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Preventing Perinatal Transmission of HIV

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PREVENTING PERINATAL TRANSMISSION OF HIV

One of the pressing challenges to improving birth outcomes in the world today is perinatal transmission of HIV. Since the start of the epidemic, it is estimated that 3.8 million children have died of AIDS, the vast majority resulting from HIV acquired from their mothers during pregnancy, around the time of childbirth, or during breastfeeding. In heavily affected populations in Sub-Saharan Africa and elsewhere, as many as 10 percent of children could become infected, and die, before they reach adulthood (calculated below). This is the equivalent of increasing the infant mortality rate by 100 per thousand, reversing decades of progress in improving birth outcomes. On the other hand, new developments in the prevention of HIV transmission – drugs delivered to the mother during pregnancy and labor and to the child after birth – offer hope that the epidemic of pediatric AIDS can be dramatically reversed in developing countries as it has been in the United States and other developed countries (Mofenson and McIntyre, 2000). Despite their promise, however, these interventions are not common in the developing world.

The aim of this chapter is to clarify the challenge of perinatal HIV transmission and identify ways to achieve the promise offered by the new therapies. It begins with a description of the extent of the HIV/AIDS epidemic in the world, and especially in heavily affected populations. The chapter continues with a review of the risks of perinatal transmission, the effectiveness of the available prevention modalities, and their costs. Cost effectiveness studies are

also reviewed, as well as the potential social, cultural, and ethical barriers to prevention.

The conclusion is that effective, practical, and cost effective strategies to prevent loss of life to HIV in children in developing countries do exist. Women can be screened for HIV in antenatal care, and those who are positive can be treated with a simple course of antiretroviral drugs before, during, and after birth. Affected infants can be treated, and alternatives to breastfeeding can also reduce the rate of transmission. These interventions substantially reduce the risk that children will be born with HIV infection. Because this approach prevents new infections rather than treats people already infected with HIV, all of this can be done ethically and at a reasonable cost compared with treatment scenarios.

DIMENSIONS OF THE HIV/AIDS EPIDEMIC

Since its recognition only two decades ago, the HIV/AIDS epidemic has grown to major proportions in many countries of the world, especially in Sub-Saharan Africa. An estimated 36 million people were living with HIV/AIDS in the world at the end of 2000, and there were approximately 3 million deaths attributed to AIDS in that year. Most of those with HIV/AIDS – approximately 25 million – lived in Sub-Saharan Africa (UNAIDS, 2000b). In some countries, especially in Africa, the prevalence of HIV in childbearing women approaches 30 percent or more. As a result, UNAIDS estimates that about half of current 15-year-olds in the worst affected countries in Africa will eventually die of the disease (UNAIDS, 2000a). One indicator of the impact of HIV/AIDS is that life expectancy in Southern Africa is expected to drop to 45 years between 2005 and 2010 because of AIDS (UNAIDS, 1999). This is a stunning reversal after life

expectancy rates had risen from 44 years in the early 1950s to 59 in the early

1990s.
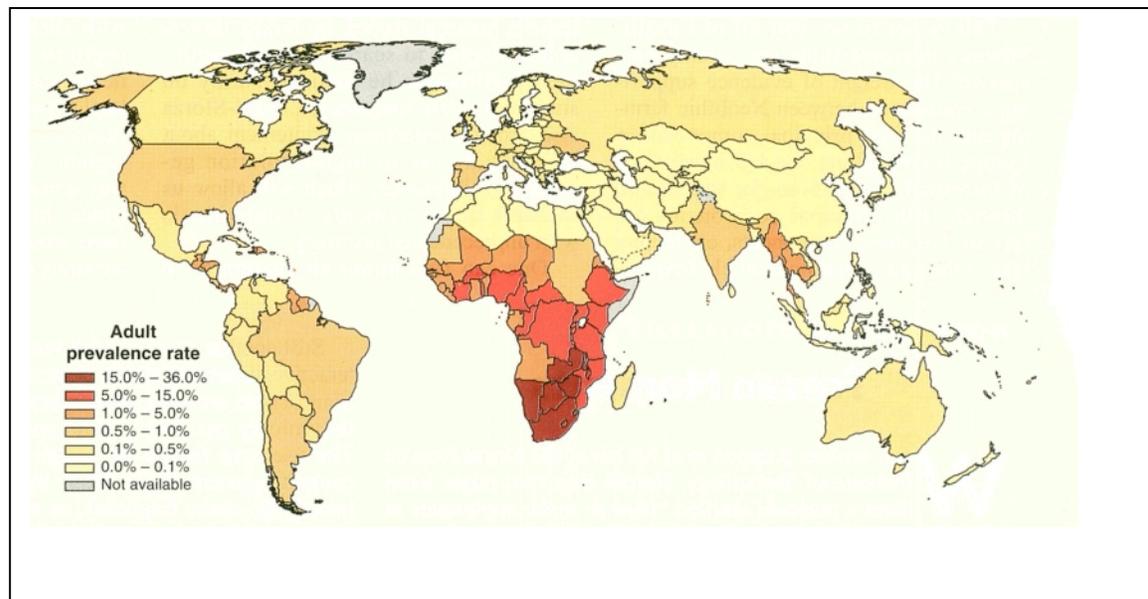
Figure 1. Worldwide HIV prevalence rates in adults at the end of 1999.
Estimates are based in large part on anonymous seroprevalence surveys of
women in antenatal care. Source: Schwärtlander et al., 2000; UNAIDS, 2000a.

Furthermore, HIV/AIDS is claiming the lives of the most educated workers,

at the most productive time of their lives. Doctors, farmers, agricultural, mining

and industrial workers and others are dying and lost to their societies as parents

and workers who contribute to the social and economic welfare of their countries.

The loss of many teachers interferes with the development of human capital, with

long-run costs for economic productivity. Absenteeism, decreased productivity,

worker turnover, training costs, funeral and death benefits are increasing across

all sectors in many African countries, draining scarce public resources and

impeding job creation and foreign investment (UNAIDS, 2000b).

Another consequence of the HIV/AIDS epidemic is large numbers of

orphaned children, some of them infected with HIV themselves, with resulting

burdens on extended families (UNAIDS, 1999; Mukwaya, 1999). UNAIDS

estimates that there have been 13.2 million AIDS orphans in the world through

1999, 12.1 million in Sub-Saharan Africa (UNAIDS, 2000b).

Although in many countries the HIV/AIDS epidemic has struck men more

than women, in many developing countries women are more heavily affected. In

Sub-Saharan Africa, where heterosexual transmission predominates, women

make up 55 percent of the adults living with HIV/AIDS. In South and South-East

Asia and the Caribbean, women make up 30 percent to 35 percent of the HIV-

infected adults. In other parts of the world, such as North America, Western and

Central Europe, Latin America, North Africa and the Middle East, approximately

20 percent of HIV-infected adults are women. The relatively high prevalence of

HIV in women of childbearing age has obvious implications for the risk that some

of them will have children who will become infected (UNAIDS, 2000b; Newell,

2000).

Biological and cultural factors also help to explain the high prevalence of

HIV infection in women. Sexually transmitted diseases (STD), for instance,

contribute to increased susceptibility. The subordinate sexual and economic

status of women in many cultures also contributes to the acquisition of STDs and

HIV infection (UNAIDS 1999c, 2000b). In Africa and South Asia, for instance, it

is common for women to be coerced or seduced by older men into having sex

with promises of gifts. In some African and Caribbean countries there is a myth

that if a man infected with any STD including HIV has sexual relations with a

virgin, he can cure himself of his disease (Mukwaya, 1999).

PERINATAL TRANSMISSION OF HIV

Transmission of HIV from mother to child can take place in utero, intrapartum or postpartum through breastfeeding (Mofenson, 1997, 1999; UNAIDS, 1999). In Sub-Saharan Africa and other developing countries, 25 to 35 percent of children born to HIV-infected mothers become infected at birth or shortly thereafter (De Cock, 2000; Brocklehurst, 2000). In industrialized countries the likelihood of transmission is approximately 15 to 25 percent (UNAIDS, 1999). In developing countries, children with HIV infection are more likely to die at a younger age. In one study, the probability of death by the age of 12 months in HIV-infected children was 23 to 35 percent, and by the age of five years 57 to 58 percent died (Tudor-Williams, 2000). A study in Malawi concluded that nearly 90 percent of African children infected with HIV do not survive beyond their third birthday (Taha, 2000).

In some populations, the estimated prevalence of HIV infection in women aged 15 to 24 is 30 percent or higher (UNAIDS, 1999), especially in Sub-Saharan Africa. The HIV prevalence rates depicted in Figure 1 above are largely based on samples of women in antenatal care. In South and South-East Asia, HIV prevalence rates of up to 5 percent have been documented in antenatal clinics, but the overall prevalence in childbearing women is likely to be much lower than in Africa. If 33 percent of the childbearing women in a population were infected with HIV, and the rate of transmission to their children was also 33 percent, the result would be that more than 10 percent of children would be infected. Because nearly all HIV-infected children will die before they reach adulthood, this is the equivalent of a 100 per thousand increase in infant mortality. Maternal mortality, whether the child is infected or not, can also

negatively affect the child's chance of survival. These estimates of prevalence and transmission are at the upper end of the range of possibilities, so in most places the impact will be less, but this calculation does illustrate the potential impact of perinatal transmission of HIV.

