Perinatal HIV and Its Prevention: Progress Toward an HIV-free Generation

Mary Glenn Fowler, MD, MPH[a,b,*], Alicia R. Gable, MPH[a], Margaret A. Lampe, RN, MPH[c], Monica Etima, MBChB, MMed[b], Maxensia Owor, MBChB, MMed[b]

KEYWORDS

- Mother-to-child transmission of HIV-1
- Epidemiology of perinatal HIV infections • Early infant diagnosis
- United States • Resource-limited settings

Since the first cases of infant HIV infection were described in the early 1980s, significant progress has been made in our understanding of risk factors for mother-to-child transmission (MTCT) of HIV as well as effective interventions to prevent transmission. MTCT of the human immunodeficiency virus type-1 (HIV-1) can occur during pregnancy particularly in the third trimester, during the intrapartum period, and for infants exposed to HIV, who are breastfed, throughout the period of lactation.[1] Before the availability of antiretroviral and obstetric interventions, about 1 in 4 infants born to women infected with HIV became infected. Among these infected infants, 50% to 60% of transmission occurred around the time of labor or delivery based on newborn infants exposed to HIV having negative cord blood or newborn polymerase chain reaction (PCR) tests that subsequently became positive within the first weeks of life.[2] Among HIV-infected breastfeeding populations, about 20% to 25% of infections occurred in utero based on positive PCRs at birth; 35% to 50% intrapartum; and another 25% to 35% of infants negative at birth and in the first 6 weeks became infected later, presumably as a result of transmission through breast milk.[1]

The authors have no conflicts of interest.

[a] Department of Pathology, The Johns Hopkins University School of Medicine, 600 North Wolfe Street, Baltimore, MD 21224, USA
[b] Makerere University-Johns Hopkins University Research Collaboration, Upper Mulago Hill Road, Kampala, Uganda
[c] Division of HIV/AIDS Prevention, Epidemiology Branch, National Center for HIV/AIDS, Viral Hepatitis, STD and TB Prevention, Centers for Disease Control and Prevention, 1600 Clifton Road, MS E-45, Atlanta, GA 30333, USA
* Corresponding author. Makerere University-Johns Hopkins University Research Collaboration, Upper Mulago Hill Road, Kampala, Uganda.
E-mail address: mgfowler@mujhu.org

Clin Perinatol 37 (2010) 699–719
doi:10.1016/j.clp.2010.09.002 **perinatology.theclinics.com**
0095-5108/10/$ – see front matter

Since the initial US Pediatric AIDS Clinical Trials Group Protocol (PACTG) 076 clinical trial results[3] were announced in 1994, which showed that giving pregnant women infected with HIV oral zidovudine from 14 weeks, intravenously at labor and delivery, and followed by 6 weeks of zidovudine prophylaxis to their newborns, could reduce transmission by two-thirds, significant progress has been made in resource-rich settings such as the United States and Europe, where combination antiretroviral drugs are routinely given during pregnancy and at labor, and where breast milk substitutes can be safely used and provided by government programs. Current transmission rates are estimated at less than 2% with the use of triple antiretroviral drugs during pregnancy.[4,5] International trials aimed at reducing transmission among women infected with HIV in resource-limited settings using simpler deliverable regimens have also been conducted and shown to be efficacious.[6–8] Recent studies[9–11] have focused on ways to make breastfeeding safer given the high risk of mortality from other causes among infants exposed to HIV who are not breastfed.

Despite this progress, researchers still have limited understanding of the exact mechanisms of transmission; including the maternal and infant host factors that either protect or increase the risk of transmission; whether mucosal exposure is the primary route of transmission during labor, or occurs by microtransfusions across the placenta during contractions; whether transmission through breast milk is primarily caused by cell-associated or cell-free virus; and how the virus is transported across the infant gastrointestinal mucosa.

This update focuses primarily on the epidemiology of MTCT of HIV-1 in the United States, briefly summarizes what is known about the timing and mechanisms of MTCT, and describes current efforts in the United States to eliminate new cases of mother-to-child HIV-1 transmission, including innovative national and state strategies. Updates on the epidemiology of the global MTCT epidemic, current prevention of mother-to-child transmission (PMTCT) strategies in international settings, as well as challenges, and future research directions in PMTCT of HIV are provided.

TIMING AND MECHANISMS OF TRANSMISSION

In Utero Infection

The placenta has proved an effective barrier to HIV transmission during pregnancy given that even before effective interventions only about 1 in 4 infants who were exposed to HIV became infected. Based on the timing of positivity, only about 20% to 25% of infections occurred in utero[1] and PCR analyses of aborted fetuses and early miscarriages indicated almost no transmission in the first trimester[12] or during the second trimester based on amniocentesis.[13] However, in the third trimester, the vascular integrity of the placenta begins to break down and statistical modeling data[14] suggest that most in utero transmissions probably occur in the last few weeks before delivery. It has been postulated that this may be caused by microtransfusions across the maternal-fetal placenta circulation during late pregnancy.[15,16] Intrauterine contractions during labor/delivery could also increase the risk of intrapartum transmission.

Intrapartum Infection

Other mechanisms that can contribute to intrapartum transmission are infant mucosal exposure to maternal blood and other HIV-infected secretions as the baby goes through the birth canal. The protective effect of scheduled cesarean delivery before labor onset with a 50% reduction in transmission risk[17–19] is potentially due to

preventing both microtransfusions during active labor and avoidance of infant gut and conjunctival exposure to HIV, which can occur during vaginal delivery. Inflammation of the placenta such as seen with malaria has also been associated with increased risk of HIV transmission in some malarial placenta studies[20,21] but not all such studies among pregnant women infected with HIV.[22,23]

Late Infection Through Breastfeeding

The exact mechanisms of transmission during breastfeeding have not yet been determined. It has been postulated that the transmission may occur via transfer across the infant gut by attachment to immature dendritic cells in the gut mucosa, which then transport the virus to lymph nodes (Peyer patches) from where HIV is then transmitted to CD4+ cells.[24] The first several days of life may be a particularly vulnerable period because of lack of acidic gastric fluid, which can inactivate HIV, and ingestion by the infant of HIV-infected macrophages present in colostrum. However, despite continual exposure to HIV in breast milk, the risk of infant infection by mouth is low (0.6%–0.8%) but cumulative for the duration of breastfeeding.[25]

There are several maternal factors in breast milk that may provide some protection against transmission including CD8+ cytotoxic T lymphocytes, secretory leukocyte protease inhibitor, other innate factors, and HIV-specific IgG and IgA immunoglobulins present in breast milk.[26] Specific IgA secretory natural antibodies in breast milk, which include anti-DC-SIGN antibodies, have been shown to prevent HIV attachment to dendritic cell membranes in vitro as well as to inhibit transfer of the HIV virus to CD4+ lymphocytes.[27] The relative contribution of cell-free versus cell-associated virus to MTCT through breast milk ingestion is not known. Early mixed feeding compared with exclusive breastfeeding during the first 3 months of life has been associated with increased risk of HIV infection among breastfed infants exposed to HIV,[28] whereas exclusive breastfeeding is associated with lowered risk.[29] Possible mechanisms of increased transmission with mixed feeding include damage to the integrity of the infant intestinal mucosa and local inflammation, which enhance the transfer of the HIV virus across the infant gut lumen.[26]

Maternal immunologic and clinical host factors also modulate the risk of transmission with documentation from several United States and European longitudinal perinatal cohorts that maternal CD4 less than 200 cells/mm^3 was a clear risk factor for transmission as was clinical AIDS.[30,31] Maternal-infant HLA incompatibility seems to afford a protective effect against transmission based on studies from Kenya.[32] In addition, clinical mastitis, breast abscess,[33] as well as subclinical mastitis based on increased sodium levels[34] are associated with increased risk of transmission during lactation.

