

# Reducing the risk of mother-to-child human immunodeficiency virus transmission: past successes, current progress and challenges, and future directions

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In the global human immunodeficiency virus (HIV) pandemic, prevention of mother-to-child transmission (PMTCT) in the United States and Europe has been one of the major success stories. Prior to effective perinatal HIV interventions, about 1 in 4 babies born to HIV-infected women became infected; whereas today an HIV-infected pregnant woman in the United States or Europe receiving highly active antiretroviral therapy (HAART) and with an undetectable viral load has only about 1-2% chance of transmitting HIV to her infant.<sup>1</sup> In international resource-limited settings, simplified, shorter-course antiretroviral regimens have also been shown in perinatal HIV clinical trials to reduce transmission among breast-feed-

Prevention of mother-to-child transmission (PMTCT) of human immunodeficiency virus (HIV) in the United States and Europe has been a tremendous success, such that transmission rates of less than 2% have been achieved. Some key successes have also been demonstrated in resource-poor countries; however, the translation of successful interventions into public health policy has been slow because of a variety of factors such as inadequate funding and cultural, social, and institutional barriers. The issue of HIV and infant feeding in settings that lack culturally acceptable, feasible, affordable, safe, and sustainable nutritional substitutes for breast milk is a continuing dilemma. An effective preventive infant HIV vaccine would be an optimal approach to reduce HIV acquisition in the first year of life among breast-feeding infants. The challenges to eliminate new perinatal HIV infections worldwide will depend on both sustaining and expanding PMTCT interventions and effective primary HIV prevention for women, adolescents, and young adults.

**Key words:** acquired immunodeficiency syndrome, human immunodeficiency virus, mother-to-child transmission, pregnancy

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ing HIV-infected women, although with less efficacy than HAART. However, translation of the findings from most of these research studies into successful national PMTCT programs and ministry of health policies has not been optimal.

## U.S. EXPERIENCE

In 1992, at the peak of the U.S. perinatal epidemic, close to 2000 babies in the United States became HIV infected, whereas currently fewer than 200 infants become HIV infected annually (see related article in this issue by McKenna et al). The dramatic success in reducing perinatal HIV transmission across the United States was due in large part to the rapid translation of research trial findings into practice. This was achieved through the combined leadership of the U.S. Public Health Service, effective partnerships of city and state health departments with university perinatal researchers and health care providers at tertiary care centers, and the strong support of national organization partners.

In 1985, 2 years after the first case of pediatric acquired immunodeficiency syn-

drome (AIDS) was described in the United States, the Centers for Disease Control and Prevention (CDC) recommended that HIV-infected women in the United States should not breast-feed, which was one of the first preventive steps that substantially reduced the risk of perinatal transmission in the United States.<sup>2</sup> Currently the vast majority of HIV-infected women in the United States avoid breast-feeding by the use of formula.

In the United States, a major breakthrough in PMTCT occurred in 1994 with the announcement of the Pediatric AIDS Clinical Trial Group Protocol 076 results.<sup>3</sup> This double-blinded, randomized, placebo-controlled trial, which included an intensive regimen of oral zidovudine (ZDV) given prenatally, intrapartum, and postpartum, decreased perinatal transmission risk by two thirds when compared with placebo. Based on these findings, the US Public Health Task Force quickly recommended that all pregnant women should be offered HIV testing and that those women who were identified as HIV infected should be given ZDV according to the PACTG

076 regimen.<sup>4</sup> Widespread implementation of these recommendations<sup>5</sup> led to sharp decreases in perinatal HIV transmission. Furthermore, since the late 1990s, most HIV-infected women in the United States have been prescribed combination regimens, which further reduced the risk.<sup>6</sup>

Elective caesarean delivery was shown to be associated with a 50% reduction in transmission in both a randomized European trial<sup>7</sup> and a large metaanalysis<sup>8</sup>; and in 2000 the American College of Obstetricians and Gynecologists (ACOG)<sup>9</sup> recommended that all women with HIV viral loads greater than 1000 copies per milliliter be counseled with regard to the benefit of caesarean delivery (see related article is this issue by Jamieson et al). However, these interventions have failed to reach certain high-risk groups. For example, to implement these interventions, both an HIV-infected pregnant woman and her health care provider must know her HIV status.