Risk factors for perinatal transmission

A series of risk factors can affect the probability and the timing of transmission. Some are maternal factors: advanced maternal disease, decreased CD4+ cell counts, increased HIV plasma RNA levels, and decreased vitamin A levels. The results of the European Collaborative Study, for instance, demonstrated a linear relationship of transmission with decreasing CD4+ cell counts, seemingly independent of other factors (Gianquinto, 1992). Other studies have also found an association between higher plasma HIV RNA levels and a significant risk of transmission from mother to infant (Garcia, 1999; Mofenson, 1999; Starr, 1999), although transmission may occur even when virus is undetectable. Separate studies of cohorts of pregnant women in Malawi and the United States have found an association between low vitamin A levels in pregnancy and increased risk of transmission (Semba, 1997), however Burns et al. (1999) do not confirm this result.

Because the child is exposed to HIV in the mother's genital tract during labor and delivery, several obstetric factors influence the rate of transmission. These factors include prolonged rupture of membranes, instrumentation, vaginal delivery, and birth trauma (UNAIDS, 1999; Mofenson, 1997, 1999). Studies in both humans and primates demonstrate the transmission of HIV through maternal blood or secretions (Mofenson, 1997). If membranes rupture

prematurely or if the mother has a hemorrhage, the child could become infected (Mofenson, 1997).

In the postpartum period, the primary mode of transmission is breastfeeding. In a randomized trial in Nairobi, Kenya comparing breastfeeding and formula feeding, the risk of HIV transmission through breastfeeding was estimated at 16.2 percent. This represents 44 percent of HIV infection in the breastfeeding arm of the study. Most – 75 percent – of the risk difference between the two arms of the study occurred in the first 6 months, but transmission continued throughout the duration of exposure (Nduati, 2000). Coutsoidis and colleagues (2001) have shown that mixed infant feeding (breast milk plus other liquids) is associated with higher transmission than exclusive breastfeeding.

PREVENTION OF HIV TRANSMISSION

Strategies to prevent the transmission of HIV fall into two categories. A number of antiretroviral drug regimens for prevention of perinatal transmission of HIV that may begin before birth, in most cases continue through labor and delivery, and may involve postpartum treatment of mothers and/or children have been evaluated. Antiretroviral therapy (ART) includes treatment with zidovudine, nevirapine, and combinations of these and other antiretroviral drugs. ART strategies are discussed first and summarized in Table 1. Non-ART strategies including cesarean section, vaginal lavage, and prepartum vitamin A therapy have also been considered, and are discussed in a second section.

Antiretroviral strategies

Zidovudine. A breakthrough study in 1994 concluded that an antiretroviral drug

zidovudine (AZT), previously known to delay disease progression in persons with

relatively advanced disease, was effective in reducing the risk of perinatal

transmission. The AIDS Clinical Trials Group (ACTG) announced that a

randomized, double-blind, placebo controlled trial of the efficacy and safety of

zidovudine (protocol number 076) resulted in reduced perinatal transmission of

HIV by about 67 percent (Connor, 1994). The women enrolled in the study had

not received previous antiretroviral therapy. The mother's regimen included 100

mg of AZT orally five times daily, beginning as early as 12 weeks before

expected delivery. During labor they received 2 mg/kg of body weight

intravenously for one hour, followed by 1 mg/kg per hour until delivery. The

newborns received 2 mg/kg orally every six hours for six weeks. The mothers

did not breastfeed.

Based on these and subsequent results, the ACTG 076 regimen has

become the minimum standard of care in industrialized countries (IOM, 1999),

and in the United States mother-to-child transmission of HIV has fallen by about

70 percent from its peak in the early 1990s (CDC, 2000).   With appropriate

antiretroviral therapy, perinatal transmission rates have fallen to less than 2

percent (Mandelbrot, 2001). The ACTG 076 regimen is considered cost-effective

in the industrialized world, but logistically infeasible or prohibitively expensive in

most developing countries.

As an alternative to the ACTG 076 regimen, a series of clinical trials of a

shorter course of zidovudine have been carried out in Sub-Saharan Africa and

Southeast Asia. The "short course" regimen, which includes daily doses of AZT

beginning late in pregnancy, has been shown to cut perinatal transmission rates by about 50 percent.

Two of the short-course zidovudine trials have been conducted in Thailand. The first, the Bangkok trial, was placebo-controlled and the women did not breastfeed. Women received 300 mg of AZT twice daily starting in the 36th week of pregnancy. During labor and delivery they received 300 mg orally every three hours, and there was no post-partum therapy. At age six months, 18.9 percent of children in the placebo group and 9.4 percent in the zidovudine group were infected, representing a 50 percent reduction in the transmission rate (Shaffer et al., 1999). The estimated cost per person was about $200 to $400 (Shaffer, 1999; Mofenson and McIntyre, 2000). In a follow-up study of 319 (81%) of the children up to 18 months of age found no significant adverse events associated with the AZT (Chotpitayasunondh, 2001).

The second Thai study, the Perinatal HIV Prevention Trial (PHPT), compared several zidovudine regimens at the same doses as the Bangkok trial. Women started at the 28th or 35th week of the pregnancy (long vs. short prenatal therapy) and newborns received 2 mg/kg of weight orally four times daily for 6 weeks or 3 days (long vs. short postnatal therapy). The short prenatal/short postnatal arm of the trial was stopped early because the transmission rate was significantly higher than in the long prenatal/long postnatal arm. At 18 months, the transmission rate was found to be significantly lower in the long prenatal treatment arms (Lallemant et al., 2000; Mofenson and McIntyre, 2000).

Two African zidovudine studies took place in Ivory Coast and Burkina Faso. Both were placebo-controlled trials in which the mothers breastfed. The trial in Ivory Coast consisted of the short course regimen where mothers took 300

mg of AZT orally twice daily starting at 36th week of pregnancy and 300 mg orally every three hours during labor and delivery. Transmission at age six months was 27.5 percent in the placebo group vs. 18.0 percent with zidovudine, representing a 35 percent reduction in the rate of transmission (Wiktor et al, 1999).

The DITRAME ANRS 049 study was conducted in Ivory Coast and Burkina Fasso with a similar study design. The antepartum treatment began at the 36th to 38th week of pregnancy and the women received 600 mg of AZT orally at the onset of labor and 300 mg orally twice daily for one week postpartum. The reduction in transmission was about 30 percent with a 30.6 percent rate of transmission in the placebo group and 21.5 percent in the study group. Researchers concluded that the post-partum course of maternal zidovudine was not significantly beneficial in breastfeeding populations (Dabis, 1999).

Combination therapy. As antiretroviral treatment standards have changed to include two and three drug combinations, and as a result viral loads have dramatically dropped, researchers have considered the possible benefits of combining zidovudine with other antiretroviral agents to prevent perinatal transmission. Mandelbrot and colleagues (2001) have shown using retrospective controls that a combination of zidovudine and lamivudine (3TC) can reduce the risk of transmission by almost 80 percent. Concerns about possible side effects and the fact that current treatment guidelines typically call for a three-drug regimen (including a protease inhibitor), however, limit the practical impact of this finding.

The PETRA trial in South Africa, Uganda and Tanzania was a placebo-controlled trial to evaluate the efficacy, tolerance and effectiveness of less

intensive regimes of this same combination of drugs – zidovudine plus

lamivudine. Mothers received 300 mg of zidovudine and 150 mg of 3TC twice

daily beginning in the 36th week of pregnancy. During delivery they received 300

mg of AZT orally every three hours and 150 mg of 3TC every 12 hours. The

mothers, most of whom breastfed, also received postpartum treatment of 300 mg

of AZT and 150 mg of oral 3TC twice daily for one week (Saba, 1999).   The

study compared this entire three-part regimen to two other versions, one

consisting of intrapartum and postpartum therapy and the other of intrapartum

therapy only. At 6 weeks postpartum, the rate of transmission was reduced by

50 percent from 17.2 percent in the placebo group to 8.6 percent in the three-part

treatment group. The two-part regimen achieved a 37 percent reduction, and the

intrapartum-only group was not significantly different from the placebo group. At

18 months the effect was attenuated, probably due to breastfeeding.

Nevirapine. The HIVNET 012 randomized controlled trial in Uganda revealed in

1999 that nevirapine (NVP), a non-nucleoside reverse-transcriptase inhibitor that

is rapidly absorbed orally was capable of reducing the risk of perinatal

transmission by 47 percent, which is comparable to a short course of zidovudine.

The regimen consists of a single intrapartum dose of NVP for the mother and a

single dose for the infant after birth, making it more affordable than zidovudine at

a cost of $4 for the entire regimen (Marseille, 1999). The HIVNET 012 trial

compared nevirapine with intrapartum and post-partum zidovudine, a regimen

not currently considered to be effective. Mothers in the treatment group received

a single 200 mg oral dose of NVP at the onset of labor and newborns received a

2 mg/kg weight oral dose 48 to 72 hours postpartum. Mothers in the comparison

group received oral AZT intrapartum (600 mg at the onset of labor and 300 mg every 3 hours until delivery) and infants received 4mg/kg orally twice daily for one week (Guay, 1999).