However, the overriding risk factor for transmission during pregnancy, intrapartum, and during breastfeeding remains increased maternal viral load in plasma or breast milk.[35–37] This risk can be sharply reduced with use of combination antiretrovirals. In the United States, there is a less than 2% risk of MTCT among women infected with HIV with very low (<1000 RNA copies/mL) or undetectable viral loads, which has been achieved using potent combination antiretroviral prophylaxis during pregnancy and intrapartum.[4,5] In resource-limited international settings, low rates of MTCT among women infected with HIV who breastfeed have also been achieved in clinical trials with use of prophylaxis during pregnancy and continued during prolonged breastfeeding.[10,11]

CURRENT EPIDEMIOLOGY OF MTCT OF HIV IN THE UNITED STATES

The annual number of children less than 13 years of age with AIDS has declined by more than 96%[38] in the United States (**Fig. 1**). Estimates of the annual number of perinatal HIV infections peaked in 1992 at 1650,[39] declined to an estimated low of 96 to 186 cases in 2004,[40] and were estimated at 215 to 370 for 2005,[41] representing an approximate 92% decline overall in perinatally acquired HIV infection. These reductions are largely attributed to routine HIV screening of women during pregnancy, the use of antiretroviral (ARV) drugs for maternal treatment and perinatal prophylaxis, the use of elective cesarean delivery when appropriate and avoidance of breastfeeding. Transmission rates of less than 1% have been achieved in some settings where pregnant women have received highly active antiretroviral therapy (HAART) and successfully suppressed their HIV viral load to undetectable levels.[42–44]

In the United States, the estimated perinatal HIV transmission rate in 2005 was 1.1% to 2.8% among infants born to women infected with HIV that year in the 15 sites conducting Enhanced Perinatal HIV Surveillance,[41] however, the substantial racial/ethnic disparities that have been observed since the early days of the US HIV/AIDS epidemic persist.[45] From 2004 to 2007, the average annual overall rate of diagnoses of perinatal HIV infection was 2.7 per 100,000 infants age 1 year or less in 34 states with name-based HIV reporting. During this same time period, the average rate of diagnoses of perinatal HIV infection was 12.3 per 100,000 among blacks, 2.1 per 100,000 among Hispanics and 0.5 per 100,000 among whites. The rates for black and Hispanic children were 23 and 4 times the rate for white children, respectively. However, from 2004 to 2007, the racial/ethnic disparity narrowed, as the annual rate of diagnoses of perinatal HIV infection for black children decreased from 14.8 to 10.2 per 100,000 ($P = .003$), and the rate for Hispanic children decreased from 2.9 to 1.7 per 100,000 ($P = .04$) (**Fig. 2**).

Further reductions in perinatal HIV transmission are achievable in the United States, toward an elimination goal of less than 1% among infants born to women

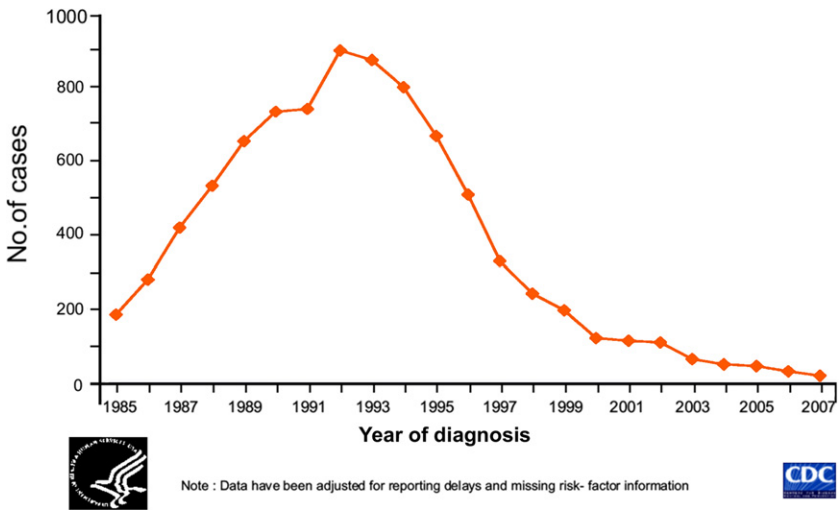

Fig. 1. Estimated numbers of perinatally acquired AIDS cases by year of diagnosis, 1985 to 2007, United States and Dependent Areas. (*From* Centers for Disease Control and Prevention. HIV/AIDS surveillance slide sets. Available at: http://www.cdc.gov/hiv/topics/surveillance/resources/slides/pediatric/index.htm.)

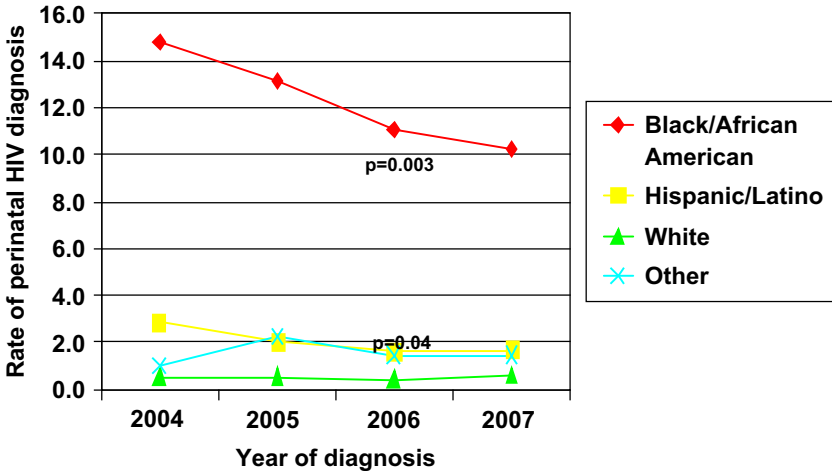

Fig. 2. Annual rate of diagnoses of perinatal HIV infection per 100,000 infants aged 1 year or less, by race/ethnicity, 34 states, 2004 to 2007. (*Data from* Centers for Disease Control and Prevention (CDC). Racial/ethnic disparities among children with diagnoses of perinatal HIV infection – 34 states, 2004–2007. CDC. MMWR Morb Mortal Wkly Rep 2010:59(4):97–101.)

infected with HIV and less than 1 transmission per 100,000 live births.[45] The Centers for Disease Control and Prevention (CDC) collaborated with 4 national organizations and published recommendations to eliminate perinatal HIV transmission in the United States.[46] The *National Organizations' Collaborative to Eliminate Perinatal HIV in the United States* recommended that to maintain the gains in PMTCT and to reach the goal of eliminating perinatal HIV in the United States, 3 strategies are needed: standardize and solidify medical interventions and policy changes that support PMTCT; institute HIV screening as part of routine health care so that HIV infection can be identified in women before pregnancy; and, most critically, focus attention and resources on the primary prevention of HIV infection in women. In addition, the investigators concluded that health care providers should incorporate HIV prevention education and routine HIV screening into women's primary health care, and public health leaders should support and fund prevention strategies directed to young women. An estimated 8700 (8663–8921) women infected with HIV gave birth to live infants in 2006,[47] representing an approximate 30% increase from the estimate of 6075 to 6422 in 2000.[48] With stable annual incidence of HIV among women,[49] and with treatment advances affording longer survival and improved quality of life, it is likely that the number of births to women infected with HIV will continue to increase. Therefore, ongoing vigilance for PMTCT in the United States will continue to be important.

HIGH-PREVALENCE STATES AND NEW STRATEGIES TO ELIMINATE PERINATAL HIV TRANSMISSION IN THE UNITED STATES

In 1999, the US Congress provided specific funding for perinatal HIV prevention. These funds were targeted at states with high prevalence to support the cascade of services needed to maximize PMTCT efforts. These include strategies to encourage routine opt-out HIV screening of all pregnant women, encourage rapid HIV testing at labor/delivery for women whose HIV status is still unknown,[50,51] and support PMTCT interventions for women found to be infected with HIV. After delivery, early

infant diagnosis, family planning, and linkage to care for mothers infected with HIV and infants exposed to HIV are crucial to the successful delivery of PMTCT services.

