Perinatal HIV Transmission

and

Prevention of Mother to Child HIV Transmission (PMTCT)

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Facts

Every year, over 2 million HIV infected pregnant women give birth to 700,000 HIV infected infants.

With access to treatment, fewer than 100 infants are born with HIV infection each year in the US.

In contrast, **1,800 infants** become infected each day in developing countries.

A single dose of the drug Nevirapine, given to the mother and infant, could prevent 300,000 infant infections each year.

In 10 years, the lives of 3 million children could be saved.

Nevirapine is effective even when breast-feeding is continued for up to 18 months.

In 1994, a clinical study, using the antiretroviral drug zidovudine reported a reduction in HIV transmission from infected mothers to their infants by 68% (1). Zidovudine treatment was initiated during the second trimester of pregnancy and was given to infants for the first six weeks after birth. The use of zidovudine therapy to prevent perinatal HIV transmission had a profound impact in developed countries, resulting in the elimination of newly infected infants in many metropolitan areas and fewer than 200 newly infected infants per year in the entire US. Aggressive prenatal HIV testing, coupled with combination antiretroviral therapy and Cesarean section further reduced HIV transmission to less than 1% in the US and Europe (2).

Good news for developed countries but what about developing countries where 1,800 infants are born HIV infected each day?

It was hoped that shorter courses of zidovudine could lower the cost of perinatal HIV prevention resulting in greater universal applicability especially in developing countries. In 1998 a CDC/Thailand clinical trial was concluded utilizing a short course of zidovudine (4 weeks) given to HIV infected pregnant women (who did not breast feed) during the last trimester of pregnancy. Infants did not receive zidovudine (3). The degree of reduction in perinatal HIV transmission was comparable to the full zidovudine treatment used in the US. The CDC/Thailand study defined a potentially less expensive approach to HIV prevention, approximately $50 vs. $900 US, but even the lower cost remained unaffordable for the majority of developing countries. Additionally, substitution of formula for breast-feeding in developing countries is both expensive

and risky – mixing formula with water that is not clean can significantly increase infant mortality from diarrhea and other infectious diseases.

How do antiretroviral drugs work to reduce HIV transmission?

Antiretroviral drugs interfere with the ability of HIV to multiply by inhibiting the enzymes that are necessary for the virus to reproduce itself. There are several classes of antiretroviral drugs. Each one works by a different mechanism. When drugs of different classes are used together, know as combination therapy, virus multiplication is suppressed to a greater degree than with a single drug (monotherapy) and it is less likely that resistance to the drugs will develop. As the virus level drops to very low levels it is less likely that the virus can be transmitted to the infant. If the virus still escapes from this potent treatment of the mother, then the infant can be protected from infection by administering one or more antiretroviral drugs to prevent the virus from infecting infant cells. This is referred to as "post exposure prophylaxis". A similar approach is used for health care workers who may have been exposed to HIV by accidentally cutting themselves or a woman who was raped by an HIV infected individual. To be effective, the antiretroviral drug must be given within the first 48 hours of exposure.

Could the cost of zidovudine or other antiretroviral therapy be brought even lower?

A retrospective analysis of HIV infection outcomes in infants born to HIV infected pregnant women who received abbreviated regimens of zidovudine suggested that this might be possible (4). The transmission rate for infants born to mothers who received prenatal zidovudine was 6%. Even when zidovudine was given to infants within 48 hours after birth, the HIV transmission rate was low. A UNAIDS study, which evaluated abbreviated courses of zidovudine in combination with lamivudine to the mother beginning at 36 weeks of gestation and continuing one week after delivery along with one week of treatment to the infant after delivery, reported a reduction in HIV transmission of 50% compared to placebo (5). Newer studies show that treatment with zidovudine plus lamivudine plus single dose nevirapine can reduce HIV transmission to less than 5%. (5)

If formula feeding could be safely provided in developing countries, millions of lives could be saved.

The annually cost of nevirapine to treat all HIV infected pregnant women and their infants is less than $2 million/year.

HIV/AIDS adds 6,000 new orphans worldwide each day – 2 million each year.

Over 20 million women are now infected with HIV. For the first time, the number of infected women equals the number of infected men.

In many countries young women of childbearing age are 4 to 6 times more likely to be HIV infected than young men.

Breast-feeding Dilemmas

In developing countries, breast-feeding offers the best opportunity for inexpensive, readily available and safe infant nutrition. In most communities breast-feeding is viewed as a caring and nurturing response of a mother toward her infant. There are many studies that document the beneficial aspects of breast-feeding in protecting against infection. However, under some circumstances infection can be transmitted by means of breast-feeding. HIV infection is one of

these. Studies have demonstrated 15 to 40% increased risk of HIV transmission for infants who were breast-fed presenting a dilemma for the mother (6).

A seemingly simple alternative to breast-feeding would be to offer formula feeding. The use of formula would not result in HIV transmission, could assist a mother who is not feeling well enough to breast-feed, or who is herself nutritionally deficient. Formula feeding could enhance nutrition under circumstances where inadequate breast milk is available and allow shared care of infants by other members of the family and community. Concerns regarding formula feeding are that, even when provided free, the formula may not be made up with clean water or reconstituted to its full strength, or it may be shared between mothers, or given to other children in the family resulting in malnutrition for the infant.

