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Prevention of mother-to-child transmission of Human Immunodeficiency Virus Type 1 (HIV): the role of neonatal and infant prophylaxis

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Summary

The prevention of mother-to-child transmission (PMTCT) of HIV is one of the great public health successes of the past 20 years. Much concerted research efforts and dedicated work have led to the achievement of very low rates of PMTCT of HIV in settings that can implement optimal prophylaxis. Though several implementation challenges remain, global elimination of pediatric HIV infection seems now more than ever to be an attainable goal. Often overlooked, the role of prophylaxis of the newborn is nevertheless a very important component of PMTCT. In this paper, we focus on the role of neonatal and infant prophylaxis, discuss mechanisms of protection, and present the clinical trial-generated evidence that led to the current recommendations for preventing infections in breastfed and nonbreastfed infants. PMTCT of HIV should not end at birth; a continuum of care extending postpartum and postnatally is required to minimize the risk of new pediatric HIV infections.

Keywords

HIV; transmission; infant; perinatal; neonatal; prophylaxis; breastfeeding; prevention; mother

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The prevention of mother-to-child transmission (PMTCT) of Human Immunodeficiency Virus Type 1 (HIV) is one of the great public health successes of the past 20 years. From a transmission rate of 25%–42% without any interventions, the rate has now been reduced to 1% or less in settings where the full array of prophylactic strategies can be implemented [201,202]. Prevention modalities include use of antiretroviral (ARV) regimens during pregnancy, labor and delivery, and postnatally to the infant; and elective cesarean delivery before amniotic membrane rupture in cases where the HIV load is still detectable in late pregnancy [202]. In settings where breastfeeding is the safest infant feeding option, use of ARV medications by the mother during the whole duration of breastfeeding is recommended by the World Health Organization (WHO) [201]. As a result of implementing these evidence-based preventive measures, fewer than 200 infants are newly infected with HIV in

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the United States annually [203]. In less advantaged settings, however, pediatric HIV infection is an ongoing epidemic, and approximately 260,000 new pediatric infections were estimated worldwide in 2012 [204], most of them acquired through MTCT, and most of them in sub-Saharan Africa, where there are many challenges in implementing clinical practice recommendations.

Even though PMTCT of HIV should be multitargeted and encompass the following: primary prevention of HIV infection among young women; prevention of unintended pregnancy among HIV-infected women; and optimal care of the HIV-infected mothers and infants; PMTCT's cornerstone (and the focus of this article) is the use of ARV agents during gestation, labor and delivery, and postpartum or postnatally to mothers and infants. In this article, we will more specifically focus on the role of neonatal and infant ARV prophylaxis.

As the evidence from the research studies detailed in the following sections demonstrates, neonatal prophylaxis is an important component of PMTCT of HIV when the mother has received ARV medications antenatally, and neonatal prophylaxis is absolutely critical when the mother has not received ARV prophylaxis before delivering the infant. The biologic basis for the efficacy of neonatal prophylaxis in preventing HIV infection in the infant is acting as pre-exposure prophylaxis (e.g., postnatal exposure to HIV during breastfeeding), or as post-exposure prophylaxis (e.g., fetal or infant exposure to infectious maternal blood and genital secretions during late gestation and labor and delivery) [1]. Infant ARV prophylaxis protects against the virus, which might have obtained access to the infant's circulation through maternal-fetal transfusion or systemic dissemination of the virus swallowed by the infant during passage through the birth canal [2]. In addition, infant ARV prophylaxis can be beneficial when the virus remains unintegrated in quiescent cells [3], and thus, when ARV prophylaxis is administered right after birth, it could even provide pre-exposure prophylaxis for late exposures during delivery.

Overview of select important studies of ARV prophylaxis to reduce perinatal HIV transmission, including neonatal prophylaxis

Pediatric AIDS Clinical Trials Group (PACTG) 076 was the first seminal study that transformed the field of HIV prevention and the first example of use of ARV as pre-exposure prophylaxis. The study was a randomized, double-blind, placebo-controlled trial [4] among HIV-infected pregnant women between 14 and 34 weeks' gestation, with CD4 counts higher than 200 cells/mm^3, who had not received antiretroviral therapy (ART) during the current pregnancy. Antenatal, intrapartum, and neonatal prophylaxis components were all included: Women received either placebo or zidovudine (ZDV) antepartum (100 mg orally 5 times daily), and intrapartum (2 mg/kg of body weight given intravenously during 1 hour, then 1 mg/kg per hour until delivery). The infant also received ZDV (2 mg/kg orally every 6 hours for 6 weeks beginning 8–12 hours after birth). Women in this study did not breastfeed their infants.