Several of the funded states have developed strategies to support these PMTCT efforts directed at eliminating new cases of HIV infection. An example of a recent accomplishment includes the work done by the Washington, DC HIV/AIDS Administration. With the addition of new staff and increased coordination of city-wide PMTCT efforts, the District improved the availability of early HIV testing, rapid HIV testing in labor and delivery, and changes in the standard of care to incorporate a second HIV test during the third trimester of pregnancy for all pregnant women. Washington, DC saw a reduction in MTCT from 10 cases in 2005 to 1 case in 2007.[52] The state of Illinois also has a long-standing comprehensive perinatal HIV prevention system. In Illinois, all pregnant women and their infants have access to HIV testing, and as a safety net, every delivery hospital in Illinois has made rapid HIV testing available for women of unknown HIV status. The State Health Department funds a quality assurance program to ensure that all mothers and infants are tested and provides technical assistance to hospitals that are not in compliance with Illinois law requiring that all women be offered testing.

Because missed opportunities for PMTCT of HIV are frequently the result of issues with local systems, CDC has worked with CityMatCH, the American College of Obstetricians and Gynecologists, and the National Fetal and Infant Mortality Review (FIMR) Program to develop a community-based, continuous quality improvement protocol called the FIMR-HIV Prevention Methodology (FHPM). This methodology is modeled on the FIMR program and was demonstrated to be an effective tool to improve perinatal HIV prevention systems in 3 pilot communities.[53] CDC has since supported a National Resource Center for the FHPM[54] and 9 communities are currently using the methodology. The FHPM is based on the premise that all cases of perinatal HIV infection in the United States are sentinel events that warrant full review. By collecting comprehensive quantitative and qualitative data about the pregnancy experiences of women with HIV infection through maternal interviews and medical record abstraction, the methodology provides an in-depth look at the systems that result in perinatal HIV exposure or transmission. This examination allows communities to identify system strengths, missed opportunities for prevention and, more rarely, failures of interventions to prevent perinatal transmission. Communities can then develop and implement improvements to systems of care for women with HIV infection and their infants. Subsequent case reviews identify any additional or ongoing systems issues that may not have been fully addressed by the community action team so that further action can be taken.

Because the clinical management of women infected with HIV and their children is complex, the Federal Health Resources and Services Administration funds the Perinatal Hotline (888-448-8765) at the National HIV/AIDS Clinicians Consultation Center in San Francisco, CA.[55] The Perinatal Hotline provides around-the-clock advice to health care providers on indications and interpretations of standard and rapid HIV testing in pregnancy, as well as consultation on antiretroviral use in pregnancy, labor and delivery, and the postpartum period. The Perinatal HIV Consultation and Referral Service also links women with HIV infection with appropriate local health care in all states.

The US Federal Government in collaboration with other key PMTCT stakeholders is considering new coordinated approaches to eliminate perinatal HIV transmission that build on the successes and proven strategies already established.

US PUBLIC HEALTH SERVICE PMTCT RECOMMENDATIONS

In 1994, following the dramatic results of the PACTG 076 trial[3] with ZDV for PMTCT, the US government created a taskforce to work with states to rapidly implement

effective and proven interventions. The Department of Health and Human Services (DHHS) Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission includes obstetric and pediatric clinician experts as well as US government experts from the National Institutes of Health (NIH), the CDC, and the US Food and Drug and Administration, and community representatives. The panel reviews and updates recommendations based on new clinical trial data, safety updates, as well as clinical practice information on use of new agents. On May 24, 2010, updated guidelines[56] were issued, which included the following key recommendations for PMTCT:

- Combined antepartum, intrapartum, and infant ARV prophylaxis are recommended for maximal PMTCT
- Combination antepartum ARV regimens containing at least 3 drugs are recommended rather than single-drug regimens
- Combined ARV prophylaxis is recommended for all pregnant women infected with HIV regardless of plasma HIV RNA copy number or CD4 cell count
- Initiating ARV prophylaxis after the first trimester, but ideally no later than 28 weeks, is recommended for pregnant women infected with who do not require ARV for their own health
- Intrapartum prophylaxis and infant ARV prophylaxis are recommended for women who do not receive antepartum ARV to reduce risk of perinatal transmission
- The addition of single-dose intrapartum/newborn nevirapine (NVP) to standard antepartum combination therapy is not recommended because of the potential risk for development of NVP resistance and lack of added efficacy based on trial results
- A 6-week ZDV chemoprophylaxis regimen is recommended for all neonates exposed to HIV and should be started as close to time of birth as possible, preferably within 6 to 12 h of delivery
- Early diagnosis of HIV infection in infants remains a priority
- Decisions regarding use of additional ARV drugs in infants exposed to HIV depends on multiple factors and should be resolved with input from a pediatric HIV specialist
- In the United States, breastfeeding should be completely avoided given the increased risk of HIV transmission to the infant and availability of safe formula replacement feeding.

The DHHS Perinatal Panel also provides guidance on preconceptual counseling, specific ARV prophylactic regimens for pregnant women based on ARV history, ARV drug resistance testing, screening for and management of pregnant women coinfected with hepatitis B and C, postnatal management of HIV-exposed neonates and those born to mothers with unknown HIV status, and long-term follow-up of infants exposed to ARV drugs.

These guidelines are generally in harmony with the Adult DHHS guidelines issued in December 1, 2009, by the DHHS Panel on the Use of Antiretroviral Agents in HIV-1 Infected Adults and Adolescents.[57] However, the perinatal recommendations differed from the adult guidelines by not generally recommending continued lifetime triple combination ARVs for women with CD4 greater than 350 cells/mm^3 who took these drugs during pregnancy solely for the purpose of perinatal prophylaxis.[56]

Important questions remain, however, about the risks and benefits of stopping or continuing ARV treatment of women infected with HIV who initiate combination ARV

drugs solely for PMTCT who do not need it for their own health. Several randomized clinical trials are underway to provide more definitive data on these issues. The NIH-funded International Maternal Adolescent and Pediatric Clinical Trials Group is conducting a large multicenter, randomized clinical trial, PROMISE (Promoting Maternal and Infant Survival Everywhere) HAART standard version in areas where antepartum HAART is the standard of care. This study will answer outstanding questions regarding the effect on maternal health by randomizing women with high CD4 cell counts to stop or continue HAART after delivery. In addition, the NIH-funded International Network for Strategic Initiatives in Global HIV Trials (INSIGHT) network is conducting the START trial (Strategic Timing of AntiRetroviral Treatment), which is a randomized, international multicenter trial that will determine whether the immediate initiation of antiretroviral treatment in treatment-naive individuals infected with HIV with CD4 counts greater than 500 cells/mm^3 is superior, in terms of morbidity and mortality, to deferral of treatment until the CD4 count declines to less than 350 cells/mm^3. It is critical that these trials continue to enroll so that definitive evidence regarding appropriate CD4 cell count for initiation of lifelong antiretroviral treatment (ART) can be gathered.

MEASURING SUCCESS: EARLY DIAGNOSIS OF INFANT HIV

Given that the primary goal of PMTCT interventions is to prevent infants exposed to HIV from acquiring HIV infection, it is critical to be able to monitor the success of interventions both for the individual infant and overall rates of MTCT transmission. In the United States and in international settings, early infant diagnosis (EID) is crucial for timely initiation of essential ART in infected infants given that approximately one-third of children infected with HIV die by age 1 year and more than half by age 2 years without treatment.[58] Early diagnosis and initiation of ART can reduce early mortality and HIV disease progression among infants infected with HIV by 75%.[59]

Since the early 1990s, significant progress has been made in early diagnosis of infant HIV by using nucleic acid tests (eg, PCR testing) that can directly detect the HIV virus. This is necessary because antibody tests cannot be used to diagnose HIV infection in children less than 18 months of age because of passive transfer of maternal anti-HIV antibodies. Virologic assays that can be used in children include HIV DNA assays, HIV RNA assays, and p24 antigen assays. The progress in early infant diagnosis in the United States and internationally are described in the article by Palumbo and colleagues in this issue.