The Mother-Infant Rapid Intervention at Delivery (MIRIAD) study attempted to reach these women with unknown HIV status by demonstrating that rapid HIV testing in labor and delivery units was feasible, acceptable, and accurate. The MIRIAD study, which was conducted in 17 hospitals in 5 urban areas, reported findings demonstrating that offering rapid HIV testing in labor and delivery settings to women whose HIV status was still unknown was feasible and deliverable. It was also demonstrated that based on these rapid test results, peripartum antiretroviral interventions to reduce the risk of transmission could then be successfully provided<sup>10</sup> (see related article is this issue by Jamieson et al). Furthermore, a critical policy event occurred in 2003 when the CDC issued a Dear Colleague letter supporting the use of the strategy of routinely screening pregnant women for HIV unless the woman declined testing, the opt-out strategy.<sup>11</sup> The use of the opt-out strategy has now been expanded by the CDC in 2006 to include routine HIV testing in health care facilities among all adults and adolescents as well as pregnant women in all antenatal settings and those women at labor/delivery whose HIV status is still unknown.<sup>12</sup>

The dramatic success in reducing perinatal HIV transmission to less than 2% across the United States<sup>1,6</sup> was due in large part to the rapid translation of research trial findings into practice. This was achieved through the combined leadership of the US Public Health Service, effective partnerships of city and state health departments with university perinatal researchers and health care providers at tertiary care centers, and the strong partnership support of national organizations.

A number of national health organizations have been particularly instrumental in supporting perinatal HIV prevention efforts. Following the release of the preliminary results from Pediatric AIDS Clinical Trials Group Protocol 076<sup>3</sup> and to help spur universal HIV screening among pregnant women, ACOG, which represents more than 90% of all board-certified US obstetricians, issued guidelines supporting routine counseling and voluntary HIV testing for all pregnant women.<sup>13</sup> With the release of an Institute of Medicine report<sup>14</sup> in 1999 that supported opt-out screening, ACOG and the American Academy of Pediatrics issued a revised Joint Statement on HIV Screening<sup>15</sup> that endorsed routine perinatal HIV testing with patient notification.

In addition, after the results of the MIRIAD study were announced, ACOG also issued guidelines<sup>16</sup> to its fellows supporting routine rapid testing at labor and delivery for women whose status was still unknown. The CDC also developed and distributed a model protocol on rapid HIV testing at labor/delivery<sup>17</sup> to provide hospitals and clinicians with implementation guidance for rapid HIV testing at labor/delivery and carried out a series of regional workshops for key hospitals to provide hands-on assistance to their staff in developing their hospital site-specific implementation plans.

Since 1999 Congress has provided substantial funding to support perinatal HIV prevention programs in high-prevalence states. These targeted federal funds have helped jump-start and sustain states' perinatal HIV prevention efforts and include funding support for social marketing; development of information and educational materials, ex-

panding voluntary HIV screening to all pregnant women seen in antenatal settings; and rapid testing during labor/delivery for pregnant women whose status was still not known (see related article in this issue by Sansom et al).

The chronology of events leading to increased uptake of HIV testing among pregnant women and interventions for HIV-infected pregnant women are shown in Table 1.

### REMAINING GAPS AND CHALLENGES IN PERINATAL HIV PREVENTION EFFORTS IN THE US

Despite the dramatic reductions in perinatal HIV and pediatric AIDS seen over the past decade, babies in the United States are still becoming HIV infected. Some of the ongoing issues and program gaps include practitioners who continue to offer HIV testing only to those women they consider at high risk despite CDC recommendations for routine HIV screening for all pregnant women unless they decline; lack of retesting to identify the subset of women who test negative early in pregnancy but then seroconvert in later pregnancy; limited resources focused on developing interventions that reduce the risk of primary HIV infection among adolescent females and adult women; and limited overall funding for perinatal HIV prevention programs at the state and community level.

