SUPPLEMENT ARTICLE

Prevention in Neglected Subpopulations: Prevention of Mother-to-Child Transmission of HIV Infection

Lynne M. Mofenson

Pediatric, Adolescent and Maternal AIDS Branch, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Rockville, Maryland

Worldwide, >1000 children are newly infected with human immunodeficiency virus (HIV) each day; the majority of these children are in sub-Saharan Africa. The primary mode of HIV acquisition is through mother-to-child transmission (MTCT) during pregnancy, childbirth, or breastfeeding. In well-resourced health care systems, like those in the United States, universal HIV testing for pregnant women, provision of antiretroviral therapy (when needed for maternal health) or prophylaxis, elective cesarean delivery, and avoidance of breastfeeding has reduced MTCT of HIV infection to 1%–2%. However, in resource-limited countries, the perinatal epidemic continues generally unabated. Clinical trials have identified simple, less expensive, effective antiretroviral prophylaxis regimens that can be implemented in resource-limited settings. However, implementation has been slow, and postnatal transmission of HIV through breastfeeding remains a significant challenge. This article will review the research on prevention of MTCT of HIV infection in resource-limited countries and the challenges to expansion of the benefits of preventive interventions for MTCT throughout the world.

An estimated 430,000 children were infected with human immunodeficiency virus (HIV) worldwide in 2008 [1]. This translates to >1000 new infections in children each day, the majority of which occur in sub-Saharan Africa. The primary mode of HIV acquisition in children worldwide is through mother-to-child transmission (MTCT) during pregnancy, childbirth, or breastfeeding. Before the development of effective interventions to reduce MTCT of HIV infection, estimated transmission rates were 15%–25% among nonbreastfeeding populations in North America and Europe and 25%–40% among breastfeeding populations in resource-limited countries [2].

In well-resourced health care systems, such as those in the United States, there has been dramatic progress in reducing MTCT of HIV infection. Early identification of HIV infection in pregnant women through routine, opt-out antenatal HIV testing; immediate assessment of HIV-infected pregnant women for their need for treatment for their own health; and provision of antiretroviral treatment when needed or antiretroviral prophylaxis if therapy is not yet required has substantially reduced the risk of infection among infants during pregnancy and delivery. When combined with elective cesarean delivery and complete avoidance of breastfeeding, these interventions have reduced the risk of HIV transmission to 1%–2% [3].

However, in resource-limited countries, the perinatal HIV epidemic continues generally unabated. Clinical trials have identified simple, effective, and relatively inexpensive antiretroviral prophylaxis regimens that can be implemented in resource-limited settings [4, 5]. However, implementation has been slow. Lack of availability and access to family planning and antenatal services, low rates of HIV testing among pregnant women, and lack of integration of CD4 cell count testing and antiretroviral treatment services into the antenatal setting, compounded by human resource constraints and a lack of political will to prioritize maternal health and

The conclusions and opinions expressed in this article are those of the author and do not necessarily reflect those of the National Institutes of Health or US Department of Health and Human Services.

Reprints or correspondence: Dr Lynne M. Mofenson, Pediatric, Adolescent and Maternal AIDS Branch, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, 6100 Executive Blvd, Rm 4B11, Rockville, MD 20852 (LM65D@nih.gov).

Clinical Infectious Diseases 2010;50(S3):S130–S148

1058-4838/2010/5010S3-0010
DOI: 10.1086/651484

prevention of MTCT, have contributed to the slow pace of expansion of prevention coverage. In addition, postnatal HIV transmission through breastfeeding remains a significant challenge.

PREVENTION OF MTCT OF HIV INFECTION AND MATERNAL HEALTH

Prevention of MTCT of HIV infection cannot be viewed in isolation from optimization of maternal health and survival. Maternal and infant health are inextricably linked; uninfected infants born to HIV-infected women have higher rates of mortality than do infants born to uninfected women, and infant mortality is associated with advanced maternal disease [6]. Often, clinical research, policies, and country programs have narrowly focused on providing antiretroviral drugs to HIV-infected women for the sole purpose of preventing transmission to the infant, without recognizing that antenatal counseling and testing may be the only entry point for an infected woman to access antiretroviral treatment for her own health.

To maximize prevention of HIV transmission and maternal and infant survival, it is critical that care of both the mother and the infant is optimized. The World Health Organization (WHO) recommends a comprehensive strategic approach that includes 4 components (Table 1), which include routine offering of HIV testing and counseling to all pregnant women, antiretroviral treatment for HIV-infected women who require treatment and antiretroviral prophylaxis for prevention of transmission for those not yet needing treatment, counseling and support for infant feeding, and continued provision of care, treatment, and support for women (and their families) infected with HIV [7].

PRIMARY PREVENTION OF HIV INFECTION IN WOMEN AND PREVENTION OF UNINTENDED PREGNANCY

Prevention of HIV infection in women of childbearing age and prevention of unintended pregnancies among women infected with HIV are among the most cost-effective ways to prevent HIV infection in children. Although this articles primarily describes interventions to prevent MTCT of HIV infection from women, we also present a brief discussion of primary prevention of HIV infection, focused on prevention of acquisition during pregnancy, and avoidance of unintended pregnancy.

Primary prevention of HIV infection in pregnant women. Although a critical focus of attention for prevention of MTCT of HIV infection is the pregnant woman already infected with HIV, primary prevention of HIV infection in pregnant women found to be uninfected is also important. Although a study in Zimbabwe did not find pregnancy to be associated with increased risk of HIV acquisition, in a large study in Uganda, pregnant women had nearly twice the risk of acquiring HIV infection, compared with nonpregnant women, irrespective of their sexual behavior or their partners' plasma viral loads; similar results were found in a recent study from South Africa [8–10]. Increased risk of HIV acquisition during pregnancy, coupled with initial high levels of viral replication during acute infection, including that in genital secretions, could make pregnancy a mechanism for efficient transmission of HIV from male sex partners to pregnant women and subsequently to their infants. In resource-rich countries, a significant proportion of remaining vertical transmission occurs among women who acquire HIV infection during pregnancy [11]. In a study in Botswana, where repeat HIV testing was offered to 400 women in maternity wards and 244 women seen 9–15 months postpartum, all of whom had previously tested negative for HIV during pregnancy, 1.3% and 2.9%, respectively, had newly positive HIV test results [12]. The authors estimated that 43% of all infant HIV infections in Botswana in 2008 were attributable to incident maternal HIV infection acquired during pregnancy or postpartum. Thus, it remains very important for antenatal programs (and programs that access breastfeeding women) to stress the need for condom use to protect both mother and infant from HIV infection and also to involve the partners of pregnant women in risk-reduction strategies. HIV retesting during late pregnancy or labor (and during the breastfeeding period) offers an opportunity to identify women experiencing seroconversion to allow interventions for prevention of MTCT of HIV infection and to ensure care for these women.

Avoidance of unintended pregnancy. Worldwide, ~80 million (38%) of the 211 million pregnancies each year are unintended [13]. Unintended pregnancies account for 14%–58% of births in countries where HIV burden is greatest [14]. Several studies suggest that the rates of unintended pregnancy among HIV-infected women may be higher than those in the general population. In a study in South Africa, 84% of pregnancies in HIV-infected women were reported to be unplanned [15]. In

Table 1. Four Components of the World Health Organization Strategic Approach to Prevention of Pediatric HIV Infection

Prevention of HIV infection among young persons and pregnant women
Prevention of unintended pregnancies in HIV-infected women
Prevention of HIV transmission from HIV-infected women to their infants
Provision of treatment, care, and support to HIV-infected women and their families

Uganda, >90% of pregnancies were unintended among women enrolled in an antiretroviral treatment program [16]. A study in Côte d'Ivoire that involved 149 women who received a diagnosis of HIV infection during a previous pregnancy found 37 repeat pregnancies, of which 51% were unintended [17]. Meeting the contraceptive needs of HIV-infected women will greatly reinforce efforts to reduce the number of HIV-infected children. It is estimated that if all women in sub-Saharan Africa who did not wish to get pregnant accessed contraceptive services, as many as 160,000 new infant HIV infections could be averted every year [18].

ANTENATAL HIV TESTING AND COUNSELING

Because access to interventions to reduce MTCT of HIV infection requires a knowledge of maternal HIV serostatus, access to voluntary HIV testing and confidential counseling is critical. However, only 21% of women who became pregnant in low- and middle-income countries in 2008 received HIV testing [13]. Although this represents an increase from 15% in 2007, it remains far too low to allow a population response to prevention of pediatric HIV infection. HIV testing coverage among pregnant women in Africa in 2008 varied from 16% in western and central Africa to 28% in sub-Saharan Africa and 43% in eastern and southern Africa [13]. Six of the 10 African countries estimated to have the largest number of HIV-infected pregnant women (Kenya, Malawi, Mozambique, South Africa, Tanzania, and Zambia) have increased HIV testing coverage among pregnant women to 60%–80%. HIV testing coverage among pregnant women in Asia and in Latin America and the Caribbean in 2008 was 12% and 54%, respectively [13].

High uptake of testing can be achieved with routine provider-initiated HIV testing and counseling, combined with use of rapid tests offering same day results in antenatal and delivery settings. Studies have demonstrated that rapid point-of-care HIV tests have high diagnostic performance [19]. In Botswana, a shift from patient-initiated testing to provider-initiated routine testing increased the proportion of antenatal clients who accepted HIV testing from 76% to 95%; in urban Zimbabwe, rates of HIV testing increased from 65% to 99% when an opt-out, provider-initiated testing program was implemented [20, 21].

In the absence of provider-initiated testing and counseling in antenatal clinics, testing rates remain low, even in settings where rates of antenatal care attendance are high. Although these low rates are primarily attributable to lack of offering of the test, other factors involved include lack of test kits, inadequate counseling, a need to discuss with a male partner before making a decision, and fear of stigmatization [22]. Provision of couple counseling and testing has been shown to increase acceptance of HIV testing by pregnant women in studies from Burkina Faso, Cambodia, Kenya, Tanzania, and Uganda [23–28]. However, even in family-focused programs with free access to antiretroviral therapy, such as the MTCT-Plus program in Côte d'Ivoire, only 53% of 568 women indicated that they had disclosed their HIV status to their male partner, with reasons for nondisclosure including fear of accusations of infidelity, abandonment, discrimination, and violence [29]. Further research surrounding the issue of disclosure and involvement of male partners is needed.

For countries where rates of antenatal care attendance and facility-based deliveries are low, identification of HIV-infected pregnant women and provision of antiretroviral interventions is even more challenging. On a global basis, almost one-quarter of pregnant women do not receive any antenatal care [1, 30]. Innovative and creative approaches are needed in such settings, including ways to use the services of midwives and traditional birth attendants in provision of HIV testing and interventions for prevention of MTCT of HIV infection.

COMPARISON OF ANTIRETROVIRAL DRUGS FOR MATERNAL TREATMENT AND PROPHYLAXIS OF MTCT OF HIV INFECTION

Clinical research, policy makers, and country programs have too often emphasized provision of antiretroviral drugs solely for preventing MTCT of HIV infection without consideration of optimal treatment for the mother. Antiretroviral drugs are now available in resource-limited countries. Women who meet the criteria for treatment have lower CD4 cell counts and higher viral load than do women who do not meet the criteria and, thus, are the group at highest risk of transmission to their infant. A key issue in decisions related to which antiretroviral regimen to choose for an HIV-infected pregnant woman is whether the antiretroviral drugs are being provided for treatment or for prophylaxis of MTCT. Treatment in this context means that antiretroviral therapy is started during pregnancy and continued throughout life; in contrast, antiretroviral drugs given solely for prophylaxis would stop when the risk of MTCT is no longer present.