INTERNATIONAL SETTINGS: GLOBAL EPIDEMIOLOGY OF MTCT OF HIV

In 2008, an estimated 430,000 new HIV infections occurred among children less than 15 years of age, most of which were caused by MTCT during pregnancy, birth, or breastfeeding.[60] In the United States, western Europe, and other resource-advantaged areas, as described earlier, MTCT has been nearly eliminated as a result of a combination of highly effective interventions including combination antiretroviral prophylaxis, elective cesarean section for women with more than 1000 copies/mm^3, and exclusive formula feeding of infants born to mother infected with HIV.[19,56] However, the incidence of MTCT in many resource-limited countries remains high because of high prevalence of HIV in women of child-bearing age, lack of universal access to antiretroviral prophylaxis, and lack of acceptable, feasible, affordable, sustainable, safe alternatives to breastfeeding. Sub-Saharan Africa has the highest burden of HIV disease overall and for MTCT, accounting for 91% (390,000) of new

infections among children less that 15 years old (**Fig. 3**).[60] The region also accounted for 86% (1.8 million) of children living with HIV and the most AIDS-related deaths in children in 2008 (**Table 1**).[60]

In 2008, an estimated 1.4 million pregnant women were living with HIV; 90% were living in 19 countries in sub-Saharan Africa and India.[61] HIV seroprevalence rates in antenatal clinics vary from less than 5% in some countries to more than one-third of pregnant women in some high-prevalence countries.[62] Sentinel surveillance at antenatal clinics in southern Africa shows extremely high rates of HIV seroprevalence among pregnant women. In some clinics in South Africa, Swaziland, Lesotho, and Botswana, HIV prevalence in pregnant women exceeds 35%.[62] HIV/AIDS is also the leading cause of mortality among women of reproductive age worldwide and is the leading cause of maternal mortality in some high-prevalence countries.[60]

Coverage of PMTCT services in low- and middle-income countries has improved in recent years. In 2008, 45% of pregnant women infected with HIV received some antiretroviral drugs either for their own health or to prevent transmission to their newborns compared with 10% in 2004.[61] Coverage of antiretroviral prophylaxis for infants born to mothers infected with HIV increased to 32% from 6% during the same time period.[61] However, there is considerable inter- and intraregional variation in coverage among low- and middle-income countries (**Fig. 4**). For example, the percentage of pregnant women infected with HIV receiving ARVs for PMTCT was 59% in eastern and southern Africa versus only 16% in western and central African countries in 2008. Regimens for PMTCT also vary considerably across countries with many women still receiving a single ARV versus more effective combination ARV regimens.[61] Data published in 2009 from the Elizabeth Glaser Pediatric AIDS Foundation and affiliated programs in 22 countries have shown some increased uptake and efficiency of PMTCT services through the use of routine opt-out testing, and by supplying ARV prophylaxis for the mother as well as for her newborn at the time of HIV diagnosis.[63] These data underscore the continued global epidemic of MTCT of HIV. Africa carries the heaviest burden but Asia and India also have a significant burden of HIV infection among infants and children.

Given the international mother-to-child epidemic, there have been intensive research efforts to find feasible cost-effective strategies to reduce MTCT of HIV. These began in the mid-1990s with interventions aimed at the intrapartum period with short-course ZDV and ZDV/lamivudine (3TC) trials from 34 to 36 weeks through to labor, and

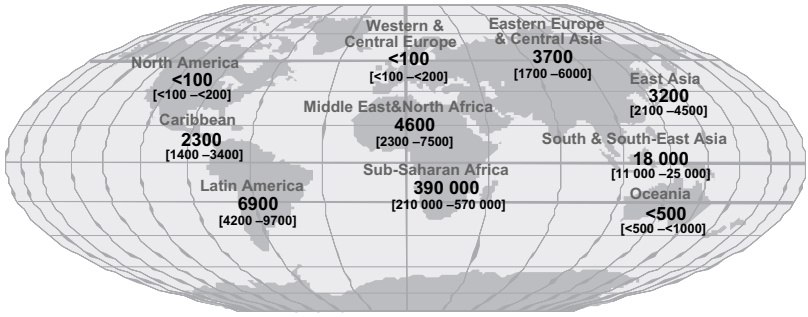

Fig. 3. Estimated number of children (<15 years) newly infected with HIV, 2008. (*Data from* World Health Organization, UNAIDS. AIDS epidemic update 2009. Geneva: World Health Organization. Available at: http://www.unaids.org/en/KnowledgeCentre/HIVData/EpiUpdate/EpiUpdArchive/2009/default.asp. Accessed July 12, 2010.)

Table 1
Regional HIV and AIDS statistics for children < 15 years old

Region	New Infections Among Children <15 Years (2001)	New Infections Among Children <15 Years (2008)	Children <15 Years Living with HIV (2008)	AIDS-related Deaths Among Children <15 Years (2008)
Sub-Saharan Africa	460,000 (260,000–640,000)	390,000 (210,000–570,000)	1.8 million (1.0–2.5 million)	230,000 (120,000–350,000)
Middle East and North Africa	3,800 (1900–64000)	4,600 (2300–7500)	15,000 (7600–24,000)	3300 (1600–5300)
Eastern Europe and Central Asia	3000 (1600–4300)	3700 (1700–6000)	20,000 (12,000–28,000)	1400 (<500–2700)
South, East, and South-east Asia	33,000 (18,000–49,000)	21,200 (13,100–29,500)	156,000 (102,000–223,000)	17,500 (5900–19,300)
Oceania	<500 (<200–<500)	<500 (<500–<1000)	1500 (<1000–2600)	<100 (<100–<500)
Latin America	6200 (3800–9100)	6900 (4200–9700)	31,000 (22,000–40,000)	3900 (2100–5700)
Caribbean	2800 (1700–4000)	2300 (1400–3400)	11,000 (7400–16,000)	1300 (<1000–2100)
North America, Western and Central Europe	<500 (<200–<500)	<500 (<200–<500)	5900 (<5000–7600)	<200 (<200–<400)
Total	510,000 (290,000–772,000)	430,000 (240,000–610,000)	2.1 million (1.2 –2.9 million)	280,000* (150,000–410,000)

* Rounded total estimates reported by UNAIDS.
Refs.[61,80]

Data from UNAIDS, World Health Organization. Epidemiology core slides - AIDS epidemic update 2009. Available at: http://data.unaids.org/pub/EPISlides/2009/2009_epiupdate_core_en.ppt. Accessed September 26, 2010.