According to preliminary results, the SAINT trial in South Africa compared nevirapine administered intrapartum and postpartum to a combination of zidovudine and lamivudine administered on the same schedule and found no significant difference in HIV infection 8 weeks postpartum. In the treatment group, mothers received 200 mg of NVP orally at the onset of labor and 200 mg orally at 24 to 48 hours postpartum and children received 6 mg of NVP orally at 24 to 48 hours postpartum. Mothers in the zidovudine group received 600 mg of AZT and 150 mg of 3TC orally at the onset of labor and 300 mg of AZT and 150 mg of 3TC orally every three hours until birth. After birth mothers received 300 mg of AZT and 150 mg of 3TC orally twice daily for one week, and children received 12 mg of AZT and 6 mg of 3TC orally twice daily for one week (Moodley, 2000 as cited in Peiperl, 2000).

Non-ART strategies

Vitamin A therapy. As discussed above, vitamin A deficiency has been associated with transmission of HIV in a study in Malawi, and other research has linked low maternal vitamin A levels with increased viral load in breast milk (Brocklehurst, 2000; Semba 1997). While this suggests that therapeutic doses of vitamin A might help prevent perinatal transmission of HIV, data from intervention studies do not support this conclusion. Moreover, since vitamin A can be teratogenic in high doses, vitamin therapy is not recommended at this time.

Cesarean section. The possibility of exposure to the mother's secretions during labor and delivery suggests that minimizing exposure by conducting a cesarean section might reduce the risk of transmission of HIV. In fact, a meta-analysis of studies North American and European studies found that elective cesarean section reduces the risk of transmission of HIV by more than 50 percent, independent of treatment with zidovudine (International Perinatal HIV Group, 1999). However, depending on the nature of the health care system, safe and effective cesarean sections may not be available in many developing countries. Some studies, for instance, have shown an increased rate of maternal complications in HIV infected women (Mofenson and McIntyre, 2000). Thus, cesarean section may be an appropriate strategy for preventing transmission of HIV in some women, but only if appropriately staffed and equipped health facilities are available.

Vaginal lavage. Another prevention approach that has been studied is viricidal cleansing of the birth canal and the infant's skin immediately after delivery. One study of this intervention in Malawi found that cleansing the newborn and the maternal birth canal at every vaginal exam before delivery with a 0.25 percent chlorhexidine solution reduced early neonatal and maternal postpartum infections in general (Taha, 1997). However, the same researchers looked at the effectiveness of this intervention in terms of HIV transmission and found it inconclusive, except when membranes were ruptured more than four hours before delivery (Biggar, 1996). Although there are no clear data indicating its efficacy, vaginal lavage is an inexpensive, low-technology strategy that bears consideration in developing countries.

Breastfeeding. After it became evident that HIV is transmitted through breast

milk, the Centers for Disease Control and Prevention (CDC) recommended HIV

infected women should not breastfeed (Dunn et al., 1995), and this became the

standard of care in the industrialized world. In the developing world, however,

there are several complicating factors. First, since breastfeeding is the norm for

infant feeding in the developing world, a woman who does not breastfeed is seen

as tacitly admitting HIV positive status and runs the risk of rejection by her mate

and community. Formula to replace breast milk is expensive, and women must

have access to clean water and formula and be trained in the proper preparation

and administration of formula. Maternal antibodies in breast milk, on the other

hand, confer immunity to the child (Nicoll, 1995), so breastfeeding has an

important protective effect where the prevalence of infectious diseases other than

HIV is high. With a focus on developing countries, UNAIDS has recommended

that woman weight the benefits and risks of breastfeeding and make their own

choice (WHO, 1998), and noted that women who choose to breastfeed are urged

to do so exclusively until a switch to an "alternative form" of feeding if possible

(WHO, 2000).

Toxicity/risks of antiretroviral therapy

Given the known vulnerability of the developing fetus to toxicity,

consideration must be given to potential side effects of any drug used in utero.

Indeed, some antiretroviral drugs have been shown to be carcinogenic in

rodents. No such effects, however, have been seen in short-term human studies

or in a registry maintained by the manufacturers of antiretroviral drugs (Culnane,

1999; Mofenson and McIntyre, 2000). Researchers have postulated a link

between mitochondrial dysfunction and exposure to zidovudine or a combination

of zidovudine and lamivudine, based on eight children born in Europe, but

recommended continued use of antiretroviral treatment with only one drug to

minimize the dangers of mitochondrial damage or toxicity (Blanche et al., 1999).

There are also concerns about the development of resistance to antiretrovirals

(Mandelbrot, 2001). Overall, it is likely that any risk of serious side effects to the

child is small compared to the reduced risk of HIV infection and death that results

from prophylaxis.

Recent evidence of toxic side effects including severe liver damage in

health care workers taking multiple doses of nevirapine as post-exposure

prophylaxis has been attributed to the multiple doses of the drug. Given the far

greater preventive benefits to pregnant women with a known HIV infection than

workers exposed to needles that may or may not be contaminated, CDC

recommends against the use of nevirapine for post-exposure prophylaxis while it

continues to recommend use of nevirapine to prevent perinatal transmission

(CDC, 2001).

**Conclusions regarding the efficacy of interventions to prevent HIV
transmission**

Of all of the options considered in this section, it seems likely that treating

pregnant women who are HIV-infected, and their babies, with simple low-cost

regimens of antiretroviral drugs is the most effective and feasible means of

preventing perinatal transmission in developing countries. Although less effective

than the ACTG 076 regimen used in developed countries, short-course

zidovudine and intrapartum nevirapine have both been shown to reduce the HIV

transmission rate by up to 50 percent at a much lower cost. Such treatment

requires knowledge of which women are HIV-infected as soon as possible --

before, or at least by, the time of delivery. Access to antenatal care is therefore

critical for preventing HIV transmission as well as other morbidity and mortality.

A single dose of nevirapine appears to be about as effective a short

course of zidovudine, and to cost far less. Moreover, it is simpler to administer

since it begins during labor and delivery rather than antenatal care, and therefore

can be administered to all HIV-positive women, even those who receive no

antenatal care. Because of these differences, nevirapine might be seen as

preferable to zidovudine in developing countries.

Although research continues, the short-course zidovudine regimen was

recommended by WHO in 1998, before the nevirapine results were available

(WHO, 1998). In October 2000, a WHO Technical Consultation concluded that

perinatal transmission prevention methods should be included in the "minimum

standard package of care for HIV-positive women and their children," and that

"there is no justification to restrict use of any of these regimens" to research. "A

number of available regimens are known to be effective and safe. ... The choice

should be determined according to local circumstances on the grounds of costs

and practicality, particularly as related to the availability and quality of antenatal

care." Referring to warnings against the widespread use of nevirapine to prevent

mother-to-infant transmission due to concerns of the development of drug-

resistant strains of HIV, the experts concluded that the benefits of preventing

transmission outweigh the "theoretical concerns" linked to development of drug

resistance. Prevention programs should also include testing and counseling

services, support for mothers and infants, and options for infant feeding (WHO,

2000).

Recently, the pharmaceutical companies that manufacture AIDS drugs

responded to concerns about the price of zidovudine, nevirapine, and other drugs

and agreed to offer them to developing countries that have been severely

affected by the AIDS epidemic at prices that have been discounted by as much

as 90 percent. The manufacturer of nevirapine has offered to provide it free to

some countries. The governments of some affected African nations were

originally reluctant to accept these offers, however, because they say it will

require the development of infrastructure for drug distribution, patient education,

and laboratory monitoring. Moreover, even at a 90 percent discount, treatments

can cost hundreds to thousands of dollars per person, an amount that is simply

unrealistic in developing countries (Gellman, 2000). In considering these factors

it is important to distinguish the simple courses of zidovudine and nevirapine that

are necessary to prevent perinatal transmission from the treatment regimens of

HIV-infected adults and children. Zidovudine, and even more so nevirapine, are

far less costly and less much dependent on a clinical infrastructure.

A second concern that has arisen is the realization that even if affordable

and feasible, treatment alone is not sufficient to deal with the world-wide

HIV/AIDS epidemic. Following the lead of the head of UNAIDS, UN Secretary

General Kofi Annan has identified prevention and reduction of mother-to-child

transmission as his leading two priorities (Crossette, 2001).

When HIV-infected mothers breastfeed their babies, the net benefits of

efforts to prevent transmission are diminished. For this reason, antiretroviral

drugs should be supplemented, if at all possible, with appropriate breastfeeding replacement strategies.

COST-EFFECTIVENESS ANALYSES

A number of cost-effectiveness analyses have been prepared for various aspects of antenatal HIV screening, a program that consists of testing women for HIV during antenatal care and treating those who are HIV-positive and their infants to prevent HIV infection. Although the details of the studies differ, all come to the same general conclusion, that perinatal HIV prevention programs can be very effective at low cost. In order to illustrate the principles of cost-effectiveness, typical results, and the amount of uncertainty inherent in this sort of calculation, this section presents a simplified analysis of HIV screening in antenatal clinics (Stoto and Goldman, 1999), then summarizes more complex models in the literature.

Simplified cost-effectiveness analysis

This analysis considers the costs and benefits of antenatal counseling and HIV testing and treatment of women who are HIV-positive with a short course of zidovudine or a single dose of nevirapine during labor to prevent transmission of HIV to the child. The results are examined in terms of the cost per case of HIV infection averted and the net cost of the program to the health care sector and society. Further details of the model are given in the annex to this chapter.

