymphocyte count is widely available and very inexpensive. Such data suggest the feasibility

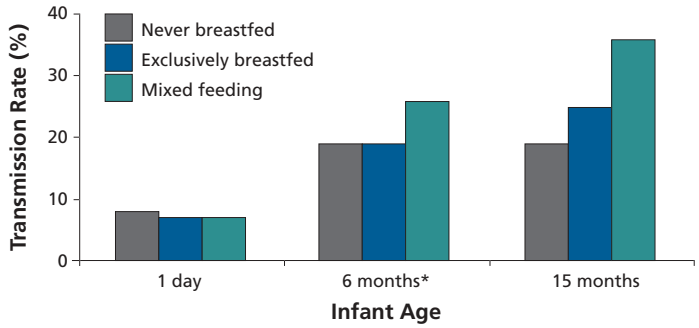

Figure **4.** HIV transmission rates in infants of HIV-infected mothers at 1 day, 6 months, and 15 months according to whether infants were exclusively breastfed (n=118), never breastfed (n=157), or had mixed feeding (n=276). *At 6 months: exclusive versus mixed relative risk=0.6 (range 0.3-1.0); exclusive versus never, 1.2 (0.6-2.2). Adapted with permission from Coutsoudis et al, XIIIth AIDS Conference, 2000.

of a strategy of performing a baseline CD4+ cell count at initiation of therapy and following patients with the total lymphocyte count. Although not ideal, this strategy may permit more money to be devoted to getting more infected individuals on appropriate antiretroviral therapy until cheaper CD4+ cell count and viral load technologies become available (Kent et al, *Clin Infect Dis*, 2003; Crowe et al, *Clin Infect Dis*, 2003).

Aspects of Current Perinatal Agenda

Zambia is a country roughly the size of Texas with a population of 10.2 million, of whom 50% live in urban areas. Lusaka, the capital city, has a population of approximately 2 million. In Lusaka, there are more than 50,000 live births per year occurring in public section birthing centers and the University Teaching Hospital. Infant mortality is at least 100 per 1000 live births. Putting this in context, infant mortality in the state of Illinois (the location of the talk upon which this article is based) is approximately 8 per 1000 live births. Maternal mortality in Lusaka is approximately 800 per 100,000 live births; maternal mortality in Illinois is approximately 1.5 per 100,000 live births.

The overall HIV prevalence in Lusaka is 25% among young adults, as estimated in the antenatal clinic population. Per capita annual income is $250 to $350. In 2002, the public health department of Lusaka had an annual budget of less than $200,000 to provide prenatal care and delivery services to 45,000 women and newborns (Moses Sinkala, personal communication). Although not all women come for antenatal services, those who do make an average of 5 visits (Robert MacDonald, unpublished data). At $0.50 per antenatal visit and $2 per delivery, the cost of delivery and antenatal care alone projected to the antenatal population exceeds the annual budget for care.

The consequences for quality of care are illustrated by the following scenario. A 1998 to 1999 chart review of 600 antenatal care clinic clients showed that 44 had positive rapid plasma reagin (RPR) testing, indicating exposure to syphilis, and only 2 had documented penicillin treatment (MacDonald, unpublished data). The RPR test kits had been donated by a foreign government; the penicillin was to have been provided by the Zambian Ministry of Health, but no shipments had been made in 3 years (Sinkala, personal communication). The untreated RPR-positive clients were written prescriptions to be filled outside the clinic, a virtual impossibility, given the financial status of these individuals. It is within this health care setting, with profound resource limitations, that both infant and maternal health programs must attempt to improve health care.

As reported by Guay and colleagues in 1999, the HIVNET 012 study in Uganda showed that voluntary counseling and testing, and a single nevirapine dose given to HIV-seropositive mothers at the beginning of labor plus 1 dose of nevirapine syrup given to the newborn in the first 72 hours reduced HIV transmission by 49%, compared with short-course zidovudine treatment (*Lancet*, 1999). A 2003 update of HIVNET 012 indicates that the benefits of nevirapine versus zidovudine treatment are maintained over 18 months of follow-up, with no diminution in protective benefit as a result of potential breastfeeding transmission (Jackson, *Lancet*, 2003). This study has had a profound effect on prevention of perinatal transmission on a global level. Within 2 years of the report's initial publication, the Elizabeth Glaser Pediatric AIDS Foundation, with funding from the Gates Foundation, had instituted its Call to Action program in 17 countries, and tens of thousands of women were receiving nevirapine shortly thereafter.