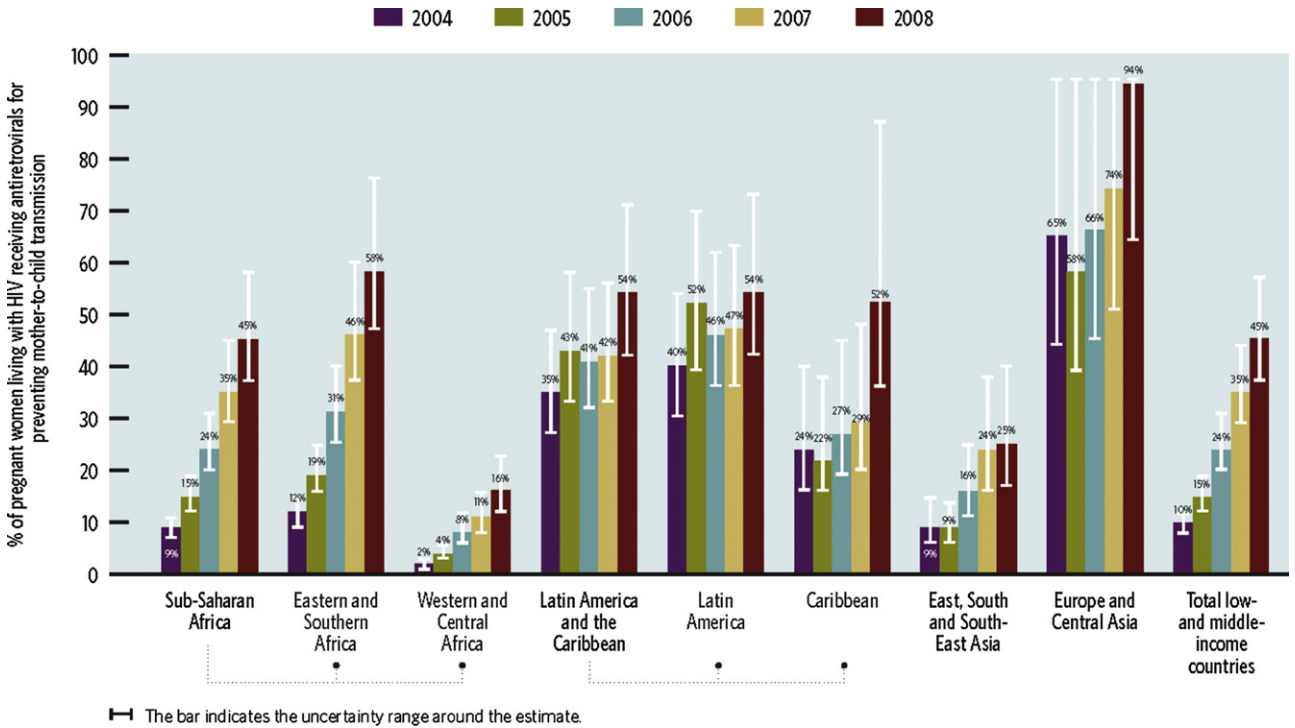

Fig. 4. Percentage of pregnant women with HIV receiving antiretrovirals for preventing mother-to-child transmission of HIV in low- and middle-income countries by region, 2004–2008. (*From* World Health Organization, UNAIDS and UNICEF. Towards universal access: scaling up priority HIV/AIDS interventions in the health sector. Progress report. 2009; Geneva (Switzerland): World Health Organization; 2009. p. 99; with permission. Available at: http://www.who.int/hiv/pub/2009progressreport/en/.)

infant prophylaxis. These randomized trials were performed in a nonbreastfeeding population in Thailand,[64] and in Africa among breastfeeding women.[6,7,65–67] In addition, in Uganda, investigators conducted a trial that focused on the peripartum period; a single tablet of NVP was given to mothers at labor onset and to their newborns.[8,68,69] Those interventions were encouraging and demonstrated between 33% and 43% efficacy compared with placebo. However, there was also loss of efficacy at 18 to 24 months for all the studies except the single-dose NVP intervention related to ongoing transmission during breastfeeding.

More recent studies have focused on antiretroviral and immune interventions to reduce the risk of transmission during breastfeeding and allow infants exposed to HIV to have the nutritional and immunologic protection of breastfeeding to improve child survival. The results of these more recent trials are quite encouraging although translation into policy and implementation in resource-limited international settings continues to lag.

RECENT INTERNATIONAL PMTCT TRIAL RESULTS

In most resource-limited settings, breastfeeding remains the cultural norm among mothers. Breast milk provides ideal nutritional food for the infant particularly in the first year of life and contains antiinfective factors that protect infants from common childhood illnesses such as pneumonia and diarrhea. In addition to its safety and birth-spacing properties, breastfeeding also offers economic and social benefits to the family.

However, breastfeeding, which is crucial to infant survival in resource-limited settings, accounts for one-third to one-half of MTCT of HIV.[1] This risk is greatest during the first 6 weeks of life and increases to an estimated 30% to 50% of all MTCT with prolonged breastfeeding into the second year.[70] Mothers with HIV therefore face a dilemma: to breastfeed their babies and risk passing on HIV or to formula feed and increase the risk of diarrhea, malnutrition, and related deaths.

Finding new strategies that can reduce the risk of MTCT of HIV among infants in settings where breastfeeding is critical to overall infant survival remains an urgent public health priority. Several trials have evaluated the use of infant NVP prophylaxis and maternal triple ARV prophylaxis as strategies to reduce the risk of HIV transmission via breastfeeding during the first months of life and offer hope to women in resource-limited settings.

Data from recent trials, including 2 randomized controlled trials support the use of infant NVP prophylaxis during the first months of life to reduce the risk of breastfeeding HIV transmission.[9,71] Results from 2 new randomized clinical trials from Malawi[10] and Botswana[11] support both maternal HAART and infant NVP prophylaxis for 6 to 7 months of breastfeeding as promising viable strategies to reduce the risk of HIV transmission among breastfeeding women infected with HIV in resource-limited settings who do not require treatment for their own health. The World Health Organization (WHO) now recommends the use of 1 of the 2 strategies.[72] These clinical trial results and the current state-of-the-art in PMTCT of HIV through breastfeeding are covered in more detail in an article by Kourtis and colleagues in this issue.

WHO STRATEGIES FOR PMTCT AND RELATED RAPID ADVICE AND GUIDELINES

Based on these and other findings on HIV prevention, the WHO in 2009 made several Rapid Advice recommendations for adult HIV treatment,[73] PMTCT,[72] and feeding of infants exposed to HIV.[74] These rapid advice reports were followed by more complete guidance released in 2010.[75–77] For PMTCT, the WHO issued a 4-pronged strategy to reduce PMTCT in low- and middle-income countries: “primary prevention of HIV

infection among women of child-bearing age; preventing unintended pregnancies among women living with HIV; preventing HIV transmission from a woman living with HIV to her infant; and providing appropriate treatment, care and support to mothers living with HIV and their children and families."[(p6)78] The general guidance from the 2009 rapid advice/2010 guidelines is listed in **Table 2** along with changes from the 2006 WHO recommendations.

The recommendations were accompanied by suggested implementation strategies including

- Universal routine voluntary HIV testing and counseling for all pregnant women
- Availability of CD4 testing and ARVs at primary care level and antenatal facilities where maternal-child health care takes place, not just in specialized centers
- Improved follow-up of pregnant women antenatally and of mothers and infants exposed to HIV after birth
- Promotion and provision of ARV prophylaxis to the mother or baby throughout breastfeeding, as well as infant feeding counseling and support
- Provision of appropriately trained staff in PMTCT.

The 2009 WHO Rapid Advice and 2010 guidelines recommendations are being carefully reviewed by national Ministries of Health and policy makers in resource-limited settings. Because several of the recommendations were based on strong expert opinion but low or moderate quality of evidence, there is still a need for further research to corroborate and strengthen the recommendations. In addition, there is an urgent need for operational research to test strategies to support rapid implementation of proven effective interventions.

CHALLENGES, GAPS, AND FUTURE RESEARCH

Although progress toward elimination of MTCT of HIV in the United States and other resource-rich settings has been steady, there are still major challenges to prevent transmission and reduce the burden of pediatric HIV infection in most of the world. Some are related to crumbling health care infrastructure in settings such as Africa, which include constrained health care staffing, limited access to training, limited numbers of laboratories, and poor health care infrastructure. In addition, logistics of delivery of ARV interventions, drug stock outs, and delivery of early infant HIV diagnostics are ever present.

Other challenges include fear of stigma and lack of disclosure among pregnant women to their partners, which can lead to poor adherence to completion of more complex PMTCT regimens even if they are available. Further challenges include cultural traditions that discourage exclusive breastfeeding for the first 6 months of life, even though exclusive breastfeeding has been demonstrated to reduce the risk of HIV transmission among mothers infected with HIV in resource-limited settings compared with early mixed feeding.