The program costs are assumed to be $4 or $8 per woman for counseling and testing, and $65 for treatment with zidovudine or $4 for treatment with nevirapine. With less intensive counseling ($4 per woman) 75 percent of women

are assumed to accept the test and 85 percent are assumed to accept the

treatment if indicated. With more intensive counseling ($8 per woman) these

proportions increase to 85 and 90 percent respectively. (Although acceptance of

testing has been lower in field trials, we assume that acceptance will improve in

the context of a national program.) The short course of zidovudine is assumed to

have an efficacy of 50 percent and nevirapine to have an efficacy of 45 percent.

Reductions in the risk of transmission of up to 50 percent have been

demonstrated for both drugs, as discussed above, but for the sake of illustration

the less expensive drug is assumed to be slightly less effective. As a sensitivity

analysis, the prevalence of HIV in women in antenatal care varies from 1 to 30

percent.

Figure 2 illustrates the cost per case averted for each of the four options.

Because the cost per woman of counseling and testing is fixed, the cost-

effectiveness ratio improves as the prevalence of HIV in the women increases.

In the nevirapine scenarios the cost per case averted is below $1,000 if the

prevalence is greater than 10 percent, and less than $500 if the prevalence is

greater than 20 percent. Considering that children born with HIV infection are not

likely to survive to adulthood, these ratios compare very favorably with other

investments to improve health. These results can also be compared in terms of

the program cost per Disability Adjusted Life Year (DALY) gained, as is common

in economic evaluations in developing countries. In these terms, the cost per

DALY gained is less than $100 as long as the prevalence of HIV in women

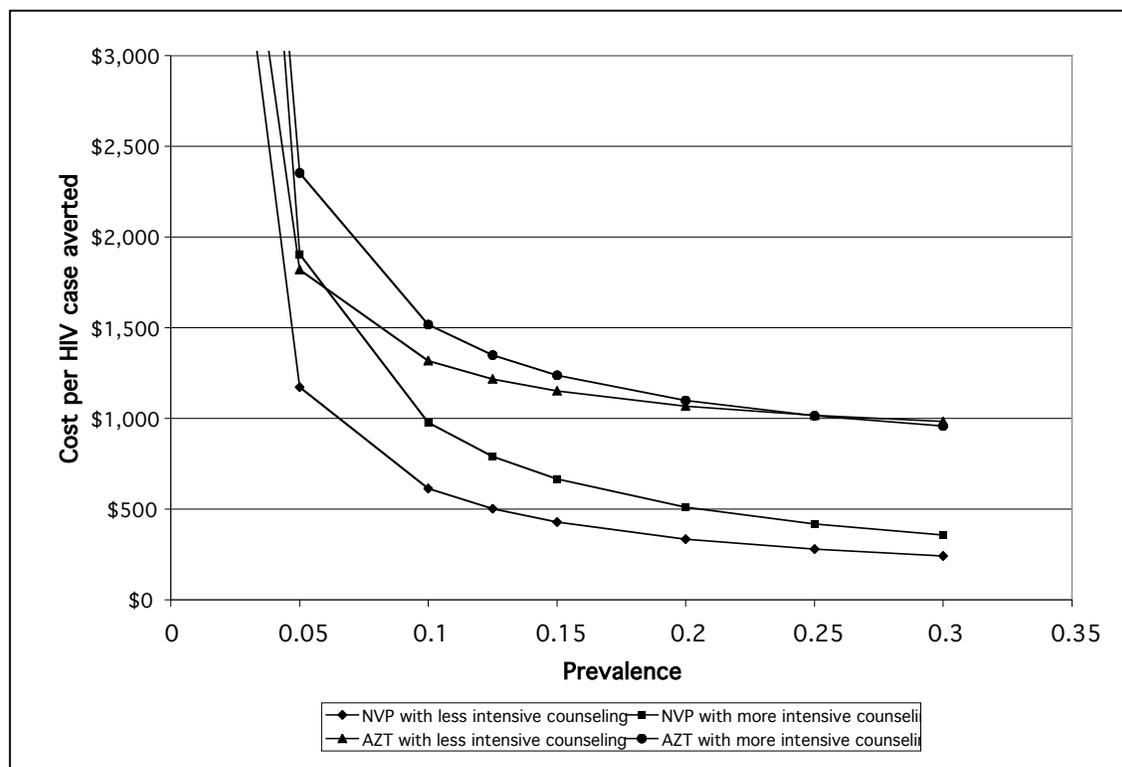exceeds 5 percent, and less than $20 if prevalence exceeds 25 percent.

Figure 2. Cost per HIV case averted under four scenarios of counseling (more or less intensive) and treatment (zidovudine vs. nevirapine). Less intensive counseling costs $4 per woman and more intensive counseling costs $8 per woman.

Figure 3 illustrates the net cost of an antenatal-screening program to a country's health sector. At an HIV prevalence rate of 12.5 percent in pregnant women, program costs range from $4.50 to $8.50 for nevirapine and $12.13 to $16.13 for zidovudine. Net cost is figured as the cost of the screening program minus the cost of health care for children with HIV/AIDS that is averted by the program's prevention efficacy (estimated at $432 per infected child as in Marseille, 1998).   The calculations show that programs incorporating nevirapine are actually cost saving as long as the prevalence of HIV in childbearing women is greater than 25 percent with more intensive counseling or 15 percent with less intensive counseling. If one considers the economic value lost when a child dies before adulthood (estimated at $3,302 as in Marseille, 1998), screening

programs incorporating either zidovudine or nevirapine are cost saving at

maternal HIV prevalence rates of 5 percent or more.
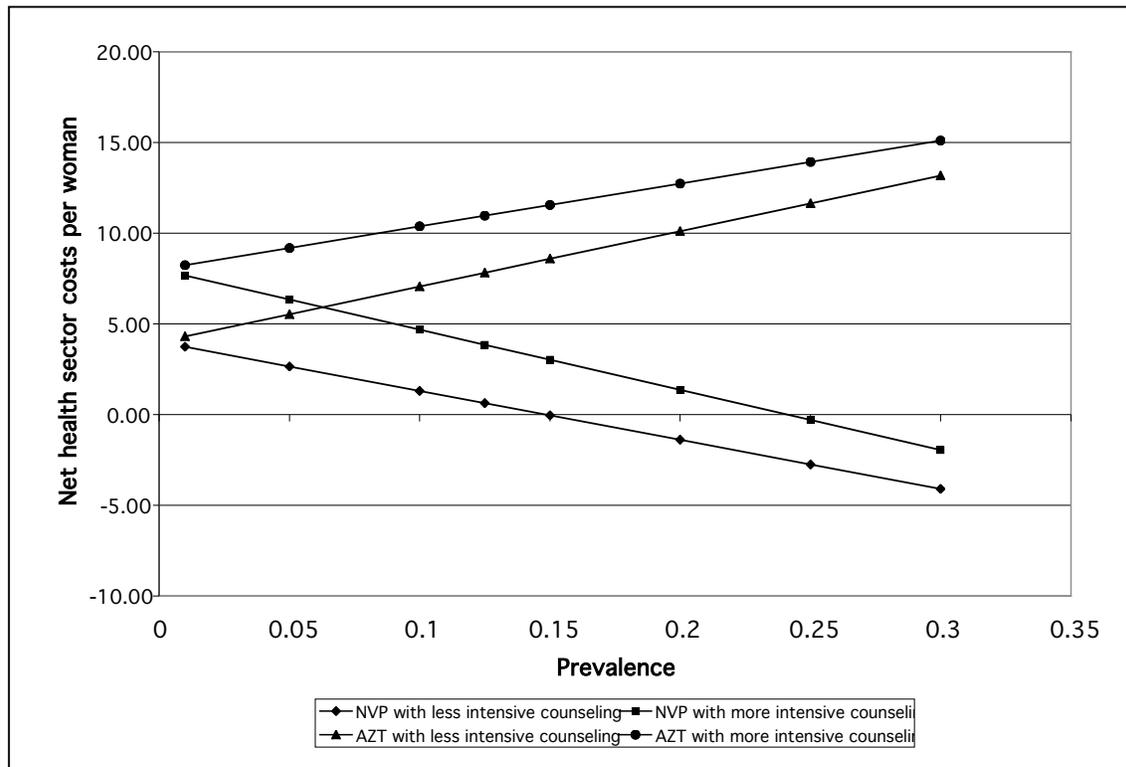
Figure 3. Net cost of an antenatal HIV screening program under four counseling (more or less intensive) and treatment (zidovudine vs. nevirapine) scenarios. Less intensive counseling costs $4 per woman and more intensive counseling costs $8 per woman.

Published cost-effectiveness analyses

Several published cost-effectiveness analyses have evaluated antenatal

HIV screening programs on the individual, health sector and social level.

Program costs include counseling women in antenatal care, testing these women

for HIV, and treating those who are found to be positive to prevent transmission

to their children. All of the costs below are based upon actual local costs for

program administration, but are expressed in terms of U. S. dollars.

In a series of articles, Mansergh and colleagues (1996, 1998) conducted

an evaluation set in sub-Saharan Africa. Their study, based on data from several

investigations, compared a short course of zidovudine which consisted of two

daily doses of 300 mg beginning 2 to 6 weeks before delivery and 300 mg per 3

three hours during labor to no intervention.   The model estimated that a testing

program in an antenatal care setting with a 12.5 percent HIV prevalence rate in

childbearing women would reduce the transmission of HIV from 42.5 to 35.8

infections per 1000 births. The cost to the health care system would be $1,269

per case prevented. On a national level, taking into account lost productivity,

such an intervention would result in savings to society of $1.06 million per

100,000 births (Mansergh, 1998).