The advantages of the nevirapine approach are that it is effective, safe, simple (apart from administrative issues), convenient, and affordable. The drug actually costs less than $4 per dose, but it is provided free by the manufacturer to developing country programs through the Axios Foundation in Ireland. One disadvantage of the nevirapine approach is that it still protects only 50% of infants from HIV transmission; potent triple-drug antiretroviral therapy reduces the perinatal transmission rate to less than 2%. Further, more than 75% of women receiving nevirapine exhibit a major nevirapine resistance mutation that may

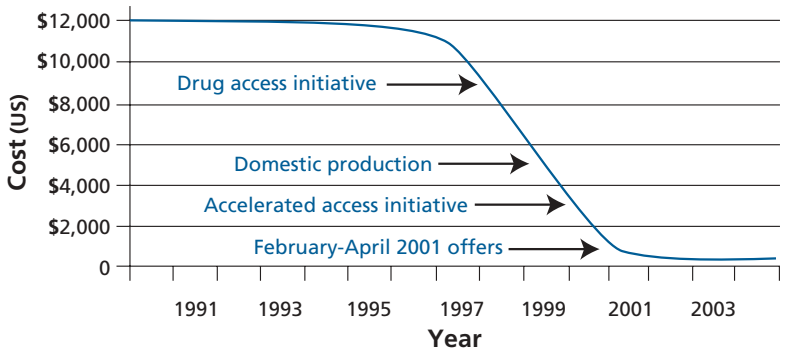

Figure **5.** Annual cost (in US dollars) per person for triple-drug antiretroviral therapy in Africa. The annual costs have declined from approximately $12,000 a year to $300. Data from UNAIDS.

compromise nevirapine use in subsequent pregnancy and use of other nonnucleoside reverse transcriptase inhibitors (NNRTIs) in potent antiretroviral therapy. About 6 to 12 months after this short treatment course, the proportion of nevirapine-resistant virus is dramatically reduced, but the resistant variants may emerge rapidly with reexposure to NNRTIs. A recent publication from Thailand suggests that women who received a single intrapartum nevirapine dose were less likely to have virologic suppression after 6 months of a nevirapine-containing triple-therapy antiretroviral regimen (Jourdain et al, *N Engl J Med*, 2004). Finally, although the nevirapine therapy itself is simple, voluntary counseling and testing programs and nevirapine programs are costly and complex at a national level.

From the point of view of care in Lusaka, Zambia, nevirapine treatment of mothers and newborns can save more than 2400 infants per year, or 50 per 1000 live births, from transmitted HIV infection. No other single intervention of an obstetrics or pediatrics provider will have nearly this magnitude of impact on childhood survival. Yet, much more needs to be done in parallel with a nevirapine program. Other key interventions include training midwives to perform appropriate obstetric services; upgrading infrastructure for providing and accessing consumables such as RPR test kits, penicillin, vitamins, gloves, antituberculosis drugs, and other antibiotics; determining the most effective ways to test pregnant women for HIV and to provide antiretroviral therapy; finding the resources to carry out and sustain current programs, such as Call to Action, PEPFAR, and the Global Fund to Fight AIDS, Tuberculosis, and Malaria; providing HIV test kits and additional antiretrovirals that could reduce mother-to-child transmission much more than 50% with full adherence; and using programs for prevention of mother-to-child transmission as bridges to potent antiretroviral therapy for HIV-infected women and infected family members (eg, by maintaining current efforts of such programs as MTCT-Plus and PEPFAR; Goldenberg et al, *J Matern Fetal Neonatal Med*, 2002).