Research gaps include limited clinical trial safety or efficacy data on using antiretrovirals for prevention of transmission during breastfeeding beyond the first 6 months of life and whether maternal triple prophylaxis or infant prophylaxis is most efficacious, has fewer side effects, and is most cost-effective during prolonged breastfeeding up to 12 months. The recent BAN trial presents some information on using these strategies up to 6 months; and a new clinical trial (IMPAACT PROMISE) will address these questions in a large multisite study. Other gaps are in the area of operational research on how best to implement WHO

Table 2
WHO guidelines and rapid advice on PMTCT, ART treatment of pregnant women, and infant feeding for resource-limited settings

Status	WHO Guidelines 2006[79,80]	WHO Rapid Advice November 2009[72–74] and 2010 Guidelines[75–77]
1. HIV pregnant woman CD4 at or less than 350 cells/mm^3 regardless of symptoms, or WHO stage 3 or 4 regardless of CD4 count		Lifelong ART irrespective of gestational age using AZT+3TC NVP/EFV TDF+3TC /(FTC)+NVP/EFV (avoid EFV during first trimester) Infant Breastfeeding infant daily: NVP from birth to 6 weeks Nonbreastfeeding infant: AZT or NVP for 6 weeks
2. HIV pregnant woman CD4 more than 350 cells/mm^3; WHO stage 1 or 2	Provision of antiretroviral prophylaxis (AZT) from 28 weeks and single-dose NVP at onset of labor with 1 week tail of AZT/3TC to prevent resistance Infant Breastfeeding or nonbreastfeeding: combination antiretroviral prophylaxis replaced single-dose nevirapine. Single-dose NVP + AZT	Provision of antiretroviral prophylaxis from 14 weeks' gestation to 1 week after all exposure to breast milk Option A: maternal daily AZT from as early as 14 weeks' gestation and continued during labor: single-dose NVP at labor onset, AZT/3TC during labor and for 1 week Infant Breastfeeding infant: daily NVP from birth until 1 week after all exposure to breast milk has ended Nonbreastfeeding infant: 6 weeks daily AZT or NVP Option B: maternal triple ARV prophylaxis regimens from as early as 14 weeks AZT+3TC+LPV/r AZT +3TC + ABC AZT + 3TC + EFV TDF+FTC +EFV Labor: continue dosing Continue through duration of breastfeeding and for 1 week after Infant Breastfeeding infant, daily NVP from birth to 6 weeks
3. HIV-positive mother and baby	Breastfeed for 2 years	Breastfeed for 2 years

Abbreviations: 3TC, lamivudine; AZT, zidovudine; EFV, efavirenz; FTC, emtricitabine; LPV/r, lopinavir/ritonavir; NVP, nevirapine; TDF, tenofovir.

guidance at a country and district level, particularly in rural settings with already constrained medical services.

Given these gaps, several research questions remain to be addressed:

- Is it better to provide infant prophylaxis or maternal triple ARV prophylaxis to prevent transmission during breastfeeding for women infected with HIV in resource-limited settings, considering both maternal disease progression and infant health and survival?
- Which strategy is most cost-effective in the short-term and in the long-term?
- What are the resistance patterns seen for mother-infant pairs exposed to long-term triple ARV interventions?
- Is it safer to stop or to continue triple ARVs used solely for PMTCT once started in 1 pregnancy among women who do not yet require treatment for their own care?
- Are there late adverse effects on physical growth, hematologic parameters, and cognitive development of infants and children exposed to PMTCT combination antiretrovirals in utero and for up to 18 months or more of breastfeeding?

Remaining key operational research questions include

- How to best integrate PMTCT efforts within the general maternal-child health framework so that it is not a vertical program operating in isolation
- How to use PMTCT funds to help support overall infant and maternal survival in resource-limited settings
- How to expand rapid development of inexpensive point-of-care early infant diagnostic testing, CD4 and viral load testing
- How to simplify ARV regimens (eg, as fixed dose once-a-day regimens) to promote adherence
- How to improve long-term adherence once individuals are feeling well
- How to set up monitoring systems to assess both short-term and long-term adverse effects of use of antiretroviral drugs for PMTCT.

SUMMARY

The progress in PMTCT has been one of the major successes in the US HIV epidemic with a greater than 96% reduction in perinatal AIDS cases from 1992 to the present. Perinatal HIV transmission rates are now less than 2% in most university medical settings where pregnant women infected with HIV receive combination antiretrovirals, scheduled cesarean delivery if they still have detectable viral load near delivery, and can safely avoid breastfeeding. The rapid implementation of effective interventions has been the result of strong collaboration and coordination between federal, state, and local agencies, dissemination of interventions, education of health care providers, and targeted funding to help support perinatal HIV prevention programs. However, the drive toward the elimination of MTCT in the United States is hampered by new incident infections among adolescents and women, late identification of their infection status leading to suboptimal late interventions among some pregnant women infected with HIV.

Internationally, clinical trial research has also shown slow but incremental progress in reducing transmission risk among women infected with HIV particularly antepartum, during labor and delivery, and during the first 6 months of breastfeeding. Finding feasible strategies to prevent transmission during more extended periods of breastfeeding remains a challenge. Current studies are addressing the use of either maternal triple ARV prophylaxis or infant ARV prophylaxis extending into the second year of life;

and assessing whether stopping of maternal ARVs may be harmful for mothers infected with HIV who do not yet meet treatment criteria. In resource-limited settings, the translation of PMTCT clinical trial findings into practice has been slow, given poor maternal-child health care infrastructure, lack of integration, and limitations on funding. In addition, primary prevention efforts to date have fallen short, with adolescents and women of child-bearing age remaining at high risk for acquiring HIV and passing it on to their infants.

An effective HIV vaccine which could be given to newborns and infants during breastfeeding; as well as to adolescents and sexually active adults would ideally be the best long-term solution to the global HIV epidemic and would eliminate new cases of MTCT. However, the quest for an efficacious vaccine remains elusive despite 30 years of intensive basic and clinical trial research. In the interim, advances in PMTCT are continuing based on research efforts and international programmatic support.

REFERENCES

1. De Cock KM, Fowler MG, Mercier E, et al. Prevention of mother-to-child HIV transmission in resource-poor countries: translating research into policy and practice. JAMA 2000;283(9):1175–82.
2. Simonon A, Lepage P, Karita E, et al. An assessment of the timing of mother-to-child transmission of human immunodeficiency virus type 1 by means of polymerase chain reaction. J Acquir Immune Defic Syndr 1994;7(9):952–7.
3. Connor EM, Sperling RS, Gelber R, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. N Engl J Med 1994;331(18): 1173–80.
4. Dorenbaum A, Cunningham CK, Gelber RD, et al. Two-dose intrapartum/newborn nevirapine and standard antiretroviral therapy to reduce perinatal HIV transmission: a randomized trial. JAMA 2002;288(2):189–98.
5. Cooper ER, Charurat M, Mofenson L, et al. Combination antiretroviral strategies for the treatment of pregnant HIV-1-infected women and prevention of perinatal HIV-1 transmission. J Acquir Immune Defic Syndr 2002;29(5):484–94.
6. Wiktor SZ, Ekpini E, Karon JM, et al. Short-course oral zidovudine for prevention of mother-to-child transmission of HIV-1 in Abidjan, Cote d'Ivoire: a randomised trial. Lancet 1999;353(9155):781–5.
7. PETRA Study Team. Efficacy of three short-course regimens of zidovudine and lamivudine in preventing early and late transmission of HIV-1 from mother to child in Tanzania, South Africa, and Uganda (PETRA study): a randomised, double-blind, placebo-controlled trial. Lancet 2002;359(9313):1178–86.
8. Jackson JB, Musoke P, Fleming T, et al. Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: 18-month follow-up of the HIVNET 012 randomised trial. Lancet 2003;362(9387):859–68.
9. Six Week Extended-Dose Nevirapine (SWEN) Study Team, Bedri A, Gudetta B, et al. Extended-dose nevirapine to 6 weeks of age for infants to prevent HIV transmission via breastfeeding in Ethiopia, India, and Uganda: an analysis of three randomised controlled trials. Lancet 2008;372(9635):300–13.
10. Chasela CS, Hudgens MG, Jamieson DJ, et al. Maternal or infant antiretroviral drugs to reduce HIV-1 transmission. N Engl J Med 2010;362(24):2271–81.
11. Shapiro RL, Hughes MD, Ogwu A, et al. Antiretroviral regimens in pregnancy and breast-feeding in Botswana. N Engl J Med 2010;362(24):2282–94.