There is growing evidence that formula feeding can be given safely when supported by well-trained healthcare workers and in settings with access to clean water. Several resource poor countries or regions or programs within a country provide both clean water and formula or alternatives to formula for HIV infected mothers (China, India, Dominican Republic) Safety of breast-feeding must also be considered form the perspective of the mother who may too ill to care for herself and her infant. (7)

The seemingly conflicting opinions on breast-feeding versus formula feeding in a developing country setting may result in confusion among healthcare staff and relationships between women, their families and their community. Recommendations for breast-feeding versus formula feeding should therefore take into consideration the availability of safe water supplies and aspects of family and community education to avoid possible stigmatization and discrimination. In settings where infant mortality is high and related to unsafe water supplies continued breast-feeding may be necessary in spite of the risk of transmitting HIV infection to the infant.

Breast-feeding adds 15 to 40% additional risk for HIV transmission.

The highest rate of HIV transmission from breast-feeding occurs in the first months of the infant's life.

Exclusive breast-feeding (no other foods or drink) is associated with less HIV transmission than mixed-feeding (breast-feeding and additional food and drink)

Early weaning could significantly reduce the risk of acquiring HIV infection form breast-feeding.

If formula feeding could be safely provided, tens of thousand of infant lives could be saved each year.

Alternative methods for providing breast-feeding have been proposed including wet-nursing, where another woman breast-feeds the mother's infant, pasteurization of expressed breast milk, or use of a disinfectant to inactivate HIV. There are difficulties with all of these approaches, which relate primarily to the fact that they are of unproven safety.

If an HIV uninfected mother were to breast-feed an infant who happened to be HIV-infected it is possible that HIV could be transmitted from the infant to the uninfected mother. The amount and duration of pasteurization (heating) that is necessary to inactivate HIV in breast milk and the impact on the nutritional value has not been clearly defined. Controlled clinical studies of chemical inactivation have not been performed.

At this time, the two options that are available for HIV-infected mothers in developing countries are to either exclusively breast-feed for a defined period of time or formula feed, if it can be done safely and without incurring discrimination (8). Exclusive breast-feeding, where breast milk is the only food or drink that baby receives, is associated with a lower rate of HIV transmission then when mixed feedings are utilized (combining breast-feeding and other forms of infant feeding such as formula or food). The protective effect of exclusive breast-feeding may be similar to other situations, where exclusive breast-feeding protected against infant diarrhea and pneumonia.

The health of the mother’s breast is important. Studies have shown that some inflammation of the breast (mastitis) or breast ulcers can increase the risk of HIV transmission. The time at which breast-feeding is discontinued may have an impact on reducing HIV infection of the infant. While the highest risk of HIV transmission from breast-feeding occurs with him the first several months after birth, it appears that maximum benefit from breast-feeding can usually be obtained by six months of age when breast-feeding can be safely discontinued (7).

Other means of prevention HIV infection

In view of the fact that perinatal HIV transmission in developing countries is unlikely to be reduced to the same degree as in developed countries using existing treatment protocols, research must continue into both the mechanisms of transmission and the mechanisms whereby HIV transmission is prevented. Chorioamnionitis and prolonged rupture of the membranes contribute to increased HIV transmission (9). Thus far there is no effective treatment for chorioamnionitis to reduce HIV transmission. If membranes are ruptured for 48 hours or longer a Cesarean section is recommended to reduce the risk of acquiring HIV during vagnal delivery.

It is clear from recent European studies that Cesarean section alone, or in combination with antiretroviral therapy can effect an additional significant reduction in perinatal HIV transmission. These results support the conclusion that some HIV infection must be acquired during passage through the vaginal canal. In non-breast feeding populations it is estimated that 50 to 70 % of HIV infection is acquired during labor and delivery and the remainder in utero. To date, studies directed at reducing exposure to HIV during birth other than Cesarean section, have not demonstrated a benefit in reducing HIV transmission. Vaginal cleansing, although demonstrating an effect on non-HIV perinatal mortality, did not have an effect on HIV transmission (10).

Treating an HIV infected woman for her infection is an important approach to preventing HIV transmission to her infant. Under circumstances where antiretroviral drugs are available and affordable, combination antiretroviral treatment offers the best hope for controlling the mother’s disease and preventing her infant from becoming infected. HIV pregnant women who are immodeficient and susceptible to opportunistic infection should receive Bactrim (trimethoprim-

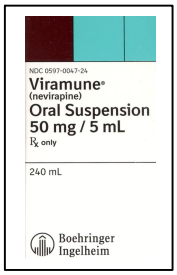
sulphamethoxazole; co-trimoxazole) prophylaxis. This inexpensive drug can prevent serious opportunistic infections and extend the life of the mother significantly.

Of course, preventing HIV infection to start with is the most important preventive measure. For this reason HIV education, testing and counseling should be offered to all women who are sexually active, who engage in risks known to be associated with HIV infection as well as women who are pregnant. In several studies over 50% of women who tested positive for HIV did not know they were infected. In some cultures sexual activity may increase during pregnancy. If the mother is uninfected, this increases her risk of infection from an infected partner.