Although guidelines in both resource-rich and resource-limited countries recommend treatment for individuals with significant HIV-related symptoms, the CD4 cell count threshold for therapy initiation in individuals with mild or no symptoms has differed. In the 2006 WHO guidelines, the CD4 cell count threshold for starting treatment in individuals with WHO stage I or II disease was <200 cells/μL, whereas guidelines from resource-rich countries have a threshold of <350–500 cells/μL (with debate about whether an even higher CD4 cell count threshold may be beneficial) [31, 32]. In December 2009, the WHO revised its guidelines for treatment of HIV-infected adults, including pregnant women, to a CD4 cell count threshold of <350 cells/μL [5, 33]. For pregnant women, this higher threshold is particularly important in resource-limited settings.

Data from Zambia indicate that 84% of maternal deaths and 82% of postnatal infant infections involve women whose CD4 cell count is <350 cells/μL; by contrast, only ~55% of maternal deaths and ~47% of postnatal infections involve women whose CD4 cell counts are <200 cells/μL (Louise Kuhn, personal communication). Therefore, a CD4 cell count threshold of <350 cells/μL seems to be a more effective threshold for starting treatment for pregnant women, as it has the potential to prevent substantially more maternal deaths and infant HIV infections than does initiation of treatment at a CD4 cell count <200 cells/μL. Recent data from Haiti also suggest significant decreases in morbidity and mortality when treatment is initiated at a higher CD4 cell count of <350 cells/μL in a resource-limited country [34].

It is therefore critical that programs that provide HIV testing and interventions for prevention of MTCT of HIV infection for pregnant women also have available CD4 cell count assays to determine the need for therapy and provide treatment to women who require it for their own health. However, many programs are located in antenatal clinics that are not equipped to provide either CD4 cell count testing or HIV treatment, which tend to be provided in stand-alone clinics to which women have to be referred, creating a significant barrier to provision of treatment to pregnant women who need it.

DEBATE REGARDING OPTIMAL ANTIRETROVIRAL PROPHYLAXIS FOR PREVENTION OF MTCT OF HIV INFECTION

Provision of triple-drug antiretroviral prophylaxis to all pregnant and breastfeeding women has been suggested as a way to simplify prevention of MTCT of HIV infection. Of note, in resource-rich countries, triple-drug regimens are often used for prevention of MTCT for women who do not yet require treatment for their own health. However, in the United Kingdom, women with a CD4 cell count >350 cells/μL and an HIV RNA level <10,000 copies/mL may receive zidovudine (AZT) alone during pregnancy combined with elective cesarean delivery; in an analysis of data from the period 2000–2006 from the United Kingdom and Ireland, the rate of transmission among 464 women who received only AZT during pregnancy and elective cesarean delivery was 0% [3]. In the Thailand Perinatal HIV Prevention Trial-2 involving nonbreastfeeding women, AZT prophylaxis starting at 28 weeks of pregnancy plus single-dose nevirapine (NVP) prophylaxis resulted in infant infection rates of 1% among women with CD4 cell counts >200 cells/μL [35]. Finally, the Kesho Bora multicountry African study (Table 2) directly compared AZT prophylaxis starting at 28 weeks of pregnancy plus single-dose NVP prophylaxis (with 1-week postpartum prophylaxis with AZT and lamivudine [3TC]) with maternal triple-drug prophylaxis from 28 weeks of pregnancy through 6 months of breastfeeding in women with CD4 counts of 200–500 cells/μL [42]. In a comparison of infection rates at birth between the 2 antepartum regimens in women in this CD4 cell count strata, transmission was 1.8% (95% confidence interval, 0.8%–3.7%) with maternal triple-drug prophylaxis and 2.2% (95% confidence interval, 1.2%–4.3%) with maternal AZT and single-dose NVP prophylaxis (the data are not statistically significantly different).

Although use of triple-drug prophylaxis for all women in resource-limited countries is a seemingly attractive alternative, there are several issues that must be considered. For women who require therapy for their own health, the benefit of reversing maternal HIV disease progression and improving survival with triple-drug antiretroviral therapy outweighs any theoretical risks of in utero exposure of the infant to multiple drugs. When 3 drugs are not being administered for maternal treatment but rather as solely prophylaxis to prevent MTCT of HIV infection, the risk of maternal drug toxicities, treatment interruption (presuming treatment stops after risk of MTCT ceases), fetal exposure to multiple drugs, and cost need to be weighed against the potential incremental benefit of triple-drug prophylaxis in preventing MTCT, compared with less complex regimens. In addition, universal triple-drug prophylaxis for pregnant women does not eliminate the need for prompt evaluation of CD4 cell count for determination of whether the drugs should be stopped after risk of MTCT has ceased, unless all pregnant women who receive triple-drug prophylaxis continue to receive lifelong therapy.

In resource-rich countries, protease inhibitor–based triple-drug prophylaxis is typically used for prophylaxis in women with CD4 cell counts >250 cells/μL [43]. In resource-limited countries, the choice of drugs for triple-drug prophylaxis is more problematic. The recommended first-line therapy in such settings is nonnucleoside reverse-transcriptase inhibitor (NNRTI)–based triple-drug prophylaxis, because of the expense of protease inhibitors [31, 33]. However, an increased risk of symptomatic and fatal acute hepatic events has been reported when NVP is used in women with higher CD4 cell counts [44, 45]. The available alternative NNRTI efavirenz may be associated with teratogenicity if received during early pregnancy, posing a problem with prolonged use during breastfeeding, when repeat pregnancy could occur [43]. The incidence of repeat pregnancy among HIV-infected women in Abidjan was 16.5 pregnancies per 100 women-years at risk during the first 24 months postpartum [46].

Safety concerns have been raised about the potential impact of receipt of repeated courses of triple-drug prophylaxis for prevention of MTCT of HIV infection during pregnancy and/or breastfeeding for women not requiring treatment for their own health. Multiple sequential pregnancies are common in resource-limited countries, where family planning is limited and there are significant cultural pressures for large families [15–17]. The Strategies for Management of Antiretroviral Ther-

Table 2. Published and/or Presented Studies of Infant Antiretroviral Prophylaxis to Prevent Postnatal HIV Transmission through Breast Milk

Study (reference)	Country (year)	Maternal antepartum and/or infant antiretroviral prophylaxis	No. of infants	Median maternal CD4 cell count, cells/μL	Infant feeding	Rate of HIV transmission at birth and at 4–6 weeks	Rate of HIV transmission at 6–7 months
Mashi (Thior et al [36])	Botswana (2006)	No CD4 cell count restriction; mother: AZT 34 weeks to delivery (with or without sdNVP); infant: AZT to 6 months if breastfeeding (with or without sdNVP)	Formula feeding: 591 infants; breastfeeding: 588 infants	372 (breastfeeding)	Formula and breastfeeding; breastfeeding median duration 5.9 months	Birth: 3.3% (19/558 breastfed); cumulative at 4 weeks: 4.6% (27/557 breastfed); increment between day 1 and 4 weeks: 1.3%	Cumulative at 7 months: 9.0% (51/541 breastfed); increment between 4 weeks and 7 months: 4.4%
Mitra (Kilewo et al [37])	Tanzania (2008)	No CD4 cell count restriction; mother: AZT plus 3TC 36 weeks to 1 week postpartum; infant: AZT plus 3TC for 1 week, then daily 3TC to 6 months	Breastfeeding: 398 infants	411 (<200 for 15.4%)	Breastfeeding only, median duration 18 weeks	Birth: No data; cumulative at 6 weeks: 3.8% (95% CI, 2.0%–5.6%)	Cumulative at 6 months: 4.9% (95% CI, 2.7%–7.1%); increment between 6 weeks and 6 months: 1.2% (95% CI, 0%–2.4%)
Simba (Vyankandondera et al [38])	Uganda, Rwanda (2003)	No CD4 cell count restriction; mother: AZT plus ddI 36 weeks to 1 week postpartum; infant: randomized at birth to daily 3TC or NVP to 6 months	Breastfeeding: 397 infants (199 randomized to 3TC, 198 to NVP; no difference between arms)	427	Breastfeeding only, median duration 100–107 days (~3.3 months)	Birth: 6.0% (24/397 infants); cumulative at 4 weeks: 6.8%; increment from 1 week to 4 weeks: 0.8% (3/373 infants)	Cumulative at 6 months: 7.6% (30/397 infants) (95% CI, 5–14%); increment between 4 weeks and 6 months: 0.8% (3/358 infants)
SWEN (SWEN Study Group [39])	Ethiopia, Uganda, India (2008)	No CD4 restriction; mother: late presenter, no antepartum antiretrovirals; infant: sdNVP, and randomized to daily placebo vs extended NVP from day 8 to 6 weeks	Breastfeeding: 2074 infants (placebo 1047, extended NVP 977); uninfected at birth and data at 6 months: placebo (928), extended NVP (831)	397	Breastfeeding only, most wean between 14 weeks (73% breastfeeding) and 6 months (31% breastfeeding)	Extended NVP arm; birth: 4.7%; cumulative at 6 weeks: 7.2%; increment from day 1 to 6 weeks: 2.5% extended NVP	Cumulative at 6 months: 11.6%; increment between 6 weeks and 6 months: 4.4%
PEPI-Malawi (Kumwenda et al [40])	Malawi (2008)	No CD4 restriction; mother: late presenter, no antepartum antiretrovirals; infant: sdNVP plus 1 week AZT, and randomized to daily placebo vs NVP vs NVP/AZT from day 7 to 14 weeks	Breastfeeding: 3016 infants (placebo 989, extended NVP 993, extended NVP/AZT 980); uninfected at birth and data at 9 months: placebo (788), extended NVP (800), extended NVP/AZT (801)	379–401	Breastfeeding only, most wean between 6 months (90% breastfeeding) and 9 months (29%–32% breastfeeding)	Extended NVP or NVP/AZT; birth: 7.1% extended NVP and NVP/AZT; cumulative at 6 weeks: 8.8% extended NVP and 8.7% NVP/AZT; increment between day 1 and 6 weeks: 1.7% extended NVP and 1.6% NVP/AZT	Cumulative at 6 months: 11.1% extended NVP, 12.3% extended NVP/AZT; increment between 6 weeks and 6 months: 2.3% extended NVP, 3.6% extended NVP/AZT
BAN (Chasela et al [41])	Kenya (2009)	Mother, CD4 cell count >250: late presenter, no antepartum antiretrovirals; infant: sdNVP plus 1 week AZT/3TC, then daily NVP from day 7 to 6 months	Breastfeeding: 848 enrolled in infant NVP arm; uninfected at birth and data at 6 months: 848	440	Breastfeeding only, duration not specified, counseled to wean at 6 months	Birth: enrolled at delivery, rates based on uninfected at 2 weeks; cumulative at 6 weeks: not specified	Cumulative at 7 months (uninfected at 2 weeks): 1.8%; increment between 2 weeks and 6 months: 1.8%

NOTE. AZT, zidovudine; BAN, Breastfeeding, Antiretrovirals and Nutrition; CI, confidence interval; ddI, didanosine; NVP, nevirapine; PEPI-Malawi, Post-Exposure Prophylaxis of the Infant–Malawi; sdNVP, single-dose NVP; SWEN, Six-Week Extended Nevirapine; 3TC, lamivudine.

apy study found an increased risk of disease progression among individuals who discontinued antiretroviral therapy when their CD4 cell count was >350 cells/μL, compared with those who received treatment and never stopped [47, 48]. Although that study was conducted among adults who required treatment for their own health, the impact of repeatedly starting and stopping triple-drug prophylaxis on women who receive it only for prevention of MTCT needs to be studied.