### INTERNATIONAL EXPERIENCE IN PMTCT

Internationally, following the results of PACTG 076, a number of randomized trials were undertaken to see whether simpler short-course regimens deliverable in resource-limited settings could also significantly reduce the risk of perinatal HIV transmission. The first of these studies' results were announced in 1998 and included 2 CDC short-course ZDV trials in Thailand and West Africa in which pregnant women were given either oral ZDV or placebo from 36 weeks through labor/delivery. In the Thailand CDC trial<sup>18</sup> in which HIV-infected women did not breast-feed and infants were formula fed, the findings reported

**TABLE 1**  
**Chronology of events: perinatal HIV prevention in United States**

Date	Event
1983	First case of pediatric AIDS in United States described
1985	CDC issues first guidelines for prevention of perinatal HIV transmission including the recommendation that HIV infected women in United States should not breast-feed
1992	Number of reported pediatric AIDS cases peaks in the United States
1994	<ul style="list-style-type: none"> <li>• PACTG 076 trial findings reported, which indicate a two thirds reduction with an intensive regimen of ZDV given to the mother from the second trimester, intravenously at labor and for 6 weeks to the newborn.</li> <li>• Food and Drug Administration licenses ZDV for perinatal HIV prevention indication</li> <li>• US Public Health Service recommends implementation of ZDV regimen for all HIV-infected pregnant women</li> </ul>
1995	CDC recommends voluntary counseling and testing for all pregnant women and offering the ZDV regimen to all HIV-infected women
1998	Institute of Medicine report released, which recommends universal HIV screening with right of refusal for all pregnant women
1999	Congress provides targeted funding for perinatal HIV prevention efforts in high prevalence states
2001	Revised CDC Counseling and Testing Guidelines for Pregnant women supports reducing barriers to offering of prenatal HIV testing to ensure routine universal testing and offering rapid HIV testing at labor/delivery for women whose HIV status is still unknown
2002-2003	CDC reports high uptake of screening of pregnant women using opt-out strategy. Dear Colleague Letter issued recommending opt-out strategy to optimally support routine universal testing of pregnant women.
2006	CDC Revised Recommendations for HIV Testing in Health Care Settings released recommending an opt-out strategy with routine HIV screening of all pregnant women as part of the routine panel of prenatal tests, a second test in the third trimester for women in areas or facilities with elevated incidence of HIV or who are known to be at high risk for HIV, and rapid HIV testing for women whose HIV status is not known at labor/delivery. Additionally, opt-out testing recommended for: all patients aged 13-64 y (annually for those likely to be at high risk for HIV); women as a component of preconception care and all patients with tuberculosis or seeking treatment for a sexually transmitted disease.

in 1998 were that this short-course ZDV regimen reduced transmission by 50%, whereas in the West African setting of Côte d'Ivoire and where HIV-infected women breast-fed, 3-month transmission was reduced by 37%.<sup>19,20</sup>

Results from other short-course trials quickly followed. The PETRA study<sup>21</sup> was a 4-armed study that compared use of 2 drugs, ZDV and 3TC, with placebo. The findings were that the longest arm of the PETRA trial, in which HIV-infected pregnant women received ZDV/3TC from 36 weeks through delivery and 1 week postpartum and their newborns also received 1 week of ZDV/3TC, was highly efficacious at 6 weeks when compared with placebo with a 67% reduction in HIV transmission.