Marseille and colleagues (1998) developed a cost-effectiveness model

adopting the health care system perspective and comparing three regimens of

short course combination therapy with no intervention. The first consisted of

zidovudine and lamivudine daily starting at 36th week of pregnancy and one week

postpartum. Assuming a 15 percent HIV prevalence rate among pregnant

women, this regimen cost the health care system $5,134 per case averted. Drug

therapy in the second regimen began at delivery and included one week

postpartum, and cost $2680 per case averted. In the final regimen the drugs

were administered intrapartum only; this cost $1,129 per case averted.

A third analysis applied to rural South Africa (Wilkinson, 1998) compared

three treatment scenarios to no intervention. HIV prevalence among pregnant

women was assumed to be 26 percent, the rate for the KwaZulu/Natal district. In

one scenario women received the ACTG 076 regimen only, and the cost to the

public health system was $5,806 per case prevented. The second scenario

resembled the first but with enhanced service infrastructure. In this scenario, the

cost per case prevented was $5,591. The final scenario consisted of a short course of zidovudine with lamivudine, cost $2,492 per case prevented.

Marseille (1999) compared intrapartum and neonatal nevirapine as in the HIVNET 012 study with the Bangkok short-course (intrapartum and neonatal) zidovudine with efficacy rates of 50 percent and 37 percent respectively. Marseille's model constructed two nevirapine scenarios. In the first, nevirapine was administered to all pregnant women without HIV testing. The second scenario targeted HIV positive women through counseling and testing. Under the universal treatment scenario at a 15 percent rate of HIV seroprevalence the cost to the public health system per HIV case averted was $276 while at a seroprevalence rate of 30 percent the cost was $138 per case averted.

Söderlund and colleagues (1999) analyzed the effectiveness of a variety of antenatal and postnatal options available in South Africa to a working class, urban community such as Soweto. Comparing three antenatal regimens – ACTG 076, PETRA arm B (zidovudine plus lamivudine during and after birth), and the Bangkok study regimen (short course zidovudine before and during birth) – they found that the low cost regimens were almost as effective as the high cost ones and thus more cost effective. The zidovudine regimen was found to be cost saving at a prevalence rate of 15% or higher. Overall, the authors concluded that HIV screening and administration of antiretroviral drugs around birth is likely to be a cost-effective intervention across a wide variety of settings, irrespective of mode of feeding. With respect to their four formula feeding scenarios – recommended from birth (with and without supplying formula and bottles) and recommended only from 4 or 7 months – they found that interventions that allow breast feeding early on seemed likely to save fewer lives and offered poorer

value for money.   Combining the "short course AZT" and "formula supplied"

approaches, the cost per life year saved is less than $100 for maternal HIV

prevalence rates of 10 percent or more, and cost saving at a prevalence of

around 20 percent.

Cost-effectiveness conclusions

Although the range of uncertainty in published cost effectiveness analyses

is high, the inescapable conclusion is that highly cost-effective strategies to

prevent loss of life to HIV in children exist, even in developing countries. The

estimated cost per pediatric case prevented runs from thousands of dollars to

hundreds, depending on the nature of the intervention and the prevalence rate.

In terms of saving lives, these are impressive figures. In areas where the

prevalence is low, the total cost of a prevention program is little more than the

cost of counseling and testing, which can be only a few dollars per woman. In

areas where the prevalence of HIV in childbearing women is high, the cost per

pediatric HIV case averted is low.

Despite these conclusions, however, only a few developing countries have

decided to implement a national strategy of antenatal HIV screening. Some

countries have pilot programs underway. Other countries have considered such

programs but declined to implement, often citing safety and ethical concerns, as

discussed elsewhere in this chapter. Economic concerns are also frequently

cited, and these deserve closer scrutiny.

For instance, one reason commonly given for not implementing an

antenatal HIV screening program is that the cost of treating individuals with HIV

is much higher than the country's national health budget on a per capita basis. In

sub-Saharan Africa, for instance, the annual budget for health care averages $24 per capita (World Bank, 1993, p. 52). Antenatal screening and treatment with nevirapine costs less than $10 per pregnant woman, most of which is for counseling and HIV testing, and only pregnant women (not the whole population) incur costs. A more relevant comparison, therefore, might be with the cost of antenatal and delivery care, which is typically $90 per woman in developing countries (World Bank, 1993, p.117). Adding HIV screening to existing antenatal care will increase costs by less than 10 percent, and substantially increase the benefit to the offspring.

Cost-effectiveness analysis allows policy makers to compare and make an informed choice among competing health care and other interventions. From the point of view of the health care sector, a program of antenatal HIV screening and prophylaxis of infected mothers saves lives and increased the quality of life more effectively than many options available to developing countries. As the example above suggests, the cost per pediatric HIV case prevented, and in developing countries essentially per life saved, is likely to be less than $1,000. If the prevalence of HIV in a group of childbearing women is high enough—on the order of 15 to 20 percent—an antenatal HIV screening program can even save money for the health care system. Few interventions in the health care sector can make such a claim.

The *World Development Report* (1993) urges that public health and health care be thought of as investments, and be compared to opportunities in the health and other sectors in terms of their contribution to a country's economic development. Given the high opportunity cost to the economy of losing a life at a young age, the cost-effectiveness analyses cited in this chapter indicate that

investment in antenatal HIV screening can be cost saving even at low prevalence rates. As indicated above, the cost effectiveness of antenatal HIV prevention programs can be substantially less than $100 per DALY saved.   This compares favorably with the four most effective public health interventions for children under 5 years of age in developing countries (control of respiratory and perinatal infections, diarrheal diseases, and vaccine-preventable diseases) each of which costs less than $100 per DALY saved (World Bank, 1993, p. 222). Given these favorable results, cost-effectiveness analyses that include economic productivity can be useful in identifying international funding for antenatal HIV screening. This would have the effect of increasing the funding available for health in a country, and antenatal screening would not have to compete against other prevention and treatment programs.

A number of caveats, however, must be born in mind when interpreting such economic analyses. First, because many assumptions must be made without hard data, there is a large amount of uncertainty in the results. These educated guesses, however, do establish the order of magnitude of the results, which sometimes is enough for policy comparisons. Second, new developments with respect to the cost and efficacy of the medication, as well as efficiencies in counseling and testing and other aspects of screening and treatment, are likely to make the economic comparisons more favorable, so the estimates in this paper should be seen as conservative.

Social, cultural, and ethical concerns

A program of antenatal HIV screening and prophylaxis of infected mothers to prevent transmission, is clearly an effective strategy to improve perinatal

outcomes. And as the cost-effectiveness analyses summarized above show,

such a program is an efficient way to save lives and in many circumstances can

be cost-saving. In light of these results, one might argue that not to implement

antenatal HIV screening is unethical. Most developing countries, however, have

not adopted such programs, in large part because of social, cultural, and ethical

concerns. These concerns can be addressed, but first they must be understood.

One set of concerns is centered on the stigma and discrimination

associated with HIV infection. In many countries, women who are known to have

AIDS or HIV infection are severely stigmatized and subject to beating and being

disowned by their family (Berer, 1999; Mukwaya, 1999). Where this happens, it

is understandable that women are concerned about HIV testing during

pregnancy, a time of great vulnerability. Concerns about stigma and

discrimination also interfere with women accepting antiviral treatment for

themselves and bottle-feeding their infants. In the long run, the stigma

associated with HIV status must be removed through extensive social programs.

In the short run, women must be counseled frankly about the costs and benefits

of HIV testing and treatment if necessary for themselves and their children and

be allowed to make their own decisions.

Another issue that arises in the context of developing countries is whether

it is appropriate to treat women to prevent transmission of HIV at birth if (a) there

is a high risk of transmission later through breast feeding and (b) parents are

likely to die of HIV disease before the infant reaches adulthood. Many observers

would answer that a life is worth saving whatever the risks that the child faces

later in life, and the antenatal HIV screening with prophylaxis offers many

children a chance to live into adulthood. Moreover, both of the risks facing

children saved from HIV infection can themselves be mitigated. The risk of

transmission through breastfeeding, for instance, can be eliminated or reduced

through the provision of alternatives such as formula. Since the mothers at risk

for transmission will have been identified during antenatal screening, only a

fraction would have to bear the costs of providing formula and clean water.

Furthermore, because extended families are already involved in child rearing in

many developing countries, many AIDS orphans who are saved from HIV

infection through antenatal screening programs, while a burden on society as

children, might have the opportunity to be raised by family members, and

eventually make contributions to society and the economy.

One might also ask whether it is ethically appropriate to treat the mother

with a short course or a single dose of antiretrovirals that benefits the child but

not the mother herself. Given the inability of many developing countries to pay

for therapy for infected individuals, the tangible benefits to the child, and the

satisfaction that many women get from doing something for their children

independent of benefit for themselves, many observers would say that an

antenatal HIV screening program is ethical in developing countries. If resources

are sufficient to provide treatment for some but not all infected persons, one

might argue that pregnant women deserve priority in order to address this ethical

dilemma. Prophylaxis of pregnant women also can be distinguished from other

treatment programs in another respect: its aim is to prevent new cases, and is far

more effective in doing so than other treatment modalities.