Controversy remains about the association of triple-drug prophylaxis during pregnancy with preterm delivery or low birth weight [49–53]. In a study involving 326 women in Côte d'Ivoire, the risk of birth weight <2500 g was significantly higher (22%) among women who received an NVP-based triple-drug regimen during pregnancy than in an earlier cohort of women with similar CD4 cell counts who received a short-course AZT or AZT plus 3TC regimen during pregnancy (12%; $P = .02$) [53]. In the Mma Bana study in Botswana, which compared 2 different triple-drug prophylaxis regimens (AZT, 3TC, and abacavir vs AZT, 3TC, and lopinavir-ritonavir), the protease inhibitor–based regimen was associated with significantly higher rates of preterm delivery than was the triple-nucleoside regimen (23% vs 15%; $P = .04$) [54]. Further evaluation of the potential association of triple-drug prophylaxis with pregnancy outcome is critically needed in resource-limited countries as use of 3-drug regimens for treatment and/or prophylaxis for MTCT of HIV infection is rolled out.

The long-term risks of fetal exposure to multiple antiretroviral drugs are not known [55, 56]. Short-term risks appear to be minimal, but there is currently <15 years of experience with administration of multiple antiretroviral drugs during pregnancy. A recent modeling study reassuringly suggested that the risk of mitochondrial toxicity due to triple-drug prophylaxis during pregnancy is at least an order of magnitude lower than the risk of HIV infection with use of less effective regimens [57]. However, long-term follow-up of antiretroviral-exposed but uninfected children in resource-limited countries is also important as triple-drug regimens for treatment and/or prophylaxis for MTCT of HIV infection are increasingly used during pregnancy.

Thus, for the subset of women with CD4 cell counts >350 cells/μL who do not meet treatment criteria, there are critical yet unanswered questions regarding the risks, benefits, and prophylactic efficacy of less complex regimens, compared with triple-drug prophylaxis. Table 3 shows ongoing and planned clinical trials that may directly address these questions in the next few years.

INFANT FEEDING AND PREVENTION OF POSTNATAL TRANSMISSION OF HIV INFECTION THROUGH BREASTFEEDING

The only method known to completely eliminate breastfeeding-associated HIV transmission is not to breastfeed; this is recommended in settings in which infant replacement feeding is affordable and sustainable, clean water is widely available, hygiene and sanitation conditions are good, and death due to diarrhea and other infectious diseases is relatively uncommon. However, this approach is neither feasible nor safe in many resource-limited countries because of cost, inadequate replacement foods to meet the nutritional needs of the infant, unsafe water supply, and/or low acceptability because of stigma associated with not breastfeeding.

Thus, there is a critical need to identify strategies to prevent breastfeeding-associated HIV transmission. Exclusive breastfeeding has been shown in observational studies to lower the risk of postnatal transmission, compared with mixed feeding, but does not eliminate risk [58–60]. Two potential prevention strategies under study in resource-limited settings are provision of antiretroviral drugs to infants exposed to HIV during breastfeeding (Table 2) and provision of triple-drug prophylaxis to lactating women (Table 4) [36–42, 54, 61–65]. However, many of these studies have treated all women the same, regardless of maternal health and CD4 cell count. HIV-infected breastfeeding women need to be assessed for their need for treatment and initiate combination antiretroviral therapy when eligible. Women who require treatment for their own health (eg, women with a CD4 cell count <350 cell/μL) are at greatest risk of postnatal transmission to their infant and should receive combination antiretroviral therapy for their own health and continue therapy after cessation of breastfeeding; this will also decrease postnatal MTCT of HIV infection. The question of what is optimal prophylaxis for postnatal transmission (in which therapy is stopped after breastfeeding cessation) should be restricted to women who do not require treatment for their own health.

Both maternal and infant antiretroviral interventions evaluated to date are predicated on early weaning of the infant, generally at or before 6 months of age. However, increasing data suggest that early weaning at 4–6 months of age may be associated with increased risk of malnutrition and infant mortality associated with infectious diseases in HIV-exposed infants [66–70]. Therefore, evaluation of the safety, additional efficacy, and cost-effectiveness of more extended postnatal prophylaxis (ie, for >6 months) to allow for more prolonged breastfeeding is warranted. Several clinical trials will evaluate longer durations of infant or maternal prophylaxis (9–18 months) (Table 3).

There are major difficulties in comparing the studies of maternal and infant prophylaxis of postnatal transmission. For example, antepartum antiretroviral drug administration and duration (if given) differ between studies but are clearly important in terms of prevention of in utero infection and comparisons of cumulative risk of infection; the duration of postnatal prophylaxis differs between studies; rates of exclusive breastfeeding differ; the duration of breastfeeding and, thus,

Table 3. Ongoing and Planned Studies on Prevention of Mother-to-Child HIV Transmission

Study (location)	Design	Infant feeding	Enrolled	Antepartum regimen	Intrapartum regimen	Postpartum maternal regimen	Postpartum Infant Regimen	Comments
BAN [41] (Malawi)	Intrapartum/postpartum intervention to reduce postnatal MTCT in women with CD4 cell count >250 cells/μL: postpartum maternal triple drug vs infant NVP prophylaxis; includes randomization to maternal nutritional supplement or not for 6 months postpartum	Breastfeeding	2637 randomized	No drugs, enrolls at labor	CD4 cell count >250 cells/μl; arm 1 (control): sdNVP/AZT/3TC; arm 2 (maternal triple-drug prophylaxis): sdNVP/AZT/3TC; arm 3 (infant prophylaxis): sdNVP/AZT/3TC	Arm 1: AZT/3TC for 1 week; arm 2: AZT/3TC for 1 week; AZT/3TC/LVP-rtv day 7 to 6 months; arm 3: AZT/3TC for 1 week	Arm 1: sdNVP plus AZT/3TC for 1 week; arm 2: sdNVP plus AZT/3TC for 1 week; arm 3: sdNVP plus AZT/3TC for 1 week; then daily NVP day 7 to 6 months	March 2008: DSMB recommended control arm 1 close as at least 1 experimental arm superior (not powered to detect difference between arms 2 and 3); 7 month MTCT (in infants uninfected at age 2 weeks): control (6.4%), maternal HAART (3.0%), infant NVP (1.8%); maternal HAART vs control ($P = .003$), infant NVP vs control ($P < .001$), maternal HAART vs infant NVP ($P = .12$)
Kesho Bora [42] (Kenya, South Africa, Burkina Faso)	Antepartum/intrapartum/postpartum intervention to reduce MTCT in women with CD4 cell count of 200–500 cells/μL: Maternal triple drug vs short course AZT/sdNVP prophylaxis; observational cohorts for women with CD4 cell count <200 cell/μL (receive triple-drug prophylaxis) and ⩾500 cells/μL (receive AZT/sdNVP)	Breastfeeding (~77%) and formula feeding	824 randomized, 250 observational	CD4 cell count of 200–500 cells/μL: starting at 34–36 weeks; arm 1 (maternal triple-drug prophylaxis): AZT/3TC/LPV-rtv; arm 2 (short course AZT): AZT	Arm 1: AZT/3TC/LPV-rtv; arm 2: AZT/sdNVP	Arm 1: AZT/3TC/LPV-rtv for 6 months; arm 2: no drugs	Arm 1: sdNVP plus AZT for 1 week; arm 2: sdNVP plus AZT for 1 week	MTCT at birth (in utero infection); maternal HAART: 1.8% (0.8%–3.7%); short course AZT: 2.2% (1.2%–4.3%); MTCT from birth 6 to months (postpartum HAART vs no prophylaxis): maternal HAART (3.1%), short course AZT (6.3%); overall MTCT at 12 months: maternal HAART (5.5%) [3.6%–8.4%]), short course AZT (9.5% [6.9%–13.0%]); difference between maternal HAART and short-course significant for strata of women with CD4 cell count of 200–350 cells/μL ($P = .044$), but not for women with CD4 cell count of 350–500 cells/μL ($P = .33$); observational CD4 cell count <200 cells/μL: MTCT at 12 months (7.6%); observational CD4 cell count ⩾500 cells/μL: MTCT at 12 months (5.8%)
Mma Bana [54] (Botswana)	Antepartum/intrapartum/postpartum intervention comparing 2 triple drug prophylaxis regimens to prevent postnatal MTCT in women with CD4 cell count ⩾200 cells/μL; observational cohort for women with CD4 cell count <200 cell/μL (receive NVP-based combination treatment)	Breastfeeding	560 randomized, 140 observational	CD4 cell count ⩾200 cells/μL; starting at 18–34 weeks; arm 1 (maternal triple-drug prophylaxis): AZT/3TC/ABC; arm 2 (maternal triple-drug prophylaxis): AZT/3TC/LPV-rtv	Arm 1: AZT/3TC/ABC; arm 2: AZT/3TC/LPV-rtv	Arm 1: AZT/3TC/ABC for 6 months; arm 2: ZDV/3TC/LPV/rtv for 6 months	Arm 1: sdNVP plus AZT for 4 weeks; arm 2: sdNVP plus AZT for 4 weeks	MTCT at birth: AZT/3TC/ABC (1.1%), AZT/3TC/LPV-r (0.4%); MTCT at 6 months (cumulative): AZT/3TC/ABC (1.8%), AZT/3TC/LPV-r (0.4%); no significant difference 6 months MTCT between HAART regimens ($P = .53$); observational CD4 cell count <200 cells/μL: MTCT at 6 months, 0.6%