12. Brossard Y, Aubin JT, Mandelbrot L, et al. Frequency of early in utero HIV-1 infection: a blind DNA polymerase chain reaction study on 100 fetal thymuses. AIDS 1995;9(4):359–66.
13. Van Dyke RB, Korber BT, Popek E, et al. The Ariel Project: a prospective cohort study of maternal-child transmission of human immunodeficiency virus type 1 in the era of maternal antiretroviral therapy. J Infect Dis 1999;179(2):319–28.
14. Kourtis AP, Lee FK, Abrams EJ, et al. Mother-to-child transmission of HIV-1: timing and implications for prevention. Lancet Infect Dis 2006;6(11):726–32.
15. Lin HH, Kao JH, Hsu HY, et al. Least microtransfusion from mother to fetus in elective cesarean delivery. Obstet Gynecol 1996;87(2):244–8.
16. Kaneda T, Shiraki K, Hirano K, et al. Detection of maternofetal transfusion by placental alkaline phosphatase levels. J Pediatr 1997;130(5):730–5.
17. European Mode of Delivery Collaboration. Elective caesarean-section versus vaginal delivery in prevention of vertical HIV-1 transmission: a randomised clinical trial. Lancet 1999;353(9158):1035–9.
18. The International Perinatal HIV Group. 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 1999;340(13):977–87.
19. Boer K, England K, Godfried MH, et al. Mode of delivery in HIV-infected pregnant women and prevention of mother-to-child transmission: changing practices in western Europe. HIV Med 2010;11(6):368–78.
20. Ayisi JG, van Eijk AM, Newman RD, et al. Maternal malaria and perinatal HIV transmission, western Kenya. Emerg Infect Dis 2004;10(4):643–52.
21. Brahmbhatt H, Sullivan D, Kigozi G, et al. Association of HIV and malaria with mother-to-child transmission, birth outcomes, and child mortality. J Acquir Immune Defic Syndr 2008;47(4):472–6.
22. Inion I, Mwanyumba F, Gaillard P, et al. Placental malaria and perinatal transmission of human immunodeficiency virus type 1. J Infect Dis 2003;188(11): 1675–8.
23. Mwapasa V, Rogerson SJ, Molyneux ME, et al. The effect of *Plasmodium falciparum* malaria on peripheral and placental HIV-1 RNA concentrations in pregnant Malawian women. AIDS 2004;18(7):1051–9.
24. Belyakov IM, Berzofsky JA. Immunobiology of mucosal HIV infection and the basis for development of a new generation of mucosal AIDS vaccines. Immunity 2004;20(3):247–53.
25. Miotti PG, Taha TE, Kumwenda NI, et al. HIV transmission through breastfeeding: a study in Malawi. JAMA 1999;282(8):744–9.
26. Kourtis AP, Jamieson DJ, de Vincenzi I, et al. Prevention of human immunodeficiency virus-1 transmission to the infant through breastfeeding: new developments. Am J Obstet Gynecol 2007;197(Suppl 3):S113–22.
27. Requena M, Bouhlal H, Nasreddine N, et al. Inhibition of HIV-1 transmission in trans from dendritic cells to CD4+ T lymphocytes by natural antibodies to the CRD domain of DC-SIGN purified from breast milk and intravenous immunoglobulins. Immunology 2008;123(4):508–18.
28. Coutsoudis A, Pillay K, Spooner E, et al. Randomized trial testing the effect of vitamin A supplementation on pregnancy outcomes and early mother-to-child HIV-1 transmission in Durban, South Africa. South African Vitamin A Study Group. AIDS 1999;13(12):1517–24.
29. Iliff PJ, Piwoz EG, Tavengwa NV, et al. Early exclusive breastfeeding reduces the risk of postnatal HIV-1 transmission and increases HIV-free survival. AIDS 2005; 19(7):699–708.

30. Pitt J, Brambilla D, Reichelderfer P, et al. Maternal immunologic and virologic risk factors for infant human immunodeficiency virus type 1 infection: findings from the women and infants transmission study. J Infect Dis 1997;175(3):567–75.
31. European Collaborative Study. HIV-infected pregnant women and vertical transmission in Europe since 1986. AIDS 2001;15(6):761–70.
32. Mackelprang RD, John-Stewart G, Carrington M, et al. Maternal HLA homozygosity and mother-child HLA concordance increase the risk of vertical transmission of HIV-1. J Infect Dis 2008;197(8):1156–61.
33. Embree JE, Njenga S, Datta P, et al. Risk factors for postnatal mother-child transmission of HIV-1. AIDS 2000;14(16):2535–41.
34. Semba RD, Kumwenda N, Hoover DR, et al. Human immunodeficiency virus load in breast milk, mastitis, and mother-to-child transmission of human immunodeficiency virus type 1. J Infect Dis 1999;180(1):93–8.
35. Sperling RS, Shapiro DE, Coombs RW, et al. Maternal viral load, zidovudine treatment, and the risk of transmission of human immunodeficiency virus type 1 from mother to infant. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. N Engl J Med 1996;335(22):1621–9.
36. Shaffer N, Roongpisuthipong A, Siriwasin W, et al. Maternal virus load and perinatal human immunodeficiency virus type 1 subtype E transmission, Thailand. Bangkok Collaborative Perinatal HIV Transmission Study Group. J Infect Dis 1999;179(3):590–9.
37. Semrau K, Ghosh M, Kankasa C, et al. Temporal and lateral dynamics of HIV shedding and elevated sodium in breast milk among HIV-positive mothers during the first 4 months of breast-feeding. J Acquir Immune Defic Syndr 2008;47(3):320–8.
38. Centers for Disease Control and Prevention (CDC). HIV/AIDS surveillance report, 2007, vol. 19. Atlanta (GA): US Department of Health and Human Services, Centers for Disease Control and Prevention; 2009. Available at: http://www.cdc.gov/hiv/topics/surveillance/resources/reports/. Accessed June 16, 2010.
39. Lindegren ML, Byers RH Jr, Thomas P, et al. Trends in perinatal transmission of HIV/AIDS in the United States. JAMA 1999;282(6):531–8.
40. McKenna MT, Hu X. Recent trends in the incidence and morbidity that are associated with perinatal human immunodeficiency virus infection in the United States. Am J Obstet Gynecol 2007;197(Suppl 3):S10–6.
41. Zhang X, Rhodes P, Blair J. Estimated number of perinatal HIV infections in the United States, 2005–2009. In: Programs and abstracts of the National HIV Prevention Conference 2009. Atlanta (GA), August 23–29, 2009.
42. Naver L, Lindgren S, Belfrage E, et al. Children born to HIV-1-infected women in Sweden in 1982–2003: trends in epidemiology and vertical transmission. J Acquir Immune Defic Syndr 2006;42(4):484–9.
43. Townsend CL, Cortina-Borja M, Peckham CS, et al. Low rates of mother-to-child transmission of HIV following effective pregnancy interventions in the United Kingdom and Ireland, 2000–2006. AIDS 2008;22(8):973–81.
44. Warszawski J, Tubiana R, Le Chenadec J, et al. Mother-to-child HIV transmission despite antiretroviral therapy in the ANRS French perinatal cohort. AIDS 2008;22(2):289–99.
45. Centers for Disease Control and Prevention (CDC). Racial/ethnic disparities among children with diagnoses of perinatal HIV infection –34 states, 2004–2007. MMWR Morb Mortal Wkly Rep 2010;59(4):97–101.
46. Burr CK, Lampe MA, Corle S, et al. An end to perinatal HIV: success in the US requires ongoing and innovative efforts that should expand globally. J Public Health Policy 2007;28(2):249–60.