In the United States, where HIV prevalence rates in childbearing women

are low and many women are well informed about HIV and AIDS, the Institute of

Medicine has recommended that HIV testing, with patient notification, be a

routine component of prenatal care for all women (IOM, 1999). Such a policy informs women about their right to refuse HIV testing but requires less intensive pretest counseling than is currently the norm in other HIV test settings. In developing countries, where women might be less aware of HIV/AIDS and where prevalence rates may be higher, counseling and informed consent for HIV testing in antenatal care should be more intensive and focused on helping women make informed choices for themselves.

The IOM's summary of the characteristics of a well-organized perinatal public health screening program (IOM, 1999), which draw upon earlier principles developed by the WHO (Wilson and Junger, 1968), are relevant to countries considering antenatal HIV screening programs. First, the goals of a screening program must be clearly specified and achievable. Second, the natural history of the condition should be adequately understood, treatment for those found positive must be widely accepted, and there should be evidence that early intervention improves health outcomes. Third, the screening test should be able to distinguish individuals likely to have the condition from those not likely to have it. Fourth, there must be adequate resources for diagnosis and resources for treatment for all who have the condition. Fifth, the test and intervention should be acceptable to the affected population. Given the evidence discussed in this chapter, and understanding "treatment" as short-course zidovudine or intrapartum nevirapine intended to prevent transmission to the infant, antenatal HIV screening programs would likely be judged to be ethically appropriate in most developing countries where the prevalence of HIV is childbearing mothers is high.

CONCLUSIONS AND RECOMMENDATIONS

According to the evidence and analyses reviewed in this chapter, the goal of preventing AIDS and an early death in substantial numbers of children born to women in developing countries with HIV infection is well within reach. In order to meet this goal, we make the following recommendations.

While no intervention is 100 percent effective, antenatal screening and prophylaxis programs employing relatively inexpensive antiretroviral treatment for HIV-positive women can save lives at the cost of hundreds of dollars per life saved, a ratio that compares favorably with other health and economic investments. In populations where the prevalence of HIV in childbearing women is high, or if looked at from a social perspective, antenatal screening programs in developing countries can even be cost-saving. In populations with low prevalence rates, the cost of an antenatal screening program is mostly counseling and testing, so the per capita cost can be low. Therefore, **antenatal screening for HIV, including simple antiretroviral prophylaxis of women who test positive, should be the standard of care in areas with moderate, high, or potentially growing HIV prevalence rates in child-bearing women.** Because such programs have been demonstrated to be cost-effective investments in health, an argument can be made for international support to supplement developing countries' limited resources.

One barrier to implementing such programs is the lack of awareness that HIV can be transmitted from HIV-infected mothers to their children, and that there are effective measures to reduce the risk of transmission. Perhaps the most significant cost of an antenatal HIV screening program is the stigma and discrimination born by women who test positive, especially in countries where

women have little power. Fear of the consequences of a positive test, coupled

with the realization that there is little to be done to treat HIV infection in

developing countries, is another strong barrier to women being tested. In order

to address both of these barriers, **antenatal screening programs should**

include an extensive educational and counseling component, focusing on

making women aware of the risks of HIV and the benefits of treatment, and

of the risks that they face if they test positive and the means to avoid

serious consequences. Given the balance of costs, risks, and benefits of

antenatal screening, informed consent must be a crucial part of any antenatal

HIV screening program in developing countries.

   Finally, given the impact of the stigma associated with AIDS on health

seeking behavior and the barriers that this stigma creates for perinatal and other

prevention programs, **it is imperative that countries use every possible**

means to reduce the stigma associated with AIDS. Incorporating HIV

screening as a routine part of antenatal care for all women can help to reduce the

stigma.

   Despite important breakthroughs in the last decade, much still remains

unknown about the more effective means to prevent perinatal HIV infection,

especially in poor settings. **More research is needed to identify:**

- **the most effective antiretroviral drugs, doses, and regimens for**
  reducing transmission;
- **the extent to which these benefits can be preserved while lowering the**
  length, intensity and cost of therapy;
- **effective alternatives to antiretroviral medications for reducing the risk**
  of transmission from mother to child, especially during breast feeding;

- **the most effective and efficient ways to implement antenatal HIV screening programs in developing country settings;**

- **barriers to women accepting HIV testing and treatment if warranted, and means to overcome them;**

- **approaches to antenatal counseling that are most effective in increasing awareness and encouraging women to make informed choices about HIV testing;**

- **how countries can most effectively reduce the stigma associated with AIDS.**

Study name and reference	Population characteristics	Treatment (Pre- and intra-partum to mother, post-partum to child)	HIV status evaluated	Risk of transmission (% of children)		Relative reduction in risk (in %)
				Control	Treatment	
ACTG 076 (Connor et al., 1994)	Non-breastfeeding women in US and France	Pre: 100 mg AZT orally 5x daily starting at 14-34 weeks gestation Intra: 2 mg/kg AZT IV for 1 hour, then 1 mg/kg AZT IV per hour until delivery Post: 2 mg/kg orally 4x daily for 6 weeks	18 mo.	25.5	8.3	67
Bangkok trial (Shaffer, 1999)	Non-breastfeeding women in Thailand	Pre: 300 mg AZT orally 2x daily starting in 36th week of pregnancy Intra: 300 mg AZT every 3 hours	6 mo.	18.9	9.4	50.0
Perinatal HIV Prevention Trial (PHPT) (Lallemant et al., 2000)	Non-breastfeeding women in Thailand	Short Pre: 300 mg AZT orally 2x daily starting at 35 weeks gestation Intra: 300 mg AZT every 3 hours Short Post: 2 mg/kg AZT orally every 6 hours for 3 days	6 mo.	--	10.5	Stopped early
		Long Pre: 300 mg AZT orally 2x daily starting at 28 weeks gestation Intra: 300 mg AZT every 3 hours Short Post: 2 mg/kg AZT orally every 6 hours for 3 days	18 mo.	--	4.7	In utero transmission higher with short maternal treatment
		Short Pre: 300 mg AZT orally 2x daily starting at 35 weeks gestation Intra: 300 mg AZT every 3 hours Long Post: 2 mg/kg AZT orally every 6 hours for 6 weeks		--	8.6	
		Long Pre: 300 mg AZT orally 2x daily starting at 28 weeks gestation Intra: 300 mg AZT every 3 hours Long Post: 2 mg/kg AZT orally every 6 hours for 6 weeks		--	6.5	
RETROCI (Wiktor et al., 1999)	Breastfeeding women in Ivory Coast	Pre: 300 mg AZT orally 2x daily starting at 36 weeks gestation Intra: 300 mg AZT every 3 hours	3 mo.	24.9 26.1	15.7 16.5	37 37
DITRAME ANRS 049 (Dabis, 1999)	Mostly breastfeeding women in Ivory Coast and Burkino Faso	Pre: 300 mg AZT orally 2x daily starting at 36-38 weeks gestation Intra: 600 mg AZT at onset of labor Post (maternal): 300 mg AZT orally 2x daily for 1 week	6 mo. 15 mo.	27.5 30.6	18.0 21.5	35 30
RETROCI & DITRAME pooled analysis (Peiperl, 2000)	As above		6 mo.	26.1	16.9	
			12 mo.	28.5	18.5	
			18 mo.	30.1	21.6	
			24 mo.	30.1	22.1	27

Study name and reference	Population characteristics	Treatment (Pre- and intra-partum to mother, post-partum to child)	HIV status evaluated	Risk of transmission (% of children)		Relative reduction in risk (in %)
				Control	Treatment	
(Mandelbrot et al., 2001)	Non-breastfeeding women in France	ACTG 076 regimen (historical controls)	18 mo.	6.8		
		ACTG 076 regimen plus 150 mg 3TC orally 2x daily starting at 32 weeks gestation and 2 mg/kg orally 2x daily for 6 weeks to child			1.6	78
PETRA (Saba, 1999)	Mostly breastfeeding women in South Africa, Tanzania, and Uganda	Intra: 300 mg AZT every 3 hours and 150 mg 3TC orally every 12 hours	6 wk.	17.2	17.1	0
		Intra: as above Post (maternal): 300 mg AZT and 150 mg 3TC orally 2x daily for 1 week		17.2	10.8	37
		Pre: 300 mg AZT and 150 mg 3TC orally 2x daily starting at 36 weeks gestation Intra: as above Post (maternal): as above		17.2	8.6	50
		Intra: 300 mg AZT every 3 hours and 150 mg 3TC orally every 12 hours	18 mo.	26.6	25.7	3
		Intra: as above Post (maternal): 300 mg AZT and 150 mg 3TC orally 2x daily for 1 week		26.6	24.4	8
		Pre: 300 mg AZT and 150 mg 3TC orally 2x daily starting at 36 weeks gestation Intra: as above Post (maternal): as above		26.6	20.7	22
HIVNET 012 (Guay, 1999)	Breastfeeding women in Uganda	Intra: 600 mg AZT orally at onset of labor and 300 mg AZT every 3 hours Post: 4 mg/kg orally 2x daily for 1 week	14-16 weeks	25.1	--	47
		Intra: 200 mg NVP orally at onset of labor Post: 200 mg/kg NVP orally at 48-72 hours postpartum		--	13.1	
		Intra: 600 mg AZT orally at onset of labor and 300 mg AZT every 3 hours Post: 4 mg/kg orally 2x daily for 1 week	1 yr.	24.1	--	35
		Intra: 200 mg NVP orally at onset of labor Post: 200 mg/kg NVP orally at 48-72 hours postpartum		--	15.7	
SAINT (Moodley, 2000)	Mostly breastfeeding women in South Africa	Intra: 600 mg AZT and 150 mg 3TC orally at onset of labor and 300 mg AZT and 150 mg 3TC orally every 3 hrs. Post: 12 mg AZT and 6 mg 3TC orally 2x daily for 1 week Post (maternal): 300 mg AZT and 150 mg 3TC orally 2x daily for 1 week	8 weeks	10.8	--	Difference not significant
		Intra: 200 mg NVP orally at onset of labor Post: 6 mg NVP orally at 24-48 hours postpartum Post (maternal): 200 mg NVP orally at 24-48 hours postpartum		--	14.0	