HPTN 046 (Uganda, Zimbabwe, South Africa, Tanzania)	Postpartum intervention comparing infant NVP prophylaxis 6 weeks vs 6 months to prevent postnatal MTCT; 2-arm randomized, placebo-controlled	Breastfeeding	1576 (enrolling)	Outside study	Outside study	Outside study	All: sdNVP plus daily NVP from age 7 days to 6 weeks, then randomized; arm 1: daily NVP from age 6 weeks to 6 months; arm 2: daily placebo from age 6 weeks to 6 months	Study enrolling
PHPT-5 (Thailand)	Antepartum/intrapartum/postpartum intervention evaluating whether maternal NVP is needed for efficacy of sdNVP, and comparing short course AZT/sdNVP to short course AZT/protease inhibitor	Formula feeding	1992	CD4 cell count >250 cells/μL; starting at 28 weeks; arm 1: AZT; arm 2: AZT; arm 3: AZT/LPV-rtv	Arm 1: sdNVP plus AZT/3TC; arm 2: placebo plus AZT; arm 3: AZT/LPV-rtv	Arm 1: AZT/3TC for 7 days; arm 2: placebo for 7 days; arm 3: no drugs	Arm 1: sdNVP birth and 48 hours plus AZT for 1 week; arm 2: sdNVP birth and 48 h plus AZT for 1 week; arm 3: AZT for 1 week	Started spring 2009
ANRS-PEP (Burkina Faso, South Africa, Uganda, Zambia)	Postpartum intervention comparing infant prophylaxis during breastfeeding for 9 months to no prophylaxis	Breastfeeding	1500 (in planning)	Infant enrolled postpartum	Infant enrolled postpartum	Infant enrolled postpartum	Arm 1: sdNVP at birth; 3TC from day 7 to 9 months; arm 2: sdNVP at birth; placebo from day 7 to 9 months	Starting late 2009
PROMISE-IMPAACT 1077 (multiple countries in Africa, Asia, South America, United States)	For women who do not require treatment for own health (CD4 cell count >350 cells/μL), will address: What is optimal antepartum regimen to prevent MTCT? What is optimal postpartum regimen to prevent postnatal MTCT? Is it safe for mothers to stop triple drug prophylaxis after receiving only for prevention of MTCT? How to maintain health of uninfected infants after weaning?; resource-limited countries: antepartum/intrapartum/postpartum intervention in women with CD4 cell count >350 cells/μL, undergo sequential randomizations; United States/South America: only participate in the maternal health randomization	Breastfeeding and formula feeding	~6000 mother-infant pairs resource-limited, 2000 United States/South America	CD4 cell count >350 cell/μL; starting at 28 weeks; antepartum randomization; arm 1 (short-course AZT): AZT; arm 2 (maternal triple-drug prophylaxis) AZT/3TC/LPV-rtv	Arm 1: sdNVP plus TDF/FTC (and for 7 days postpartum); arm 2: AZT/3TC/LPV-rtv (and for 7 days postpartum)	CD4 cell count >350 cells/μL; new Postpartum randomization at day 7: arm 3 (infant prophylaxis): no ART, arm 4 (maternal triple-drug prophylaxis): TDF/FTC/ LPV-rtv from day 7 to cessation breastfeeding (up to 18 months); Maternal Health randomization: (a) if formula feeding and mother on triple-drug prophylaxis (arm 2), at day 7–12 if CD4 cell count >350 cells/μL; (b) if breastfeeding and mother on triple-drug prophylaxis (arm 4), at cessation of weaning, if CD4 cell count >350 cells/μL; (c) if in United States/South America receive triple-drug prophylaxis during pregnancy and if CD4 cell count >400 cells/μL: randomize to arm 1: stop triple-drug prophylaxis; arm 2: continue triple-drug prophylaxis	New Postpartum randomization at day 7 arm 3 (infant prophylaxis): sdNVP plus AZT for 7 days then infant NVP from day 7 to cessation breastfeeding (up to 18 months); arm 4 (maternal triple-drug prophylaxis): sdNVP plus AZT for 7 days; new Infant Health randomization: breastfeeding, infant uninfected and <12 months at time breastfeeding cessation; arm 1: TMP-SMX to 18 months; arm 2: TMP-SMX placebo to 18 months	In planning, to start: United States/South America (winter 2009), resource-limited countries (2010)
ANRS 12200 (Côte d'Ivoire)	Antepartum/intrapartum/postpartum intervention comparing 2 triple-drug prophylaxis regimens to prevent MTCT; randomized trial (noninferiority design)	Breastfeeding and formula feeding	Unknown	Starting at 20 weeks; arm 1 (maternal triple-drug prophylaxis): TDF/FTC/EFV; arm 2 (maternal triple-drug prophylaxis): AZT/3TC/LPV-rtv	Arm 1: TDF/FTC/EFV; arm 2: AZT/3TC/LPV-rtv	If breastfeeding, continue 6–9 months postpartum; arm 1: TDF/FTC/EFV; arm 2: AZT/3TC/LPV-rtv	AZT for 1 week?; arm 1: AZT for 1 week? arm 2: AZT for 1 week?	In planning, to start 2010

NOTE. ABC, abacavir; ANRS-PEP, Agence Nationale de Recherche sur le SIDA Post-Exposure Prophylaxis; ART, antiretroviral therapy; AZT, zidovudine; BAN, Breastfeeding, Antiretrovirals and Nutrition; EFV, efavirenz; FTC, emtricitabine; HAART, highly active antiretroviral therapy; HPTN 046, HIV Prevention Trials Network protocol 046; LPV-rtv, lopinavir-ritonavir; MTCT, mother-to-child transmission; NVP, nevirapine; PHPT-5, Perinatal HIV Prevention Trial-5; PROMISE-IMPAACT 1077, Promoting Maternal Infant Survival Everywhere–International Maternal Pediatric Adolescent AIDS Clinical Trials Network protocol 1077; sdNVP: single-dose NVP; TDF, tenofovir; 3TC, lamivudine; TMP-SMX, trimethoprim-sulfamethoxazole.

the time at risk of postnatal infection, is not specified in several studies; and several studies do not provide birth infection rates, making it difficult to compare incremental benefit of interventions during the breastfeeding period, because the proportion of transmission occurring in utero cannot be determined.

Given these caveats, the currently available data suggest that provision of antiretroviral prophylaxis to the breastfeeding infant may have comparable efficacy to provision of triple-drug prophylaxis to the lactating mother. Early postnatal infection rates (from birth to 4–6 weeks of age) were 0%–1.5% in the 4 maternal studies (Amata, Kisumu Breastfeeding Study [KiBS], Kesho Bora, and Mma Bana) (Table 4) and 0.8%–2.5% in the 4 infant studies (Mashi, Post-Exposure Prophylaxis of the Infant [PEPI]–Malawi, Simba, and Six-Week Extended Nevirapine [SWEN] study) (Table 2), with adequate data for a meaningful comparison. Late postnatal infection rates (from 4–6 weeks to 6–9 months of age) were 0.4%–3.0% in the 7 maternal studies (Amata; Breastfeeding, Antiretroviral and Nutrition [BAN] study; Dream; Kesho Bora; KiBS; Mitra-Plus; and Mma Bana) (Table 4) and 0.8%–4.4% in the 4 infant studies in which prophylaxis was given for 6 months (BAN, Mashi, Mitra, and Simba) (Table 2), to allow comparison of prophylaxis administered over periods similar to those in the maternal studies.

The Mitra study of infant prophylaxis and the Mitra-Plus study of maternal prophylaxis provide a better comparison of interventions, because both were conducted sequentially in the same clinics, both provided some maternal antepartum antiretroviral prophylaxis, and both provided the same duration (6 months) of maternal or infant postnatal prophylaxis [37, 64]. The cumulative transmission risk at 6 months was 4.9% with infant prophylaxis in Mitra and 5.0% with maternal prophylaxis in Mitra-Plus, and the risk of late transmission from 6 weeks to 6 months was 1.2% with infant prophylaxis and 1.0% with maternal prophylaxis.

Data from a randomized comparison of maternal and infant interventions for prevention of postnatal transmission are available from the BAN study, which compared 6 months of postnatal maternal HAART or infant NVP prophylaxis with a control short-course arm with no extended maternal or infant prophylaxis during breastfeeding (Table 2) [41]. The transmission rate at age 7 months among infants uninfected at 2 weeks of age was 6.4% in the control arm, compared with 3.0% in the maternal HAART arm ($P = .003$) and 1.8% in the infant NVP arm ($P < .001$). Although the transmission rate in the infant NVP arm was lower than that in the maternal HAART arm, there was not a significant difference between the 2 rates ($P = .12$), and the study was not powered to detect a difference between these 2 arms.

REVISED DECEMBER 2009 WHO GUIDELINES FOR PREVENTION OF MTCT OF HIV INFECTION

The WHO recently revised their guidelines on use of antiretroviral drugs for prevention of MTCT of HIV infection; on the basis of the aforementioned studies, for the first time, these guidelines include recommendations for antiretroviral prophylaxis to prevent transmission through breastfeeding [5]. These recommendations place increased emphasis on improving maternal health while providing maximal protection against HIV transmission to the infant. Lifelong treatment with combination antiretroviral therapy, started as soon as possible during pregnancy, is recommended for all pregnant women with severe or advanced clinical disease or with a CD4 cell count <350 cells/μL, regardless of symptoms. For women with a CD4 cell count >350 cell/μL, earlier initiation of antiretroviral prophylaxis (at 14 weeks or as soon as possible thereafter) is recommended. Two different options are discussed for prophylaxis: (1) maternal antepartum AZT with intrapartum single-dose NVP, AZT plus 3TC continued for 7 days postpartum, and daily infant NVP from birth to the end of the breastfeeding period or (2) a 3-drug regimen given to the mother during pregnancy until the end of the breastfeeding period, with 6 weeks of infant antiretroviral prophylaxis after birth. Currently available data suggest that both prophylaxis approaches would have similar efficacy, and choice involves weighing a number of considerations, including relative costs, feasibility, risks, and benefits of the intervention, as discussed above.

Infant feeding guidelines have also been revised to recommend that national or subnational health authorities should decide whether health services will principally counsel and support HIV-infected mothers to either avoid all breastfeeding or to breastfeed and receive infant or maternal antiretroviral prophylaxis [71]. If the approach chosen is to recommend breastfeeding, HIV-infected women should exclusively breastfeed their infants for the first 6 months of life and introduce complementary foods thereafter while continuing breastfeeding for the first 12 months of life; breastfeeding should stop after a nutritionally adequate and safe diet without breast milk can be provided. Gradual weaning over the course of 1 month is recommended, with infant or maternal antiretroviral prophylaxis continued until 1 week after breastfeeding is fully stopped. Because laboratory evidence demonstrates that heat treatment of expressed milk can inactivate HIV [72], the guidelines also note that use of heat-treated, expressed breast milk may be considered as an interim feeding strategy in special circumstances (eg, if the mother is temporarily unable to breastfeed, if antiretroviral drugs are temporarily not available, or to assist in stopping breastfeeding).

ANTIRETROVIRAL DRUG RESISTANCE

Selection of NNRTI-resistance mutations after use of single-dose NVP for prevention of MTCT of HIV infection in women and in infants who become infected despite prophylaxis is well documented and is attributable to the long half-life of NVP, coupled with the fact that a single mutation in the viral codon confers drug resistance [73]. There is a wide range in resistance rates, which vary by maternal CD4 cell count and viral load at the time of exposure, viral subtype, whether other antiretroviral drugs were given in addition to single-dose NVP, the type of resistance assay, and for infants, whether the mother received single-dose NVP (Table 5) [74–97]. Women who require treatment for their own health are also at greatest risk for development of resistance after single-dose NVP treatment; identification of such women and initiation of lifelong combination antiretroviral therapy during pregnancy will avoid the development of resistance in this group.

Although resistance is frequent during the first few weeks to months after exposure, frequency of detection decreases with time. However, low levels of virus with resistance mutations can persist for prolonged periods and, in some cases, can remain present in latently infected cells [98, 99]. The long-term relevance of the selection of NNRTI resistance for response to future antiretroviral therapy in both women and infected children is under study; current data suggest that women starting NNRTI-based therapy within 12–24 months after single-dose NVP exposure have higher rates of viral failure than do those without single-dose NVP exposure [100–103].

However, administration of antiretroviral drugs for a period after single-dose NVP therapy (use of a "tail" regimen) can reduce the development of resistance to very low levels. Regimens studied for prevention of resistance include administration of AZT and 3TC for 4–7 days after single-dose NVP therapy; tenofovir and emtricitabine as a single dose during labor or for 7 days postpartum; administration of AZT, didanosine, and lopinavir-ritonavir for 7 or 30 days; and administration of AZT and didanosine for 30 days (Table 5) [89–95]. NNRTI resistance rates of 0%–7% at 2–6 weeks postpartum, as determined by ultrasensitive assays, have been reported with use of some of these tail regimens (Table 5) [91–95]. Thus, use of a minimum of 7 days of a tail regimen after use of single-dose NVP (alone or with AZT) as prophylaxis for MTCT is recommended to reduce drug resistance in women. Resistance among infants who become infected despite single-dose NVP therapy can also be reduced by the addition of a short course of antiretroviral treatment (Table 5); rates of resistance were lower among infants who received 3–7 days of AZT or AZT plus 3TC therapy after single-dose NVP therapy [89, 95, 96].