In Uganda, a simpler regimen tested in the HIVNET 012 trial<sup>22,23</sup> used a single dose of nevirapine (SD NVP) given to the mothers at labor onset and to their newborns. This regimen was found to be highly efficacious and deliverable. It re-

duced transmission by 42% when compared with an ultrashort course of ZDV given at labor onset and for 1 week postpartum to mothers and their newborns. Building on the 2 successful regimens, a study in Thailand<sup>24</sup> combined the short-course ZDV regimen from 28 weeks' gestation with SD NVP plus 1 week of ZDV to the infant and reduced transmission to 2%. This combined, 2-drug strategy in Thailand among non-breast-feeding women was found to be as effective in reducing transmission as the HAART interventions being used in the United States and Europe. When used in breast-feeding settings in West Africa, the regimens of ZDV or ZDV/3TC in the last trimester plus SD NVP at labor and to the newborn demonstrated a transmission rate of about 6-9%<sup>25</sup> (see also related article in this issue by Kourtis et al).

Based on the results of these trials, international agencies and donor groups including the World Health Organization (WHO), the Joint United Nations Programme on HIV/AIDS (UNAIDS),

the United Nations Children's Fund (UNICEF), The Bill and Melinda Gates Foundation, the Elizabeth Glaser Pediatric AIDS Foundation, and US and European governments provided funding for implementing and scaling up these short-course interventions in resource-limited settings (see related articles in this issue by Bolu et al and Sripipatana et al). A chronology of major international milestones relevant to PMTCT is summarized in Table 2.

### INTERNATIONAL TRIALS AIMED AT REDUCING TRANSMISSION AMONG HIV-INFECTED WOMEN WHO BREAST-FEED

Current international trials are directed at maximally reducing the risk of transmission among breast-feeding HIV-infected women in resource-limited settings in which breast-feeding is the norm and in which not breast-feeding is associated with high infant mortality. A number of different trials are currently

**TABLE 2**  
**Chronology of events: PMTCT in international settings**

Date	Event
1998	Efficacious short-course ZDV results reported from Thailand and west Africa
1999	Results of 2 successful trials: PETRA using SC ZDV/lamivudine; and HIVNET 012 using SD NVP given to the mother at labor onset and to the newborn are announced
1999-2000	UNAIDS/UNICEF launches pilot projects using SC ZDV and offering of formula in a number of east and west African countries
2000-2001	US presidential monies made available to support PMTCT. Activities in 15 resource limited international countries. Gates Foundation provides CTA funding to Elizabeth Glaser Pediatric AIDS Foundation to launch use of SD NVP regimen. Boehringer Ingelheim and Abbot provide SD NVP and determine rapid HIV test kits to support scaling up of PMTCT through the AXIOS donation program.
2000	WHO UNAIDS recommends use of any of 3 options for PMTCT: SC regimens (ZDV, ZDV/3TC) from 36 weeks and SD NVP and exclusive breast-feeding with early weaning for HIV-infected women in situations in which use of breast milk substitutes is not safe, sustainable, or affordable
2003 to present	US Presidential Emergency Funding for AIDS Relief provides substantial funding for treatment and prevention activities to 15 countries, rolling in PMTCT activities
2004	Renewal and expansion of CTA funding for PMTCT under PEPFAR initiative
2004	Combined SC ZDV and SD NVP results published from Thailand demonstrating further reduction in transmission to 2% with this combined regimen among formula-fed infants. In West Africa, 6 week transmission rates of 4-6% were reported in programs using a similar regimen (SC ZDV/3TC + SD NVP or SC ZDV + SD NVP) from 32 weeks in a population in which some women breast-feed. WHO recommends SC ZDV plus SD NVP as the first-line regimen for PMTCT among women who do not require HAART for their own care; and HAART for HIV-infected pregnant women who meet WHO treatment criteria
2005	MASHI trial from Botswana finds reduced HIV transmission but overall similar infant HIV-free survival similar because of more deaths from other causes in trial comparing mother infant pairs randomized with either formula from birth and 1 month of infant ZDV prophylaxis versus exclusive breast-feeding for 6 months and 6 months of infant ZDV
2006	WHO convenes expert consultations on infant feeding to consider consequences of early weaning and consultation on early infant diagnosis to aid early initiation of antiretroviral treatment for infants and children. Also releases updated recommendations for use of antiretrovirals among pregnant women.