Annex: A simple cost-effectiveness model

The calculations and results presented in this paper are based on the following assumptions, which are grounded where possible in the available data. The base HIV prevalence rate in women in antenatal care is 12.5 percent. As a sensitivity analysis we vary this rate from 1 to 30 percent. Two simultaneous EIA tests will be used, with no Western blot for confirmation. This combination has a sensitivity of 99.8 percent and a specificity of 99.9 percent (Mansergh, 1996). Consistent with the literature, the cost of counseling and testing for women in antenatal care is $4 or $8 per woman. With low-intensity counseling ($4), 75 percent of women will accept the HIV test and 85 percent of women will accept treatment if found to be HIV positive. With high-intensity counseling ($8) the proportions accepting testing and treatment increase to 85 and 90 percent respectively.

We investigate two treatment regimens for infected women. Short course zidovudine costs a total of $65, and reduces the risk that the child will be infected by 50 percent. A dose of intrapartum nevirapine costs $4 and reduces the risk that the child will be infected by 45 percent. We also assume that women begin antenatal care early enough for HIV testing to allow short-course zidovudine therapy, and make no allowance for increased costs of labor and delivery to prevent HIV transmission. We assume that HIV testing and perinatal treatment have no effect on transmission through breastfeeding; in other words 12 percent of children who are not infected at birth will become infected through breastfeeding later, regardless of prenatal and intrapartum treatment.

We examine the results from two perspectives. From a health sector perspective, we assume that the value of preventing a case of HIV infection in a

child is the lifetime medical cost of treating that child for HIV/AIDS, $432

(Mansergh, 1998), which will be averted. From a social perspective, the value of

preventing one case also includes the projected economic contribution lost when

a child is born with HIV infection and does not live to adulthood; estimated to be

$3302 (Mansergh, 1998). In terms used in World Bank and other calculations,

averting one case of perinatal AIDS is also equivalent to gaining 18.7 Disability

Adjusted Life Years (DALYs) (Marseille, 1998). These are typical values for sub-

Saharan Africa, intended to illustrate the order of magnitude of the economic

results.

Using these assumptions, Table 2 compares the possible interventions in

terms of program costs and HIV cases averted. In a population of 10,000

childbearing women with a 12.5 percent prevalence of HIV, with no testing and

treatment an estimated 313 children would be born with HIV infection. The effect

of screening programs depends upon the sensitivity and specificity of the testing

program, the proportion of women who accept testing and treatment if indicated,

and the efficacy of the intervention in those treated. Based on the assumptions

stated above, a screening program using short course zidovudine for treatment

would cost $12.13 per woman with less intensive counseling and result in 213

children being born with infection. As a result 100 cases (313 minus 213) would

be averted. With more intensive counseling, a screening program would cost

$16.13 per woman and result in 120 cases averted. Intrapartum NVP would cost

$4.50 per woman with less intensive counseling and $8.50 with more intensive

counseling, and would result in 90 or 108 fewer HIV cases in children

respectively.

Dividing the program cost ($12.13) by the number of cases averted (100), this translates into $1,217 per case averted with less intensive counseling and $1349 per case averted with more intensive counseling for a program of short-course zidovudine. For nevirapine, the cost per HIV case averted is $502 with less intensive counseling and $790 with more intensive counseling. Intrapartum NVP is thus clearly preferred to short-course zidovudine since in either scenario it is more cost effective.

Table 2. Program costs, HIV cases averted, and net health sector and social costs per woman in antenatal care.

	No screening	Short course AZT	Intrapartum NVP
Less intensive counseling and testing ($4 per woman)			
Program costs	$0.00	$12.13	$4.50
HIV+ children*	313	213	223
HIV cases averted*		100	90
Cost per HIV case averted		$1,217	$502
Net health sector costs		$7.82	$0.63
Net social costs		($20.70)	($25.10)
More intensive counseling and testing ($8 per woman)			
Program costs	$0.00	$16.13	$8.50
HIV+ children*	313	193	205
HIV cases averted*		120	108
Cost per HIV case averted		$1,349	$790
Net health sector costs		$10.96	$3.85
Net social costs		($23.34)	($27.02)
*per 10,000 women			
( ) indicates negative net costs			

Table 2 also shows the net costs to the health sector, and to society as a whole, of each intervention. Short-course zidovudine costs the health sector $7.82 per woman in antenatal care with less intensive counseling and $10.96 with more intensive counseling. Taking into account the lost lifetime economic productivity of HIV-infected children (the societal perspective), short-course zidovudine saves $20.70 per woman in antenatal care with less intensive

counseling and $23.34 with more intensive counseling. Nevirapine's net health

sector costs are $0.63 (less intensive counseling) to $3.85 (more intensive

counseling), and net social savings are $25.10 (less intensive counseling) to

$27.02 (more intensive counseling). Because of its lower cost per woman and

almost equal efficacy in reducing the transmission of HIV, intrapartum nevirapine

is economically more favorable. Recent offers to supply the drug without cost

obviously improves the economic outlook of this approach.

Table 3 illustrates the sensitivity of the cost effectiveness analysis to the

assumed prevalence of HIV in childbearing women, focusing on nevirapine

therapy. In general, higher HIV prevalence rates translate into lower costs per

HIV case averted, because program costs depend mostly on the number of

women screened, not on those who are HIV positive. Similarly, higher

prevalence rates translate into net savings, since there are more cases to be

averted. Under each scenario, antenatal HIV screening becomes cost saving to

the health sector somewhere between 12.5 and 30 percent prevalence, and cost

saving to society between 1 and 5 percent prevalence.

Table 3. Costs per HIV case averted, and net health sector and social costs per
woman in antenatal care, assuming treatment with a single dose of nevirapine
and a prevalence of HIV in childbearing women of 1, 5, 12.5, 20 or 30 percent.

	Prevalence of HIV in childbearing women				
	1%	5%	12.5%	20%	30%
Less intensive counseling and testing ($4 per woman)					
Cost per HIV case averted	$5633	$1171	$502	$335	$242
Cost DALY averted	$301	$63	$27	$18	$13
Net health sector costs	$3.73	$2.65	$0.63	($1.40)	($4.09)
Net social costs	$1.67	($7.64)	($25.10)	($42.56)	($65.84)
More intensive counseling and testing ($8 per woman)					
Cost per HIV case averted	$9342	$1906	$790	$511	$356
Cost DALY averted	$500	$102	$42	$27	$19
Net health sector costs	$7.67	$6.34	$3.85	$1.36	($1.95)
Net social costs	$5.20	($6.01)	($27.02)	($48.04)	($76.05)

This simple illustrative analysis can be summarized as follows. The cost effectiveness of an antenatal HIV screening and nevirapine treatment program is highly dependent on the prevalence of HIV in childbearing women. If the prevalence exceeds 20 percent, the cost per pediatric HIV case averted goes below $500. With less intensive counseling, this threshold is reached at a prevalence rate of 12.5 percent. If the prevalence exceeds 25 percent (20 percent with more intensive counseling), the program becomes cost saving from the perspective of the health sector; that is, the cost of the screening program is more than offset by the lower cost of treating children born with HIV infection. From a social perspective, treating a child born with HIV infection is the equivalent of a $3302 loss to society, the screening program becomes cost saving at a prevalence rate of well below 5 percent.

References

Berer, M, 1999. Reducing perinatal HIV transmission in developing countries through antenatal and delivery care, and breastfeeding: supporting infant survival by supporting women's survival, *Bulletin of the World Health Organization* 77(11): 871-877.

Biggar R, Miotti P, Taha T, *et al.*, 1996. Perinatal intervention trial in Africa: effect of a birth canal cleansing intervention to prevent HIV transmission, *Lancet* 347: 1647-1650.

Blanche S, Tardieu M, Rustin P, 1999. Persistent mitochondrial dysfunction and perinatal exposure to antiretroviral nucleoside analogues, *Lancet* 354: 1084-1089.

Brocklehurst P, 2000. Interventions aimed at decreasing the risk of mother-to-child transmission of HIV infection (Cochrane Review). In: The *Cochrane Library*, Issue 2. Oxford: Update Software.

Burns DN, FitzGerald G, *et al.*, 1999. Vitamin A deficiency and other nutritional indices during pregnancy in human immunodeficiency virus infection: prevalence, clinical correlates, and outcome. *CID* 29:328-334.

Centers for Disease Control and Prevention (CDC), 2000. *HIV/AIDS Surveillance Report*, 11(2).

CDC, 2001. Serious adverse events attributed to nevirapine regimens for postexposure prophylaxis after HIV exposures – Worldwide, 1997-2000. *MMWR*, 49(51); 1153-6.