RESISTANCE AND POSTNATAL INFANT OR MATERNAL PROPHYLAXIS FOR TRANSMISSION THROUGH BREAST MILK

There are also concerns regarding potential drug resistance in infants infected postnatally despite either infant or maternal antiretroviral prophylaxis interventions, and additional studies are needed to better define risk. High rates of NVP resistance were seen in breastfed infants in the SWEN study of infant NVP prophylaxis: 92% of infants who became infected during the first 6 weeks of life—during the period of NVP prophylaxis—had NNRTI resistance, compared with 38% in the control arm who were exposed to single-dose NVP only (Table 5) [39, 97]. However, the risk of NNRTI resistance among infants who became infected after prophylaxis had ceased (after 6 weeks of age) was similar (15% among infants exposed to single-dose NVP prophylaxis and among infants who received the extended 6-week NVP infant prophylaxis regimen). Whether the extended NVP plus AZT infant prophylaxis regimen in the PEPI-Malawi study (Table 2) will reduce NVP resistance in infants infected despite prophylaxis is under study [40].

Antiretroviral drug resistance has also been observed in infants infected despite maternal triple-drug prophylaxis. Drug-resistant virus was identified in 67% of the 24 infants infected postnatally in the KiBS (Table 4) of maternal triple-drug prophylaxis for postnatal transmission [63, 104]. Some antiretroviral drugs are known to enter breast milk in varying amounts. 3TC appears to concentrate in breast milk and is present at levels 3–5 times those in maternal plasma, and AZT appears to be present in breast milk at levels similar to or somewhat less than those in maternal plasma [105]. NVP levels in breast milk are only 60%–75% of those in maternal plasma, and the protease inhibitors that have been studied have had very limited penetration in milk [106]. Thus, breastfed infants of mothers receiving triple-drug prophylaxis who become infected may be ingesting subtherapeutic levels of antiretroviral drugs present in breast milk and, therefore, can develop drug-resistant virus.

OBSTACLES, GAPS, AND THE WAY FORWARD

Although debate remains regarding the optimal antiretroviral intervention to reduce MTCT of HIV infection and results from ongoing and new clinical trials are eagerly awaited, there is no doubt that we currently have the tools to significantly impact the HIV epidemic affecting children. The ability to implement programs for prevention of MTCT of HIV infection is less tied to financing the purchase of the drug regimens or choice of regimen than to the development and support of the maternal-child health infrastructure required for implementation of such programs.

Table 4. Published and Presented Studies of Maternal Triple–Antiretroviral Drug Prophylaxis to Prevent Postnatal HIV Transmission through Breast Milk

Study (reference)	Location (year)	Maternal triple-drug administration	No. of participants	Median maternal CD4 cell count, cells/μL	Infant feeding	HIV transmission at birth and 4–6 weeks	HIV transmission at 6–7 months
Dream (Marazzi et al [61])	Mozambique (2007)	No CD4 cell count restriction; median 26.8 weeks gestation to 6 months postpartum if breastfeeding	985 mothers enrolled; 707 infants tested at 1 month, 467 infants tested at 6 months; did not specify percentage formula feeding vs breastfeeding	489	Formula and breastfeeding; breastfeeding duration not specified	Birth: no data; cumulative at 4 weeks: 3.8% (95% CI, 3.1%–4.5%)	Cumulative at 6 months: 5.3%; increment between 4 weeks to 6 months: 1.5% (95% CI, 0.9%–2.1%)
Dream (Palombi et al [62])	Mozambique (2007)	No CD4 cell count restriction; 25 weeks gestation to 6 months postpartum if breastfeeding	Formula feeding: 891, data on 809 infants; breastfeeding: 341 infants tested at 1 month, 251 infants tested at 6 months	Not specified	Formula and breastfeeding; breastfeeding duration not specified	Birth: no data; cumulative at 4 weeks: 1.2% (4/341 breastfed)	Cumulative at 6 months: 2.0% (6/266 breastfed) (95% CI, 0.6%–3.8%); increment between 4 weeks to 6 months: 0.8% (2/251 breastfed) (95% CI, 0.1%–2.8%)
KiBS (Thomas et al [63])	Kenya (2008)	No CD4 cell count restriction; 34 weeks gestation to 6 months postpartum	Breastfeeding: 497 infants	394 (24% ≤250)	Breastfeeding only, duration not specified	Birth: 2.4% (95% CI, 1.4%–4.2%); cumulative at 6 weeks: 3.9% (95% CI, 2.5%–6.0%); increment between day 1 and 6 weeks: 1.5%	Cumulative at 6 months: 5.0% (95% CI, 3.4%–6.3%); increment between 1 week and 6 months: 2.6%
Mitra-Plus (Kilewo et al [64])	Tanzania (2009)	No CD4 cell count restriction; 34 weeks gestation to 6 months postpartum	501 mothers enrolled, 441 with data; breastfeeding: 441 infants	415 (17.5% <200)	Breastfeeding only, median duration 24 weeks	Birth: no data; cumulative at 6 weeks: 4.1% (18/423 infants) (95% CI, 2.2%–6.0%)	Cumulative at 6 months: 5.0% (22/397 infants) (95% CI, 2.9%–7.1%); increment between 6 weeks and 6 months: 1.0%

Amata (Peltier et al [65])	Rwanda (2009)	No CD4 cell count restriction; 28 weeks gestation to 7 months postpartum if breastfeeding	562 mothers enrolled, 551 delivered, 532 infants alive at 2 days; breastfeeding: 227 infants; formula feeding: 305 infants	477 overall (498 breastfeeding; 434 formula feeding)	Formula (57%) and breastfeeding (43%), breastfeeding duration not specified	Birth: 1.3% (3/227 breastfeeding); cumulative at 6 weeks: 1.3% (95% CI, 0.4%–4.1%); increment between birth and 6 weeks: 0%	Cumulative at 9 months: 1.8% (4/227 breastfeeding) (95% CI, 0.7%–4.8%); increment between 6 weeks and 9 months: 0.5% (95% CI, 0.1%–3.4%)
BAN (Chasela et al [41])	Kenya (2009)	Mother, CD4 cell count >250 cells/μL, randomized trial; late presenter, no antepartum antiretrovirals; intrapartum sdNVP plus 1 week AZT/3TC, then daily triple drug prophylaxis from day 7 to 6 months	Breastfeeding: 851 enrolled in maternal triple drug prophylaxis arm; uninfected at birth and data at 6 months: 851	428	Breastfeeding only, duration not specified, counseled to wean at 6 months	Birth: enrolled at delivery, rates based on uninfected at 2 weeks; cumulative at 6 weeks: not specified	Cumulative at 7 months (uninfected at 2 weeks): 3.0%; increment between birth and 6 months: 3.0%
Kesho Bora (de Vincenzi et al [42])	Kenya, South Africa, Burkina Faso (2009)	Mother, CD4 cell count 200–500 cells/μL, randomized trial: 28–36 weeks gestation to 6.5 months postpartum if breastfeeding	413 mothers enrolled in maternal triple drug prophylaxis arm, 402 live births	335	Formula (23%) and breastfeeding (77%), median duration 21.4 months; 46% exclusive breastfeeding at 3 months	Birth: 1.8% (0.8%–3.7%); cumulative at 6 weeks: 3.3% (95% CI 1.9%–5.6%); increment between birth and 6 weeks: 1.5%	Cumulative at 6 months: 4.9% (95% CI, 3.1%–7.5%); increment between 6 weeks and 6 months: 1.6%
Mma Bana (Shapiro et al [54])	Botswana (2009)	Mother, CD4 cell count >200 cells/μL, randomized trial of 2 triple-drug prophylaxis regimens: 26–34 weeks gestation to 6 months postpartum	Breastfeeding, 560 mothers enrolled, 553 infants with 6 month data	398–403	Breastfeeding only; 71% breastfed for ⩾5 months but <1% after 6 months; 93% reported exclusive breastfeeding to weaning	Maternal triple drug prophylaxis arms combined; birth: 0.7% (4/553); no 6 week data but no intrapartum transmission; thus, increment between birth and 4 weeks: 0%	Cumulative at 6 months: 1.1% (95% CI, 0.5%–2.0%); increment between birth and 6 months: 0.4%

NOTE. AZT, zidovudine; BAN, Breastfeeding, Antiretrovirals and Nutrition; DREAM, Drug Resource Enhancement against AIDS and Malnutrition; KiBS, Kisumu Breastfeeding Study; sdNVP, single-dose NVP; 3TC, lamivudine.

Table 5. Studies of Antiretroviral Drug Resistance in Women and Infants Infected Despite Prophylaxis after Single-Dose Maternal/Infant (or Extended Infant) Nevirapine for Prevention of Mother-to-Child HIV Transmission

Study, reference[s]	Country	No. of participants	HIV subtype	Time of testing	Antepartum/intrapartum	Maternal or infant postpartum[a]	Resistant, %	
							Standard assay	Sensitive assay
Maternal drug resistance studies								
NVAZ, HIVNET 012 [75, 76]	Malawi, Uganda	306	A, C, D	6–8 weeks	sdNVP	…	69 (subtype C), 36 (subtype D), 19 (subtype A)	70 (subtype C), 55 (subtype D), 42 (subtype A)
TOPS [89]								
Regimen 1	South Africa	68	C	2–6 weeks	sdNVP (control arm)	…	57	…
Regimen 2	South Africa	67	C	2–6 weeks	sdNVP plus AZT/3TC	AZT/3TC for 4 days	13	…
Regimen 3	South Africa	68	C	2–6 weeks	sdNVP plus AZT/3TC	AZT/3TC for 7 days	9	…
BAN [92]								
Regimen 1	Malawi	66	C	6 weeks	sdNVP (Call to Action Program, comparison)	…	52	…
Regimen 2	Malawi	123	C	6 weeks	sdNVP plus AZT/3TC (BAN control arm)	AZT/3TC for 7 days	8	…
[77]	South Africa	31	C	6 weeks	sdNVP	…	52	87
Mashi [78]	Botswana	155	C	4 weeks	AZT/sdNVP	…	45	…
PHPT-2 [79]	Thailand	209	CRF, B, C	10 days	AZT/sdNVP	…	32	…
NCT 00204308 [90]								
Regimen 1	Zambia	166	C	6 weeks	AZT/sdNVP (control arm)	–	25	–
Regimen 2	Zambia	173	C	6 weeks	sdNVP plus sdTDF/FTC	…	12	…
Repeat Pregnancy Study [80]	Uganda	91	A, C, D, CRF	6 weeks	sdNVP	…	…	23
[81]	South Africa	76	C	60 days	AZT/sdNVP	…	17	…
PACTG 316 [82]	United States, France	217	B	6 weeks	70% combination ARV /sdNVP	…	15	…
ANRS 12109 [94]	Côte d'Ivoire, Cambodia, South Africa	38	CRF, A, C	28 days	AZT/sdNVP plus sdTDF/FTC	TDF/FTC for 7 days	0	…
ANRS 1201.1 [95]	Côte d'Ivoire	88	CRF, A	4 weeks	AZT plus 3TC/sdNVP plus 3TC	AZT/3TC for 3 days	1	…
P1032 [91]								
Regimen 1	Thailand	56	E, B	2–6 weeks	AZT/sdNVP plus ddI/LPV-rtv	AZT/ddI/LPV-rtv for 7 days	0	3.6
Regimen 2	Thailand	56	E, B	2–6 weeks	AZT/sdNVP plus ddI	AZT/ddI for 30 days	0	7.1
Regimen 3	Thailand	57	E, B	2–6 weeks	AZT/sdNVP plus ddI/LPV-rtv	AZT/ddI/LPV-rtv for 30 days	0	5.3
PHPT-4 [93]	Thailand	222	E, B	7–120 days	AZT/sdNVP plus ddI	AZT/ddI for 30 days	0	1.8