CTA, Call to Action; PEPFAR, Presidential Emergency Funding for AIDS Relief; SC, short course.

underway or about to begin in east, west, and southern Africa. Strategies being assessed include the following: (1) use of 2 antiretrovirals such as short-course zidovudine/lamivudine or ZDV plus SD NVP at labor/delivery; (2) maternal HAART during the last trimester of pregnancy, at labor, and for up to 6 months following delivery with a goal of minimizing maternal viral load in plasma and breast milk; (3) interventions directed at protecting the infant during 3-6 months of exclusive breast-feeding followed by early weaning; and (4) active or passive immune strategies that boost infant immune responses during the period of breast milk exposure. Results from these trials will be available over the next several years and should provide guidance on the most effective

strategies to reducing the risk of transmission during breast-feeding.

### CURRENT CHALLENGES AND PROGRAM GAPS INTERNATIONALLY

Despite the impressive efficacy of the short-course PMTCT regimens in research clinical trial settings, the translation into public health policy in resource-limited international settings has been disappointingly slow, compared with the rapid widespread implementation seen from the mid-1990s in resource-rich settings. This is due to a variety of factors including weak and crumbling health care infrastructure in some settings, lack of integration of PMTCT programs into maternal child health services, limited donor funding

support, PMTCT drug and HIV test kit stockouts, the fact that many women in resource limited settings deliver at home or outside medical facilities in which PMTCT services are available, and competing public health priorities in the context of limited overall health care funding available in resource-constrained countries in Africa and Asia.

Other challenges include lack of male involvement in HIV testing including couple testing (see related article is this issue by Abrams et al); issues of disclosure by women of their HIV status that may prevent HIV-infected women from receiving appropriate antiretroviral interventions for both PMTCT and their own treatment; and competition for limited resources setting up artificial and unnecessary

tensions between HIV prevention and care/treatment programs.

Lack of family-planning services has been another major programmatic gap area. In settings with high HIV prevalence rates among women of reproductive age, combined with high rates of unintended pregnancy, there is an urgent need for programs that integrate family planning and PMTCT programs. Unfortunately, PMTCT programs often lack the funding, organizational structure, and technical expertise to provide comprehensive contraceptive services for HIV-infected women.<sup>26</sup> High rates of unintended pregnancy among participants in antiretroviral treatment programs have recently been reported<sup>27,28</sup> and highlight this gap in services. Efforts must be made to make contraceptive services easily accessible to HIV-infected women in care and/or on antiretroviral therapy by closely linking contraceptive counseling and services to PMTCT programs.

Likewise, although simple, inexpensive drug regimens for PMTCT are available, there are still barriers to widely implementing and national scaling up of these regimens because of inadequate funding, sociocultural, and institutional barriers. Currently it is estimated that less than 10% of HIV-infected women in sub-Saharan Africa receive any antiretrovirals during pregnancy or delivery.<sup>29</sup> In addition, as concerns are raised about reduced efficacy of simplified regimens such as single-dose nevirapine, compared with more intense regimens as well as the possible effect of transient nevirapine resistance on later treatment outcomes, the medical community has increasingly recommended more complex regimens for perinatal prophylaxis (see related article in this issue by McConnell et al). Particularly, efficacious and sustainable interventions for prevention of HIV infection during the postnatal breast-feeding period are urgently needed.