Antiretroviral Treatment for PMTCT – No Longer a Cost Issue

> In 1999 the NIH reported the results of a study performed in HIV infected pregnant women in Uganda. A single dose of nevirapine given to the mother at the time of labor and a single dose to the infant at 48 to 72 hours of age reduced HIV transmission by 50%. Even when breast-feeding was continued for as long as 18 months, a reduction in HIV infection continued to be observed.
> *Lancet 362:859-68, 2003.*

An interesting turn of events occurred with the demonstration in Uganda that nevirapine, at a current cost of only 85 cents US can prevent 50% of perinatal HIV transmission. Some individuals have suggested that in extremely resource poor countries, it might be more economical to treat all pregnant women and their infants with nevirapine especially in countries with seroprevalence rates of greater than 30% (11). This would eliminate the need for costly counseling and testing and permit the use of economic resources for other public health priorities. Arguments against “universal” treatment include the loss of opportunities to counsel women about HIV transmission and prevention and the possible long term safety and efficacy issues associated with the use non nucleoside reverse transcriptase inhibitors which result in the rapid induction of HIV resistance.



Combination antiretroviral treatment – highly effective in reducing HIV transmission to levels less than 5%

Pregnant women who need combination antiretroviral therapy for their own health should receive it. This treats both the mother’s HIV infection and reduces HIV transmission to the baby. When antiretroviral therapy for the mother is not indicated or is not feasible, antiretroviral prophylaxis should be used for PMTCT. The most effective antiretroviral prophylaxis regimen for women who do not require antiretroviral therapy for their own health is a 2-drug regimen: ZDV, from 28 weeks' gestation, with a single dose of NVP at the onset of labor for the mother, and a single dose NVP for the infant between 48 and 72 hours after birth plus 1 week of ZDV for the infant. Additional preliminary studies suggest that provision of zidovudine for 4 weeks to the mother and/or breast feeding infant may also result in reduced to transmission levels to <10% even with continued breast feeding. Provision of combination therapy and single dose nevirapine

for PMTCT is solely an issue of economics and infrastructure. Single dose nevirapine should be considered as foundational treatment with additional preventive therapy introduced as funding and infrastructure increase. Given the results of several recent clinical trails trials (see the Overview of Perinatal Intervention Trials table on the "Women, Children, and HIV" http://www.womenchildrenhiv.org/), zidovudine + lamivudine plus single dose nevirapine may also prove to be effective in prevent resistance to antiretroviral drugs administered during pregnancy.

> The addition of combination antiretroviral drugs, longer duration of treatment, formula feeding and cesarean section are incremental steps as infrastructure and funding become available.

Why aren't antiretroviral drugs more widely used in developing for PMTCT?

A recent survey suggested that less than 5% of pregnant women in developing countries receive HIV prevention counseling; less than 10% of HIV infected pregnant women receive any antiretroviral drug to prevent infection of their infants, in spite of the fact that the effectiveness of antiretroviral drugs was reported over 10 years ago (13). This discouraging result is likely a result of several factors including, inadequate health care resources, inadequate numbers of trained health care workers, political and bureaucratic obstacles and continued discrimination and stigmatization of HIV infected women.

Arguments have been presented that the use of antiretroviral treatment for perinatal prevention focuses solely on the infant and ignores the HIV infection status of the mother. This is a shortsighted view and ignores the benefits of HIV prevention. There is substantial benefit to an HIV infected mother and to the health care community in having an HIV uninfected child rather than a chronically or severely ill child. There is also benefit to HIV counseling and testing in preventing transmission of HIV to sexual partners, understanding the risk of HIV transmission for future pregnancies, and planning future pregnancies. Finally, there are other inexpensive treatments, which must be considered if antiretroviral treatment for HIV is not available in a developing country. Several studies have shown that prophylactic Bactrim at a yearly cost of just $8 can significantly reduce mortality when given to HIV infected adults.

Summary

Both scientific and economic studies demonstrated that PMTCT, using antiretroviral drugs, is one of the most cost effective means for HIV prevention (10). Prenatal HIV testing, coupled with voluntary counseling and testing for all women, could result in reduced HIV infection in all populations saving millions of lives each year. Now there is an important opportunity for governments, NGOs and Faith Based organizations in developing countries to distinguish themselves by implementing prevention programs to protect women and infants from become infected with HIV. As Gro Brundtland, WHO's former director general, and Nobel laureate economist Amartya Sen have suggested, "Investing in health will help the world extricate itself from the mire of poverty". Moving forward with the implementation of perinatal HIV prevention by means of antiretroviral treatment could reduce the number of new HIV infections in children by 3 million over the next decade. As with many areas of progress, new issues have been encountered. Rather than retreat, each new problem, whether orphans, viral resistance, or treatment of mothers, must be addressed and resolved. A window of opportunity, provided by the

ability to prevent HIV infection of infants, should serve as the megaphone for HIV prevention, increasing hope that the epidemic can be brought under control.

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