Infant resistance studies								
SWEN [97]								
Regimen 1	India	12	C	6 weeks	sdNVP	NVP for 6 weeks	92	92
Regimen 2	India	29	C	6 weeks	sdNVP	sdNVP (control arm)	38	59
NVAZ [83, 96]								
Early presenter regimen 1	Malawi	23	C	6–8 weeks	sdNVP	sdNVP	87	…
Early presenter regimen 2	Malawi	19	C	6–8 weeks	sdNVP	sdNVP plus AZT for 7 days	57	…
Late presenter regimen 1	Malawi	21	C	6–8 weeks	…	sdNVP	74	…
Late presenter regimen 2	Malawi	15	C	6–8 weeks	…	sdNVP plus AZT for 7 days	27	…
SWEN [84]								
Regimen 1	Uganda	25	A, D	6 weeks	sdNVP	NVP for 6 weeks	84	…
Regimen 2	Uganda	24	A, D	6 weeks	sdNVP	sdNVP (control arm)	50	…
TOPS [89]								
Regimen 1	South Africa	9	C	2–6 weeks	sdNVP (control arm)	sdNVP	56	…
Regimen 2	South Africa	8	C	2–6 weeks	sdNVP plus AZT/3TC	sdNVP plus AZT/3TC for 4 days	13	…
Regimen 3	South Africa	7	C	2–6 weeks	sdNVP plus AZT/3TC	sdNVP plus AZT/3TC for 7 days	14	…
HIVNET 012 [85]	Uganda	24	A, D	6–8 weeks	sdNVP	sdNVP	46	…
[86]	India	13	C	8 weeks	sdNVP	sdNVP	46	…
[87]	South Africa	42	C	12 weeks	sdNVP	sdNVP	45	…
HIVNET 024 [88]	Tanzania	16	A, C, D	4–6 weeks	sdNVP	sdNVP	44	…
Repeat Pregnancy Study [80]	Uganda	17	A, C, D, CRF	6 weeks	sdNVP	sdNVP	…	41
ANRS 1201.1 [95]	Côte d'Ivoire	16	CRF, A	4 weeks	AZT plus 3TC/sdNVP plus 3TC	sdNVP plus AZT for 7 days	25	…

NOTE. ANRS, Agence Nationale de Recherche sur le SIDA; ARV, antiretroviral; AZT, zidovudine; BAN, Antiretrovirals and Nutrition; ddI, didanosine; FTC, emtricitabine; HIVNET 012, HIV Network for Prevention Trials 012; LPV-rtv, lopinavir/ritonavir; NVAZ, NPT/AZT Trial; sdNVP, single-dose nevirapine; PACTG 316, Pediatric AIDS Clinical Trials Group protocol 316; PHPT, Perinatal HIV Prevention Trial; P1032, International Maternal Pediatric Adolescent AIDS Clinical Trials Group protocol 1032; SWEN, Six-Week Extended Nevirapine; TDF, tenofovir; TOPS, Treatment Options Preservation Study; 3TC, lamivudine.

[a] Maternal postpartum regimens are shown for maternal resistance studies, and infant postpartum regimens are shown for infant resistance studies.

Structural factors in country health systems are one of the largest challenges to implementing effective programs for prevention of MTCT of HIV infection. At the country level, maternal, newborn, and child health services, in which programs for prevention of MTCT are targeted, are usually separate from programs, laboratories, and services for treatment and care of HIV infection. Thus, antepartum and postpartum care systems are not equipped to test all women for HIV, conduct CD4 cell count testing to stage disease in HIV-infected women, and provide antiretroviral treatment to women who need it and antiretroviral prophylaxis to the others. The success in resource-rich countries in perinatal prevention lies not only in the antiretroviral regimen provided for prevention of MTCT but also in the integration of the entire array of services needed for identification, care, and treatment of an HIV-infected woman and her infant in the antepartum obstetric and child health infrastructure. Implementation of programs for prevention of MTCT in resource-limited countries offers a unique opportunity to link prevention and treatment efforts, rather than viewing these as competing efforts.

Particularly in rural areas of resource-limited countries, health services remain hard to access or are too expensive. Despite having effective prevention regimens that can be implemented even in settings where women may have only limited antenatal care or present to the health care system for the first time in labor, women must be able to access the health care system to be able to receive such interventions; this may be difficult in rural settings, where many deliveries occur at home with use of traditional birth attendants. There is a need for the development of innovative delivery systems for provision of preventive regimens in such settings.

Human resource limitations are also a significant constraint toward implementation of programs for prevention of MTCT of HIV infection [107]. Task shifting from professional health workers to nonprofessionals could help facilitate scale-up of prevention services. Donor investment in strengthening and expansion of human resource capacity in health systems is critical not just for programs for prevention of MTCT but also for enabling treatment programs for expanded populations of infected individuals as treatment guidelines move toward earlier initiation of therapy.

Systematic evaluation of program effectiveness is needed to measure the impact of programs for prevention of MTCT of HIV infection and to determine best practices. Indicators to measure performance have been poorly defined and not systematically collected. Data on the traditional "prevention of MTCT cascade" (ie, antenatal attendance, uptake of HIV testing, and use of any antiretroviral drugs during pregnancy) are inadequate to address the true impact of programs for prevention of MTCT. Data on numbers of women who have had clinical staging and CD4 cell count testing and who require and receive antiretroviral treatment, as well as the antiretroviral prophylaxis regimens that are given to women not receiving treatment, are needed. Data on the impact of services for prevention of MTCT on HIV transmission to the infant and, more importantly, on survival among HIV-uninfected children should be considered as the gold standard to measure the effectiveness of programs for prevention of MTCT [108].

Stigmatization, discrimination, and violence remain realities in the lives of many HIV-infected women and are another barrier to uptake of services. Even in settings where HIV counseling and testing services are available, the social stigma associated with HIV infection inhibits many women from accessing services to learn their HIV infection status, and, therefore, from taking steps to prevent transmission of HIV to their infant. Further research on this subject is needed.

The limited availability of family planning services in resource-limited countries is a major challenge. Provision of safe and effective family planning to women of childbearing age is a key element of perinatal prevention, and capacity for family planning needs to be included in programs caring for HIV-infected women. Finally, primary prevention of HIV infection in women holds the true key to perinatal prevention.

It is easy to get overwhelmed by the enormity of the worldwide perinatal HIV epidemic and the extent of resource and infrastructure needs; however, this cannot be an excuse for inaction. Implementation will be challenging. However, the cost of indecision and delay in program implementation is high, because every pediatric HIV infection that is not prevented increases the ultimate economic and social cost to each family, community, and country.

Acknowledgments

I thank Dr. Elaine J. Abrams and Dr. D. Heather Watts for their helpful reviews and comments on this article.

Potential conflicts of interest. L.M.M.: no conflicts.

Supplement sponsorship. This article is part of a supplement entitled "Synergistic Pandemics: Confronting the Global HIV and Tuberculosis Epidemics," which was sponsored by the Center for Global Health Policy, a project of the Infectious Diseases Society of America and the HIV Medicine Association, through a grant from the Bill & Melinda Gates Foundation.

References

1. World Health Organization/UNAIDS. AIDS Epidemic Update: December 2009. Geneva, Switzerland: Joint United Nations Programme on HIV/AIDS and World Health Organization, **2009**. http://data.unaids.org/pub/Report/2009/2009_epidemic_update_en.pdf. Accessed 17 December 2009.
2. DeCock 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**; 283:1175–1182.
3. Townsend CL, Cortina-Boria 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**; 22:973–981.
4. World Health Organization. Antiretroviral drugs for treating pregnant women and preventing HIV infection in infants in resource-limited