And finally, the optimal strategy for infant feeding of HIV-infected mothers in resource-limited settings has yet to be delineated. Balancing the benefits of breast-feeding in settings with unsafe water, poor hygiene, and lack of afford-

able nutritional substitutes for breast milk against the risk of postnatal HIV transmission to the infant is complex. The issue of HIV and the best infant feeding choice has also been a continuing dilemma for international agencies, ministries of health and HIV-infected mothers in resource-limited settings in which use of breast milk substitutes is not culturally acceptable, feasible, affordable, safe, or sustainable. Recent data presented at a 2006 WHO consultation on HIV and Infant Feeding<sup>30</sup> and the 14th Conference on Retroviruses and Opportunistic Infections<sup>31-33</sup> underscore the risk of increased infant gastroenteritis morbidity and overall infant mortality associated with early breast-feeding cessation and the introduction of contaminated complementary foods.

#### FUTURE DIRECTIONS FOR PMTCT IN THE US AND INTERNATIONALLY

In the United States, the translation of PMTCT research into practice has been 1 of the major successes in public health efforts to prevent HIV infection. However, lessons from experiences with other diseases such as tuberculosis demonstrate that when successful public health efforts are taken for granted, the gains may be temporary. To sustain achievements, not only do the efforts that led to the declines in perinatal HIV transmission need to continue, but ongoing surveillance of the scope and breadth of perinatal transmission in the United States needs to be strengthened. Recent CDC recommendations that HIV screening should be a routine part of health care<sup>12</sup> and a key component of preconception care<sup>34</sup> should be supported and implemented, increasing the likelihood of HIV-infected women learning their status prior to pregnancy so that they can make informed choices about pregnancy and take full advantage of life-saving interventions.

Even in the event of screening prior to pregnancy, all women should be offered testing early in prenatal care for every pregnancy. To support this goal, CDC is launching the One Test, Two Lives campaign in the United States to encourage

obstetrical providers in all settings to offer early HIV testing as a routine, opt-out practice for their pregnant patients and to counsel them to accept an HIV test in the event of an initial decline. The campaign offers a full suite of information and materials, both for providers and their patients. (For more information about One Test, Two Lives or free materials for your practice, visit the campaign website at [www.cdc.gov/1test2lives](http://www.cdc.gov/1test2lives) or contact the National Prevention Information Network at [www.cdcnpin.org](http://www.cdcnpin.org) or 800-458-5231.)

Clinical management of HIV-infected pregnant women is increasingly complex (see related article in this issue by Jamieson et al), and obstetric clinicians need education and support to provide medical care, particularly to women who have a positive rapid HIV test during labor and delivery. The Health Resources and Services Administration and the CDC jointly support the National Clinical Consultation and Referral Service's Perinatal Hotline (see related article in this issue by Fogler et al). Ongoing and expanded education and resources for obstetric clinicians are needed especially as rapid HIV testing for women in labor with unknown HIV status becomes the standard of care.

Whereas there are highly effective antiretroviral interventions for PMTCT, similar interventions are not yet available to prevent primary HIV infection in women. Studies of vaccines, antiretroviral prophylaxis, and microbicides have yet to demonstrate efficacy in preventing HIV in women, although some promising possibilities are actively being explored. Until HIV is controlled in women, the promise of eliminating perinatal HIV transmission is unlikely to be realized.

In international settings, effective strategies to make breast-feeding safer for HIV-exposed infants through the first year of life are urgently needed. Trials currently underway include maternal HAART during breast-feeding and extended infant antiretroviral prophylaxis, and immune-based strategies. A preventive infant HIV vaccine, if proven efficacious, would be an optimal approach to both reducing the risk of breast-feeding

transmission of the HIV virus during the first year of life while providing the infant with adequate nutrition and the continued protection of breast milk against other infectious causes of morbidity and mortality. This strategy has the benefit of reducing the risk HIV acquisition while maintaining breast milk as a source of life-saving nutrition.

In conclusion, as documented throughout this supplement, much progress has been made in PMTCT of HIV both in the United States and internationally. However, the challenges of complete elimination of new perinatal HIV infections will depend on not only PMTCT interventions worldwide but also effective primary HIV prevention interventions among adolescents and young adults. ■

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