47. Whitmore SK, Zhang X, Taylor AW, et al. Estimated number of infants born to HIV-infected women in the United States and five dependent areas 2006 [abstract 924]. In: Program and abstracts of the 16th Conference on Retroviruses and Opportunistic Infections. Montréal (Canada), February 8–11, 2009.
48. Fleming P, Lindegren M, Byers R, et al. Estimated number of perinatal HIV infections, U.S., 2000. The XIV International AIDS Conference. Barcelona (Spain), July 11–16, 2002.
49. Hall HI, Song R, Rhodes P, et al. Estimation of HIV incidence in the United States. JAMA 2008;300(5):520–9.
50. Jamieson DJ, Cohen MH, Maupin R, et al. Rapid human immunodeficiency virus-1 testing on labor and delivery in 17 US hospitals: the MIRIAD experience. Am J Obstet Gynecol 2007;197(Suppl 3):S72–82.
51. ACOG Committee on Obstetric Practice. ACOG committee opinion number 304, November 2004 Prenatal and perinatal human immunodeficiency virus testing: expanded recommendations. Obstet Gynecol 2004;104(5 Pt 1): 1119–24.
52. Government of the District of Columbia. Annual report 2009 update HIV/AIDS, hepatitis, STD and TB epidemiology. 2009. Available at: http://www.doh.dc.gov/hahsta. Accessed June 15, 2010.
53. Lampe MA, Thompson B, Carlson R, et al. All perinatal HIV transmission is local: using FIMR to identify and address missed prevention opportunities. abstract C16-1. In: National HIV Prevention Conference 2009. Atlanta (GA), August 23–29, 2009.
54. National Resource Center. FIMR-HIV prevention methodology. Available at: http://www.fimrhiv.org/. Accessed October 26, 2010.
55. American Academy of Pediatrics (AAP). Perinatal HIV hotline. AAP News 2008; 29(12):26.
56. Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. Recommendations for use of antiretroviral drugs in pregnant HIV-1-infected women for maternal health and interventions to reduce perinatal HIV transmission in the United States. May 24, 2010. p. 1–117. Available at: http://aidsinfo.nih.gov/ContentFiles/PerinatalGL.pdf. Accessed June 1, 2010.
57. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. 2009. p. 1–161. Available at: http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed May 2, 2010.
58. Newell ML, Coovadia H, Cortina-Borja M, et al. Mortality of infected and uninfected infants born to HIV-infected mothers in Africa: a pooled analysis. Lancet 2004;364(9441):1236–43.
59. Violari A, Cotton MF, Gibb DM, et al. Early antiretroviral therapy and mortality among HIV-infected infants. N Engl J Med 2008;359(21):2233–44.
60. UNAIDS, World Health Organization. Epidemiology core slides - AIDS epidemic update 2009. Available at: http://data.unaids.org/pub/EPISlides/2009/2009_epiudate_core_cn.ppt. Accessed September 26, 2010.
61. World Health Organization, UNAIDS, UNICEF. Towards universal access: scaling up priority HIV/AIDS interventions in the health sector: Progress report 2009. Geneva (Switzerland): World Health Organization; 2009. Available at: http://data.unaids.org/pub/Report/2009/20090930_tuapr_2009_en.pdf. Accessed May 1, 2010.

62. US Census Bureau, Population Division, International Programs Center, Health Studies Branch. HIV/AIDS surveillance data base, Table 1: HIV1 seroprevalence. Available at: http://hivaidssurveillancedb.org/hivdb/MAP/tab1.htm. Accessed October 26, 2010.
63. Spensley A, Sripipatana T, Turner AN, et al. Preventing mother-to-child transmission of HIV in resource-limited settings: the Elizabeth Glaser Pediatric AIDS Foundation experience. Am J Public Health 2009;99(4):631–7.
64. Shaffer N, Chuachoowong R, Mock PA, et al. Short-course zidovudine for perinatal HIV-1 transmission in Bangkok, Thailand: a randomised controlled trial. Bangkok Collaborative Perinatal HIV Transmission Study Group. Lancet 1999; 353(9155):773–80.
65. Leroy V, Karon JM, Alioum A, et al. Twenty-four month efficacy of a maternal short-course zidovudine regimen to prevent mother-to-child transmission of HIV-1 in West Africa. AIDS 2002;16(4):631–41.
66. Gray GE, Urban M, Chersich MF, et al. A randomized trial of two postexposure prophylaxis regimens to reduce mother-to-child HIV-1 transmission in infants of untreated mothers. AIDS 2005;19(12):1289–97.
67. Dabis F, Msellati P, Meda N, et al. 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 multicentre trial. DITRAME Study Group. Diminution de la Transmission Mere-Enfant. Lancet 1999;353(9155):786–92.
68. Guay LA, Musoke P, Fleming T, et al. Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: HIVNET 012 randomised trial. Lancet 1999; 354(9181):795–802.
69. Guay LA, Hom DL, Kabengera SR, et al. HIV-1 ICD p24 antigen detection in Ugandan infants: use in early diagnosis of infection and as a marker of disease progression. J Med Virol 2000;62(4):426–34.
70. Nduati R. Breastfeeding and HIV-1 infection. A review of current literature. Adv Exp Med Biol 2000;478:201–10.
71. Kumwenda NI, Hoover DR, Mofenson LM, et al. Extended antiretroviral prophylaxis to reduce breast-milk HIV-1 transmission. N Engl J Med 2008;359(2): 119–29.
72. World Health Organization. Rapid advice: use of antiretroviral drugs for treating pregnant women and preventing HIV infection in infants. Geneva (Switzerland): World Health Organization; 2009. p. 1–23. Available at: http://www.searo.who.int/LinkFiles/HIV-AIDS_Rapid_Advice_MTCT%28web%29.pdf. Accessed May 20, 2010.
73. World Health Organization. Rapid advice: antiretroviral therapy for HIV infection in adults and adolescents. Geneva (Switzerland): World Health Organization; 2009. p. i–25. Available at: http://www.who.int/hiv/pub/arv/rapid_advice_art.pdf. Accessed May 20, 2010.
74. World Health Organization. Rapid advice: revised WHO principles and recommendations on infant feeding in the context of HIV. Geneva (Switzerland): World Health Organization; 2009. p. i–24. Available at: http://www.searo.who.int/LinkFiles/HIV-AIDS_Rapid_Advice_Infant_feeding%28web%29.pdf. Accessed May 20, 2010.
75. World Health Organization. Antiretroviral therapy for HIV infection in adults and adolescents: recommendations for a public health approach. 2010 revision. Geneva (Switzerland): World Health Organization; 2010. p. 1–145.

Available at: http://whqlibdoc.who.int/publications/2010/9789241599764_eng.pdf. Accessed August 18, 2010.
76. World Health Organization. Guidelines on HIV and infant feeding. Principles and recommendations for infant feeding in the context of HIV and a summary of evidence. 2010. p. 1–49. Available at: http://whqlibdoc.who.int/publications/2010/9789241599535_eng.pdf. Accessed August 18, 2010.
77. World Health Organization. Antiretroviral drugs for treating pregnant women and preventing HIV infection in infants. Recommendations for a public health approach. Geneva (Switzerland): WHO; 2010. p. 1–105. Available at: http://whqlibdoc.who.int/publications/2010/9789241599818_eng.pdf. Accessed August 18, 2010.
78. World Health Organization. PMTCT strategic vision 2010–2015: preventing mother-to-child transmission of HIV to reach the UNGASS and millennium development goals. Geneva (Switzerland): World Health Organization; 2010.
79. World Health Organization. Antiretroviral drugs for treating pregnant women and preventing HIV infection in infant: towards universal access. Recommendations for a public health approach. Geneva (Switzerland): World Health Organization; 2006. p. 1–92. Available at: http://www.who.int/hiv/pub/mtct/antiretroviral/en/index.html. Accessed May 30, 2010.
80. World Health Organization, UNICEF, UNAIDS, UNFPA. HIV and infant feeding: updated based on the technical consultation held on behalf of the inter-agency team (IATT) on prevention of HIV infections in pregnant women, mothers and their infants. Geneva (Switzerland), October 25–27, 2006. Geneva (Switzerland): World Health Organization; 2007. Available at: http://www.who.int/child_adolescent_health/documents/9789241595964/en/index.html. Accessed August 18, 2010.