Connor E, Sperling R, Gelber R, *et al.*, 1994. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment, *New England Journal of Medicine* 331(18): 1173-1180.

Coutsoudis A, Pillay K, Spooner E, *et al.*, 2001. Method of feeding and transmission of HIV-1 from mothers to children by 15 months of age: prospective cohort study from Durban, South Africa. *AIDS* 15(3):379-387.

Crossette, B, 2001. Experts say that cheaper drug treatments alone are not enough. *New York Times*, April 30, 2001.

Culnane M, Fowler MG, Lee S, *et al.*, 1999. Lack of long-term effects of in utero exposure to zidovudine among uninfected children born to HIV-infected women,' *Journal of the American Medical Association* 281(2): 151-157.

Dabis F, Msellati P, Meda N *et al.*, 1999. 6-month efficacy, tolerance, and acceptability of a short regimen of oral zidovudine to reduce vertical transmission of HIV in breastfed children in Cote d'Ivoire and Burkina Faso: a double-blind placebo-controlled multi-center trial, *Lancet* 353: 786-792.

DeCock K, Fowler MG, Mercier MD, *et al.*, 2000. Prevention of mother-to-child HIV transmission in resource-poor countries, *Journal of the American Medical Association* 283(9): 1175- 1182.

Dunn DT, Newell ML, Ades AE, *et al.*, 1992. Risk of human immunodeficiency virus type 1 transmission through breastfeeding, *Lancet* 340: 585-588.

Garcia P, Kalish L, Minkoff H, *et al.*, 1999. Maternal levels of plasma human immunodeficiency virus type I RNA and the risk of perinatal transmission. *N Engl J Med* 341(6):394-402.

Gellman B, 2000. A turning point that left millions behind, *The Washington Post*, December 28.

Giaquinto *et al.*, 1992. Risk factors for mother-to-child transmission of HIV- 1, *Lancet* 339: 1007-1012.

Guay L, Musoke P, Fleming T, *et al.*, 1999. Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: HIVNET 012 randomized trial, *Lancet* 354: 795-802.

Institute of Medicine (IOM), 1999. *Reducing the Odds: Preventing Perinatal Transmission of HIV in the United States.* Stoto MA, Almario DA, McCormick MC., eds. National Academy Press: Washington, DC.

International Perinatal HIV Group, 1999. The mode of delivery and the risk of vertical transmission of human immunodeficiency virus type 1 – a meta-analysis of 15 prospective cohort studies. *N Engl J Med* 340(13):977-987.

Lallemant M *et al.*, 2000. A trial of shortened zidovudine regimens to prevent mother-to-child transmission of human immunodeficiency virus type I. *N Engl J Med* 343:982-991.

Mandelbrot L, Landreau-Mascaro A, Rekacewicz C, *et al.,* 2001. Lamivudine-zidovudine combination for prevention of maternal-infant transmission of HIV-1. *JAMA* 285(16):2083-2093.

Mansergh G, Haddix AC, *et al.,* 1996. Cost-effectiveness of short-course zidovudine to prevent perinatal HIV Type I. *JAMA* 276:139-145.

Mansergh G, Haddix AC, *et al.*, 1998. Cost-effectiveness of zidovudine to prevent mother-to-child transmission of HIV in sub-Saharan Africa. *JAMA* 280(1):30-31.

Marseille E, Kahn JG, Saba J, 1998. Cost-effectiveness of antiviral drug therapy to reduce mother-to-child HIV transmission in sub-Saharan Africa. *AIDS* 12: 939-948.

Marseille E, Kahn J, Mmiro F, *et al.*, 1999. Cost-effectiveness of single-dose nevirapine regimen for mothers and babies to decrease vertical HIV-1 transmission in sub-Saharan Africa, *Lancet* 354: 803-809.

Mofenson, L, 1997. Mother-child HIV- 1 transmission: timing and determinants, *Obstetrics and Gynecology Clinics of North America* 24(4): 759-784.

Mofenson LM, Lambert JS, *et al.*, 1999. Risk factors for perinatal transmission of human immunodeficiency virus type 1 in women treated with zidovudine. *N Engl J Med* 341(6):385-393.

Mofenson LM and McIntyre JA, 2000. Advances and research directions in the
     prevention of mother-to-child HIV-1 transmission. *Lancet* 355:2237-2244.

Moodley D, 2000. The SAINT trial; Nevirapine (NVP) versus zidovudine (ZDV) +
     lamivudine (3TC) in prevention of peripartum HIV transmission. Abstract
     LbOrl. XIII International AIDS Conference. Durban, July 9-14, 2000.

Mukwaya J, 1999, The AIDS Emergency. In: *The Progress of Nations*, UNICEF
     1999: 17-19.

Newell, M, 2000. Vertical transmission of HIV-1 infection, *Transactions of the
     Royal Society of Tropical Medicine and Hygiene* 94: 1-2.

Nduati R, John G, *et al.*, 2000. Effect of breastfeeding and formula feeding on
     transmission of HIV-1. *JAMA* 283(9):1167-1174.

Nicoll A, Newell M, Van Praag E, *et al.*, 1995. Infant feeding policy and practice
     in the presence of HIV-1 infection, *AIDS* 9(2): 1995: 107-119.

Peiperl L, 2000. Antiretroviral treatments to reduce mother-to-child transmission
     of HIV, August 25, 2000
     [http://hivinsite.ucsf.edu/topics/pregnancy_and_childbirth/].

Saba, J, 1999. Interim analysis of early efficacy of three short ZDV/3TC
     combination regimens to prevent mother-child transmission of HIV-1: the
     PETRA Trial. Abstract S7. 6th conference on Retroviruses and
     Opportunistic Infections. Chicago, January 31 – February 4, 1999.

Schwärtlander B, Garnett G, Walker N, Anderson R, 2000. AIDS in a new
     millennium. *Science* 289: 64-67.

Semba RD, 1997. Overview of the potential role of vitamin A in mother-to-child
     transmission of HIV, *Acta Paediatr Suppl* 421: 107-112.

Shaffer N, Chuachoowong R, Mock P, *et al.*, 1999. Short-course zidovudine for
     perinatal HIV-1 transmission in Bangkok, Thailand: a randomised
     controlled trial, *Lancet* 353: 773-780.

Shaffer N, Roongpisuthipong A, Siriwasin W, 1999. Maternal virus load and
     perinatal human immunodeficiency virus type 1 subtype E transmission,
     Thailand, *Journal of Infectious Diseases* 179: 590-599.

Söderlund N, Zwi K, Kinghorn A, Gray G, 1999. Prevention of vertical
     transmission HIV: analysis of cost effectiveness options available in South
     Africa. *BMJ* 318:1650-1656.

Starr SE, Fletcher CV, *et al.*, 1999. Combination therapy with efavirenz,
     nelfinavir, and nucleoside reverse-transcriptase inhibitors in children
     infected with human immunodeficiency virus type 1. *N Engl J Med*
     341(25):1874-1881.

Stoto M, Goldman A, 1999. Cost-effectiveness of Prenatal HIV Screening in
     Africa. Poster: Presented at the International Epidemiology Association
     meeting, Florence, Italy, September, 1999 and at the Second Conference
     on Global Strategies for the Prevention of HIV Transmission from Mothers
     to Infants, Montreal, Canada, September 1999.

Taha T, Biggar R, Broadhead R, *et al.*, 1997. Effect of cleansing the birth canal with antiseptic solution on maternal and newborn morbidity and mortality in Malawi: clinical trial, *British Medical Journal* 315: 216-220.

Taha T, Graham SM, Kumwenda NI, 2000. Morbidity among human immunodeficiency Virus-1-infected and –uninfected African children. *Pediatrics* 106 (6).

Tudor-Williams G, 2000. HIV infection in children in developing countries, *Transactions of the Royal Society of Tropical Medicine and Hygiene* 94, 2000: 3-4.

UNAIDS, 1999. *AIDS Epidemic Update: December 1999.*

UNAIDS, 2000a. New UN report estimates over one-third of today's 15-year-olds will die of AIDS in worst affected countries. Press release, Geneva, 27 June 2000.

UNAIDS, 2000b. *AIDS Epidemic Update: December 2000.*

Wiktor S, Ekpini E, Karon J, 1999. Short-course oral zidovudine for prevention of mother-to-child transmission of HI-1 in Abidjan, Cote d'Ivoire: A randomised trial. *Lancet* 353: 781-85.

Wilkinson D, Floyd K, Gilks CF, 1998. Antiretroviral drugs as a public health intervention for pregnant HIV-infected women in rural South Africa: an issue of cost-effectiveness and capacity. *AIDS* 12(13): 1675-82

Wilson JMG, Jungner F, 1968. Principles and practice of screening for disease. Public Health Paper 34. Geneva: WHO.

World Bank, 1993. World Development Report 1993: Investing in Health. New York, NY: Oxford University Press.

World Health Organization (WHO), 1998. *HIV and Infant Feeding, Guidelines for Decision Makers,* WHO/FRH/NUT/CHD/98.1, Geneva.

WHO, 1998. Recommendations on the safe and effective use of short-course ZDV for prevention of mother-to-child transmission of HIV. *Weekly Epidemiological Record*, 9 October 1998.

WHO, 2000. *New Data on the Prevention of Mother-to-Child Transmission of HIV and their Policy Implications: Conclusions and Recommendations.* Geneva, 11-13 October 2000 [http://www.unaids.org/publications/documents/].