settings; towards universal access—recommendations for a public health approach 2006. Geneva, Switzerland: World Health Organization, **2006**.
5. World Health Organization. Rapid advice: use of antiretroviral drugs for treating pregnant women and preventing HIV infection in infants—November 2009. Geneva, Switzerland: World Health Organization, **2009**. http://www.who.int/hiv/pub/mtct/rapid_advice_mtct.pdf. Accessed 17 December 2009.
6. Chilongozi D, Wang L, Brown L, et al. Morbidity and mortality among a cohort of human immunodeficiency virus type 1-infected and uninfected pregnant women and their infants from Malawi, Zambia, and Tanzania. Pediatr Infect Dis J **2008**; 27:808–814.
7. World Health Organization. Strategic approaches to the prevention of HIV infection in infants: report of a WHO meeting, Morges, Switzerland, 20–22 March 2002. WHO, **2003**. http://www.who.int/hiv/mtct/StrategicApproaches.pdf. Accessed 17 December 2009.
8. Morrison CS, Wang J, van der Pol B, et al. Pregnancy and the risk of HIV-1 acquisition among women in Uganda and Zimbabwe. AIDS **2007**; 21:1027–1034.
9. Gray R, Li X, Kigozi G, et al. Increased risk of incident HIV during pregnancy in Rakai, Uganda: a prospective study. Lancet **2005**; 366: 1182–1188.
10. Moodley D, Esterhuizen TM, Pather T, Chetty V, Ngaleka L. High HIV incidence during pregnancy: compelling reason for repeat HIV testing. AIDS **2009**; 23:1255–1259.
11. Patterson KB, Leone PA, Fiscus SA, et al. Frequent detection of acute HIV infection in pregnant women. AIDS **2007**; 21:2303–2308.
12. Lu L, Legwaila K, Motswere C, et al. HIV incidence in pregnancy and the first post-partum year and implications for PMTCT programs, Francistown, Botswana, 2008. In: Program and abstracts of the 16th Conference on Retroviruses and Opportunistic Infections (Montreal). **2009**. Abstract 91.
13. World Health Organization. Towards universal access: scaling up priority HIV/AIDS interventions in the health care sector– progress report 2009. Geneva, Switzerland: World Health Organization, **2009**. http://www.who.int/hiv/pub/tuapr_2009_en.pdf. Accessed 17 December 2009.
14. Reynolds HW, Janowitz B, Wilcher R, Cates W. Contraception to prevent HIV-positive births: current contribution and potential cost-savings in PEPFAR countries. Sex Transm Infect **2008**; 84(Suppl 2): 49–53.
15. Rochat TJ, Richter LM, Doll HA, et al. Depression among pregnant rural South African women undergoing HIV testing. JAMA **2006**; 295:1376–1378.
16. Homsy J, Bunnell R, Moore D, et al. Reproductive intentions and outcomes among women on antiretroviral therapy in rural Uganda: a prospective cohort study. PLoS ONE **2009**; 4:e4149.
17. Desgrees-du-Lou A, Msellati P, Viho I, et al. Contraceptive use, protected sexual intercourse, and incidence of pregnancies among African HIV-infected women. Int J STD AIDS **2002**; 13:462–468.
18. Reynolds HW, Steiner MJ, Cates W Jr. Contraception's proved potential to fight HIV. Sex Transm Infect **2005**; 81:184–185.
19. Pai NP, Tulsky JP, Cohan D, et al. Rapid point of care HIV testing in pregnant women: a systematic review and meta-analysis. Trop Med Int Health **2007**; 12:162–173.
20. Creek TL, Ntumy R, Seipone K, et al. Successful introduction of routine opt-out HIV testing in antenatal care in Botswana. JAIDS **2007**; 45:102–107.
21. Chandisarewa W, Stranix-Chibanda L, Chirapa E, et al. Routine offer of antenatal HIV testing ("opt-out" approach) to prevent mother to child transmission of HIV in urban Zimbabwe. Bull WHO **2007**; 85: 843–850.
22. Medley A, Garcia-Moreno C, McGill S, Maman S. Rates, barriers and outcomes of HIV serostatus disclosure among women in developing countries: implications for prevention of mother-to-child transmission programmes. Bull WHO **2004**; 82:299–307.
23. Kakimoto K, Kanal K, Mukoyama Y, et al. Influence of the involvement of partners in the mother class with voluntary confidential counseling and testing acceptance for prevention of mother to child transmission of HIV programme (PMTCT programme) in Cambodia. AIDS Care **2007**; 19:381–384.
24. Msuya SE, Mbizvo EM, Hussain A, et al. Low male partner participation in antenatal HIV counseling and testing in northern Tanzania: implications for preventive programs. AIDS Care **2008**; 20:700–709.
25. Kizito D, Woodburn PW, Kesande B, et al. Uptake of HIV and syphilis testing of pregnant women and their male partners in a programme for prevention of mother-to-child HIV transmission in Uganda. Trop Med Int Health **2008**; 13:680–682.
26. Sarker M, Sanou A, Snow R, et al. Determinants of HIV counseling and testing participation in a prevention of mother-to-child transmission programme in rural Burkina Faso. Trop Med Int Health **2007**; 12:1475–1483.
27. Homsy J, King R, Malamba SS, et al. The need for partner consent is a main reason for opting out of routine HIV testing for prevention of mother-to-child transmission in a rural Ugandan hospital. JAIDS **2007**; 44:366–369.
28. Farquhar C, Kiarie JN, Richardson BA, et al. Antenatal couple counseling increases uptake of interventions to prevent HIV-1 transmission. JAIDS **2004**; 37:1620–1626.
29. Tonwe-Gold B, Ekouevi DK, Bosse CA, et al. Implementing family-focused HIV care and treatment: the first 2 years' experience of the mother-to-child transmission-plus program in Abidjan, Côte d'Ivoire. Trop Med Int Health **2009**; 14:204–212.
30. UNICEF. Children and HIV and AIDS. http://www.unicef.org/aids/index.php. Accessed 26 November 2009.
31. World Health Organization. Antiretroviral therapy for HIV infection in adults and adolescents in resource-limited settings: toward universal access, recommendations for a public health approach 2006 revision. Geneva, Switzerland: World Health Organization, **2006**.
32. Panel on Antiretroviral Guidelines for Adult and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. 1 December **2009**:1–161. http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed 17 December 2009.
33. World Health Organization. Rapid advice: antiretroviral therapy for HIV infection in adults and adolescents– November 2009. Geneva, Switzerland: World Health Organization, **2009**. http://www.who.int/hiv/pub/arv/rapid_advice_art.pdf. Accessed 17 December 2009.
34. Severe P, Pape J, Fitzgerald DW, et al. A randomized clinical trial of early versus standard antiretroviral therapy for HIV-infected patients with a CD4 T cell count of 200–350 cells/mL (CIPRAHT001). In: Program and abstracts of the 49th Interscience Conference on Antimicrobial Agents and Chemotherapy (San Francisco). **2009**. Abstract H-1230.
35. Lallemant M, Jourdain G, Le Coeur S, et al. Single-dose perinatal nevirapine plus standard zidovudine to prevent mother-to-child transmission of HIV-1 in Thailand. N Engl J Med **2004**; 351:217–228.
36. Thior I, Lockman S, Smeaton LM, et al. Breastfeeding plus infant zidovudine prophylaxis for 6 months vs formula feeding plus infant zidovudine for 1 month to reduce mother-to-child HIV transmission in Botswana: a randomized trial: the Mashi Study. JAMA **2006**; 296: 794–805.
37. Kilewo C, Karlsson K, Massawe A, et al. Prevention of mother-to-child transmission of HIV-1 through breast-feeding by treating infants prophylactically with lamivudine in Dar es Salaam, Tanzania: the Mitra Study. JAIDS **2008**; 48:315–323.
38. Vyankandondera J, Luchters S, Hassink E, et al. Simba—Stopping Infection from Mother to Child via Breastfeeding in Africa. In: Program and abstracts of the 3rd International AIDS Society Conference on HIV Pathogenesis (Paris, France). **2003**. Abstract LB07.
39. Six Week Extended-Dose Nevirapine (SWEN) Study Team. 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**; 372:300–313.

40. Kumwenda NI, Hoover DR, Mofenson LM, et al. Extended antiretroviral prophylaxis to reduce breast-milk HIV-1 transmission. N Engl J Med **2008**; 359:119–129.
41. Chasela C, Hudgens M, Jaimeson D, et al. Both maternal HAART and daily infant nevirapine (NVP) are effective in reducing HIV-1 transmission during breastfeeding in a randomized trial in Malawi: 28 week results of the Breastfeeding, Antiretroviral and Nutrition (BAN) Study. In: Program ans abstracts of the 5th International AIDS Society Conference on HIV Pathogenesis, Treatment, and Prevention (Capetown, South Africa). **2009**. Abstract WeLB C103.
42. de Vincenzi I, Kesho Bora Study Group. Triple-antiretroviral prophylaxis during pregnancy and breastfeeding compared to short-ARV prophylaxis to prevent mother-to-child transmission of HIV-1: the Kesho Bora randomized controlled clinical trial in five sites in Burkina Faso, Kenya and South Africa. In: Program and abstracts of the 5th International AIDS Society Conference on HIV Pathogenesis, Treatment, and Prevention (Capetown, South Africa). **2009**. Abstract LBPE C01.
43. Perinatal HIV Guidelines Working Group. Public health service task force recommendations for use of antiretroviral drugs in pregnant HIV-infected women for maternal health and interventions to reduce perinatal HIV transmission in the United States. 29 April **2009**:1–90. http://aidsinfo.nih.gov/ContentFiles/PerinatalGL.pdf. Accessed 17 December 2009.
44. Phanuphak N, Apornpong T, Teeratakulpisam S, et al. Nevirapine-associated toxicity in HIV-infected Thai men and women, including pregnant women. HIV Med **2007**; 8:357–366.
45. McKoy JM, Bennett CL, Scheetz MH, et al. Hepatotoxicity associated with long versus short-course HIV-prophylactic nevirapine use: a systematic review and meta-analysis from the Research on Adverse Drug Events and Reports (RADAR) Project. Drug Safety **2009**; 32:147–158.
46. Desgrees-du-Lou A, Msellati P, Viho I, et al. Incidence of pregnancies among African HIV-infected women, Abidijan, 1995–2000. AIDS **2001**; 15:2327–2330.
47. El-Sadr WM, Lundgren JD, Neaton JD, et al.; Strategies for Management of Antiretroviral Therapy (SMART) Study GroupCD4$^+$ count-guided interruption of antiretroviral treatment. N Engl J Med **2006**; 355:2283–2296.
48. El-Sadr WM, Grund B, Neuhaus J, et al.; SMART Study Group. Risk for opportunistic disease and death after reinitiating continuous antiretroviral therapy in patients with HIV previously receiving episodic therapy: a randomized trial. Ann Intern Med **2008**; 149:289–299.
49. Townsend CL, Cortina-Borja M, Peckham CS, Tookey PA. Antiretroviral therapy and premature delivery in diagnosed HIV-infected women in the United Kingdom and Ireland. AIDS **2007**; 21: 1019–1026.
50. Cotter AM, Garcia AG, Duthely ML, et al. Is antiretroviral therapy during pregnancy associated with an increased risk of preterm delivery, low birth weight, or stillbirth? J Infect Dis **2006**; 193:1195–1201.
51. Tuomala RE, Shapiro DE, Mofenson LM, et al. Antiretroviral therapy during pregnancy and the risk of an adverse outcome. N Engl J Med **2002**; 346:1863–1870.
52. Machado ES, Hofer CB, Costa TT, et al. Pregnancy outcome in women infected with HIV-1 receiving combination antiretroviral therapy before versus after conception. Sex Transm Infect **2009**; 85:82–87.
53. Ekouevi DK, Coffie PA, Becquet R, et al. Antiretroviral therapy in pregnant women with advanced HIV disease and pregnancy outcomes in Abidjan, Côte d'Ivoire. AIDS **2008**; 22:1815–1820.
54. Shapiro R, Hughes M, Ogwu A, et al. The Mma Bana Study: randomized trial comparing highly active antiretroviral therapy regimens for virologic efficacy and the prevention of mother-to-child HIV transmission among breastfeeding women in Botswana. In: Program and abstracts of the 5th International AIDS Society Conference on HIV Pathogenesis, Treatment, and Prevention (Capetown, South Africa). **2009**. Abstract WeLB B101.
55. Barret, B, Tardieu, M, Rustin, P, et al. Persistent mitochondrial dysfunction in HIV-1-exposed but uninfected infants: Clinical screening in a large prospective cohort. AIDS **2003**; 17:1769–1785.
56. Thorne C, Newell ML. Safety of agents used to prevent mother-to-child transmission of HIV: is there any cause for concern? Drug Safety **2007**; 30:203–213.
57. Ciarnello AL, Seage GR 3rd, Freedberg KA, et al. Antiretroviral drugs for preventing mother-to-child transmission of HIV in sub-Saharan Africa: balancing efficacy and infant toxicity. AIDS **2008**; 22: 2359–2369.
58. Coovadia HM, Rollins NC, Bland RM, et al. Mother-to-child transmission of HIV-1 infection during exclusive breastfeeding in the first 6 months of life: an intervention cohort study. Lancet **2007**; 369: 1107–1116.
59. Bland RM, Little KE, Coovadia HM, et al. Intervention to promote exclusive breast-feeding for the first 6 months of life in a high HIV prevalence area. AIDS **2008**; 22:883–891.
60. Kuhn L, Reitz C, Abrams EJ. Breastfeeding and AIDS in the developing world. Curr Opin Pediatr **2009**; 21:83–93.
61. Marazzi C, Germano P, Liotta G, et al. Implementing anti-retroviral triple therapy to prevent HIV mother-to-child transmission: a public health approach in resource-limited settings. Eur J Pediatr **2007**; 166: 1305–1307.
62. Palombi L, Marazzi MC, Voetberg A, Magid NA. Treatment acceleration program and the experience of the DREAM program in prevention of mother-to-child transmission of HIV. AIDS **2007**; 21(Suppl 4):S65–S71.
63. Thomas T, Masaba R, Ndivo R, et al. Prevention of mother-to-child transmission of HIV-1 among breastfeeding mothers using HAART: the Kisumu Breastfeeding Study, Kisumu, Kenya, 2003–2007. In: Program and abstracts of the 14th Conference on Retroviruses and Opportunistic Infections (Boston). **2008**. Abstract 45aLB.
64. Kilewo C, Karlsson K, Ngarina M, et al. Prevention of mother-to-child transmission of HIV-1 through breastfeeding by treating mothers prophylactically with triple antiretroviral therapy in Dar es Salaam, Tanzania—the Mitra PLUS study. JAIDS **2009**; 52(3):406–416.
65. Peltier CA, Ndayisaba GF, Lepage P, et al. Breastfeeding with maternal antiretroviral therapy or formula feeding to prevent HIV postnatal mother to child infection in Rwanda. AIDS **2009**; 23:2415–2423.
66. Kuhn L, Aldrovandi GM, Sinkala M, et al. Effects of early, abrupt weaning on HIV-free survival of children in Zambia. N Engl J Med **2008**; 359:130–141.
67. Kafulafula G, Hoover D, Taha TE et al. Frequency of gastroenteritis and gastroenteritis-associated mortality with early weaning in HIV-1-uninfected children born to HIV-infected women in Malawi. J Acquir Immune Defic Syndr **2010**; 53:6–13.
68. Thomas T, Masaba R, van Eijk A, et al. Rates of diarrhea associated with early weaning among infants in Kisumu, Kenya. In: Program and abstracts of the 14th Conference on Retroviruses and Opportunistic Infections (Boston). **2008**. Abstract 774.
69. Mach O, Lu L, Creek T, et al. Population-based study of a widespread outbreak of diarrhea associated with increased mortality and malnutrition in Botswana, January-March 2006. Am J Trop Med Hyg **2009**; 80:812–818.
70. Homsy J, Moore D, Barasa A, et al. Breastfeeding, mother-to-child HIV transmission, and mortality among infants born to HIV-infected women on highly active antiretroviral therapy in rural Uganda. J Acquir Immune Defic Syndr **2010**; 53:28–35.
71. World Health Organization. Rapid advice: infant feeding in the context of HIV—November 2009. Geneva, Switzerland: World Health Organization, **2009**. http://www.who.int/hiv/pub/paediatric/rapid_advice_infant.pdf. Accessed 17 December 2009.
72. Israel-Ballard K, Donovan R, Chantry C, et al. Flash-heat inactivation of HIV-1 in human milk: a potential method to reduce postnatal transmission in developing countries. JAIDS **2007**; 45:318–323.
73. Cressey TR, Jourdain G, Lallemant MJ, et al. Persistence of nevirapine exposure during the postpartum period after intrapartum single-dose