A nevirapine program seems simple. In practice, it is not (Stringer, *AIDS*, 2003; Temmerman, *AIDS*, 2003). To maximize population coverage of such a program, pregnant women must have access to antenatal care. For women who do not come into the clinic for delivery or antenatal care, traditional birth attendants must be involved. Once a woman is within the care structure, she needs to be offered the intervention; thus, a voluntary counseling and testing program must be available, along with access to nevirapine treatment. A woman has to accept the counseling and testing and the nevirapine treatment; it should be noted that some 20% to 50% of women in Call to Action sites around the world refuse testing with such statements as: "I know I'm positive," "I don't need to know," "I don't want to know," "I have to ask my husband. He'll say no," or "If I'm infected, what is the sense of saving my baby, because I will die and there will be no one to take care of him." Once a woman who is giving birth at home has accepted participation in the intervention, support from the family or nurse-midwife is needed to carry through the intervention, including ensuring that she takes her nevirapine dose at the onset of labor and providing the nevirapine dose to the newborn.

In the initial experience of Dr Jeffrey Stringer and colleagues with trained midwives in Lusaka, it was found that the dose for the newborn was frequently omitted. The difficulties inherent in carrying out such a program are reflected in the fact that in their first year of operating the program in Lusaka, only 30% of eligible pregnant HIV-positive women received the complete nevirapine treatment, as assessed by directly observed therapy for the infant and measurement of nevirapine levels in cord blood. In the following year, the rate of successfully delivered treatment increased to 40% (Stringer, unpublished data).

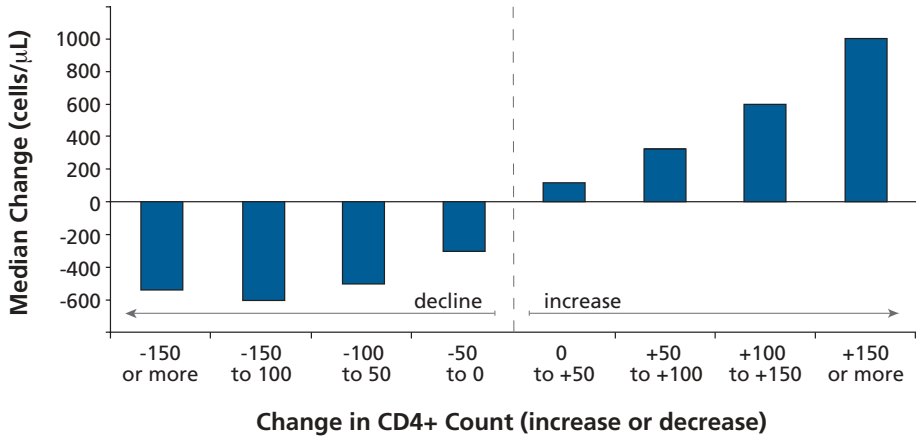

Figure **6.** Median change in total lymphocyte count by change in CD4+ cell count from baseline in patients receiving antiretroviral therapy. Adapted from data published in Kumarasamy, *J Acquir Immune Defic Syndr*, 2002, and Kumarasamy, *Lancet Infect Dis*, 2002.

Challenges

The prevention of mother-to-child transmission of HIV in Zambia and elsewhere requires novel antiretroviral regimens that are as "simple" as but more effective than single-dose nevirapine and that do not induce high-level drug resistance in the mother. Improved strategies for preventing HIV transmission through breastfeeding are also needed. Of course, from a societal perspective, great improvements are needed in efficient delivery of antiretroviral therapy for all who are HIV-infected, along with access to low-cost diagnostics and monitoring, improved training for health services personnel, and general health services improvements. HIV-related care must not come at the expense of deteriorations in other aspects of public health; this has been observed in some locales, in which funding for tuberculosis treatment and prevention programs has been diverted to HIV programs, with a resultant increase in tuberculosis rates. In short, effective delivery of HIV-related care in places such as Zambia ultimately will require sustainable programs that address all of the issues raised in providing care in industrialized countries, as well as issues related to implementing such programs across great financial and cultural divides.

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