nevirapine in addition to zidovudine prophylaxis for the prevention of mother-to-child transmission of HIV-1. JAIDS **2005**; 38:283–288.
74. Arrive E, Newell M-L, Ekouevi DK, et al. Prevalence of resistance to nevirapine in mothers and children after single-dose exposure to prevent vertical transmission of HIV-1: a meta-analysis. Int J Epidemiol **2007**; 36:1009–1021.
75. Eshleman SH, Hoover DR, Chen S, et al. Nevirapine (NVP) resistance in women with HIV-1 subtype C, compared with subtypes A and D, after the administration of single-dose NVP. J Infect Dis **2005**; 192: 30–36.
76. Flys TS, Chen S, Jones DC, et al. Quantitative analysis of HIV-1 variants with the K103N resistance mutation after single-dose nevirapine in women with HIV-1 subtypes A, C and D. JAIDS **2006**; 42: 610–613.
77. Loubser S, Balfe P, Sherman G, et al. Decay of K103N mutants in cellular DNA and plasma RNA after single-dose nevirapine to reduce mother to child HIV transmission. AIDS **2006**; 20:995–1002.
78. Shapiro RL, Thior I, Gilbert PB, et al. Maternal single-dose nevirapine vs placebo as part of an antiretroviral strategy to prevent mother to child HIV transmission in Botswana. AIDS **2006**; 20:1281–1288.
79. Jourdain G, Ngo-Giang-Huong N, Le Coeur S, et al. Intrapartum exposure to nevirapine and subsequent maternal responses to nevirapine-based antiretroviral therapy. N Engl J Med **2004**; 351:229–240.
80. Flys TS, McConnell MS, Matovu F, et al. Nevirapine resistance in women and infants after first vs repeated use of single-dose nevirapine for prevention of HIV-1 vertical transmission. J Infect Dis **2008**; 198: 465–469.
81. Van Zyl GU, Claassen M, Engelbrecht S, et al. Zidovudine with nevirapine for the prevention of HIV mother-to-child transmission reduces nevirapine resistance in mothers from the Western Cape, South Africa. J Med Virol **2008**; 80:942–946.
82. Cunningham CK, Chaix M-L, Rekacewicz C, et al. Development of resistance mutations in women receiving standard antiretroviral therapy who received intrapartum nevirapine to prevent perinatal human immunodeficiency virus type 1 transmission: a substudy of Pediatric AIDS Clinical Trials Group Protocol 316. J Infect Dis **2002**; 186: 181–188.
83. Eshelman SH, Hoover DR, Chen S, et al. Resistance after single-dose nevirapine prophylaxis emerges in a high proportion of Malawian newborns. AIDS **2005**; 19:2167–2168.
84. Church JD, Omer SB, Guay LA, et al. Analysis of nevirapine (NVP) resistance in Ugandan infants who were HIV-infected despite receiving single-dose (SD) NVP versus SD NVP plus daily NVP up to 6 weeks of age to prevent HIV vertical transmission. J Infect Dis **2008**; 198:1075–1082.
85. Eshleman SH, Mracna M, Guay LA, et al. Selection and fading of resistance mutations in women and infants receiving nevirapine to prevent HIV-1 vertical transmission (HIVNET 012). AIDS **2001**; 15: 1951–1957.
86. Kurle SN, Gangakhedkar RR, Sen S, et al. Emergence of NNRTI drug resistance mutations after single-dose nevirapine exposure in HIV type 1subtype C-infected infants in India. AIDS Res Hum Retroviruses **2007**; 23:682–685.
87. Martinson NA, Morris L, Gray G, et al. Selection and persistence of viral resistance in HIV-infected children after exposure to single-dose nevirapine. JAIDS **2007**; 44:148–153.
88. Nelson JAE, Loftis AM, Kamwendo D, et al. Nevirapine resistance in human immunodeficiency virus type 1-positive infants determined using dried blood spots stored for up to six years at room temperature. J Clin Microbiol **2009**; 47:1209–1211.
89. McIntyre JA, Hopley M, Moodley D, et al. Efficacy of short-course AZT plus 3TC to reduce nevirapine resistance in the prevention of mother-to-child HIV transmission: a randomized clinical trial. PLoS Med **2009**; 6:e1000172.
90. Chi BH, Sinkala M, Mbewe F, et al. Single-dose tenofovir and emtricitabine for reduction of viral resistance to non-nucleoside reverse transcriptase inhibitor drugs in women given intrapartum nevirapine for perinatal HIV prevention: an open-label randomised trial. Lancet **2007**; 370:1698–1705.
91. Van Dyke R, Jourdain G, Shapiro D, et al. A phase II study of the incidence of nevirapine resistance mutations in HIV-infected Thai women receiving a single intrapartum dose of NVP followed by a postpartum tail of ZDV/ddI or ZDV/ddI/LPV/r: IMPAACT P1032. In: Program and abstracts of the 16th Conference on Retroviruses and Opportunistic Infections (Montreal). **2009**. Abstract 95aLB.
92. Farr S, Nelson J, Ng'ombe T, et al. Addition of 7 days of zidovudine + lamivudine to peripartum single-dose nevirapine effectively reduces nevirapine resistance at 2 and 6 weeks post-partum in HIV-infected mothers: Lilongwe, Malawi. In: Program ans abstracts of the 16th Conference on Retroviruses and Opportunistic Infections (Montreal). **2009**. Abstract 958b.
93. Lallemant M, Ngo-Giang-Huong N, Jourdain G, et al.; PHPT-4 Study Team. Efficacy and safety of 1-month postpartum zidovudine-didanosine to prevent HIV-resistance mutations after intrapartum single-dose nevirapine. Clin Infect Dis **2010**; 50:898–908.
94. The TEmAA ANRS 12109 Study Group; Arrivé E, Chaix ML, Nerrienet E, et al.. Tolerance and viral resistance after single-dose nevirapine with tenofovir and emtricitabine to prevent vertical transmission of HIV-1. AIDS **2009**; 23:825–833.
95. Chaix ML, Ekouevi DK, Rouet F, et al. Low risk of nevirapine resistance mutations in the prevention of mother-to-child transmission of HIV-1: Agence Nationale de Recherches sur le SIDA Ditrame Plus, Abidjan, Côte d'Ivoire. J Infect Dis **2006**; 193:482–487.
96. Eshleman SH, Hoover DR, Hudelson SE, et al. Development of nevirapine resistance in infants is reduced by use of infant-only single-dose nevirapine plus zidovudine postexposure prophylaxis for the prevention of mother-to-child transmission of HIV-1. J Infect Dis **2006**; 193:479–481.
97. Moorthy A, Gupta A, Bhosale R, et al. Nevirapine resistance and breast-milk HIV transmission: effects of single and extended-dose nevirapine prophylaxis in subtype C HIV-infected infants. PLoS ONE **2009**; 4:e4096.
98. Flys TS, Donnell D, Mwatha A, et al. Persistence of K103N-containing HIV-1 variants after single-dose nevirapine for prevention of HIV-1 mother-to-child transmission. J Infect Dis **2007**; 195:711–715.
99. Wind-Rotolo M, Durand C, Cranmer L, et al. Identification of nevirapine resistant HIV-1 in the latent reservoir after single-dose nevirapine to prevent mother-to-child transmission of HIV-1. J Infect Dis **2009**; 199:1301–1309.
100. Coovadia A, Hunt G, Abrams EJ, et al. Persistent minority K103N mutations among women exposed to single-dose nevirapine and virologic response to nonnucleoside reverse-transcriptase inhibitor-based therapy. Clin Infect Dis **2009**; 48:462–472.
101. Lockman S, Shapiro RL, Smeaton LM, et al. Response to antiretroviral therapy after a single, peripartum dose of nevirapine. N Engl J Med **2007**; 356:135–147.
102. Chi BH, Sinkala M, Stringer EM, et al. Early clinical and immune response to NNRTI-based antiretroviral therapy among women with prior exposure to single-dose nevirapine. AIDS **2007**; 21:957–964.
103. Lockman S and A5208/OCTANE Study Team. Lopinavir/ritonavir + tenofovir/emtricitabine is superior to nevirapine + tenofovir/emtricitabine for women with prior exposure to single-dose nevirapine: A5208 ("Octane"). In: Program and abstracts of the 16th Conference on Retroviruses and Opportunistic Infections (Montreal). **2009**. Abstract 94LB.
104. Zeh C, Weidle P, Nafisa L, et al. Emergence of HIV-1 drug resistance among breastfeeding infants born to HIV-infected mothers taking antiretrovirals for prevention of mother-to-child transmission of HIV: The Kisumu Breastfeeding Study, Kenya. In: Program and abstracts of the 15th Conference on Retroviruses and Opportunistic Infections (Boston). **2008**. Abstract 84LB.
105. Mirochnick M, Thomas T, Capparelli E, et al. Antiretroviral concen-

trations in breast-feeding infants of mothers receiving highly active antiretroviral therapy. Antimicrob Agents Chemother **2009**; 53: 1170–1176.
106. Colebunders R, Hodossy B, Burger D, et al. The effect of highly active antiretroviral treatment on viral load and antiretroviral drug levels in breast milk. AIDS **2005**; 19:1912–1915.
107. Nakakeeto ON, Kumaranayake L. The global strategy to eliminate HIV infection in infants and young children: a seven country assessment of costs and feasibility. AIDS **2009**; 23:987–995.
108. Stringer EM, Chi H, Chintu N, et al. Monitoring effectiveness of programmes to prevent mother to child HIV transmission in lower income countries. Bull WHO **2008**; 86:57–62.