The results were dramatic. HIV transmission rates at 18 months were 8.3% among the ZDV group versus 25.5% among the placebo group, corresponding to a 67.5% relative reduction in the risk of transmission of HIV to infants. The results of this study were rapidly

disseminated in 1994 and adopted as the standard of care in resource-advantaged countries [5]. Epidemiologic data from the United States and France confirmed the regimen's effectiveness in decreasing perinatal HIV infection within a few years [6].

For resource-limited countries, however, the PACTG 076 regimen posed implementation challenges [7]. In response to this, several studies were conducted in Thailand and sub-Saharan Africa of simplified, shorter regimens to reduce the risk of MTCT of HIV [8-12]. Among them, the Petra Study was a randomized, double-blind, placebo-controlled trial to evaluate the safety and efficacy of three short-course combination regimens of ZDV and lamivudine (3TC) in preventing MTCT of HIV in Tanzania, South Africa, and Uganda [12]. The Petra Study evaluated the relative importance of starting ARV antepartum versus intrapartum, and included a neonatal component. HIV-infected pregnant women were randomly assigned to one of four regimens: group A (antepartum oral ZDV plus 3TC twice daily from 36 weeks' gestation, intrapartum oral ZDV plus 3TC, and postpartum oral ZDV plus 3TC twice daily to the mothers and oral ZDV plus 3TC twice daily to the infants for 7 days); group B (the intrapartum and postpartum components of the group A regimen); group C (the intrapartum component of the group A regimen); or placebo. At 6 weeks, the HIV transmission rates were 5.7% for group A, 8.9% for group B, 14.2% for group C, and 15.3% for the placebo group, which corresponded to an efficacy of 63% for regimen A and 42% for regimen B. 74% of infants were breastfed (median duration 28 weeks). Comparing groups B and C, the importance of neonatal prophylaxis is self-evident, when ARV interventions are not initiated until the intrapartum period.

A subsequent milestone on the path of prevention of MTCT of HIV was the HIVNET 012 study, a randomized trial comparing intrapartum and neonatal single-dose nevirapine (NVP) with ZDV among a breastfeeding population (99% breastfeeding with median duration of 9 ½ months) in Uganda [11,13]. HIV-infected pregnant women were randomly assigned to either the NVP arm (intrapartum single-dose NVP orally at onset of labor and postpartum single-dose NVP to the infant orally within 72 hours of birth), or to the ZDV arm (intrapartum ZDV orally at onset of labor and every 3 hours until delivery and to the infant twice daily for 7 days). HIV transmission rates at 6–8 weeks were 11.8% among the NVP group and 20.0% among the ZDV group, corresponding to a 42% relative reduction in the risk of transmission to infants in the NVP group. This regimen was a new breakthrough—a simple, inexpensive, and efficacious treatment that acted as both pre- and post-exposure neonatal prophylaxis targeted at the time of perinatal exposure because of the long half-life of NVP. Plans were made for widespread rollout of this regimen in Africa. However, it quickly became apparent that use of the single-dose NVP regimen led to the development of resistance to NVP and other drugs in its class [14]. Efforts to reduce NVP resistance after single-dose peripartum administration, which were shown effective, included the addition of a short "tail" regimen of ARV, such as 1 week of ZDV and 3TC [15,16], or addition of a single dose of tenofovir (TDF) and emtricitabine (FTC) [17].

To elucidate which prophylaxis component (maternal or neonatal) had the greatest benefit and what its optimal duration was, the Perinatal HIV Prevention Trial (PHPT-1), conducted in Thailand, compared four ZDV regimens of varying duration among mothers and infants in a randomized, double-blind design [18]. The maternal long regimen was oral ZDV from

28 weeks' gestation and intrapartum, and the short regimen was oral ZDV from 35 weeks' gestation and intrapartum. For infants, the long regimen was 6 weeks of oral ZDV, and the short regimen was 3 days of oral ZDV. Women agreed not to breastfeed as part of the inclusion criteria for the study. There were four groups in the study to evaluate the different combinations of long and short regimens for mothers and infants. After the first interim analysis, the regimen where both the mother and infant were receiving the short-course (the short-short regimen) was stopped because of higher rates of perinatal HIV transmission (10.5%) compared with the long-long regimen (4.1%). For the entire study period, the groups that remained open to enrollment showed equivalent efficacy (no statistically significant difference), with HIV transmission rates of 6.5% for the long–long regimen, 4.7% for the long–short regimen, and 8.6% for the short–long regimen. In utero transmission was significantly higher with the two regimens that had shorter maternal treatment (5.1%) than with the two with longer maternal treatment (1.6%). With longer duration of antenatal ZDV, however, increasing the length of neonatal prophylaxis did not seem as important.

The Perinatal HIV Prevention Trial (PHPT-2), also conducted in Thailand, was a randomized, double-blind trial of three treatment regimens to evaluate the addition of single-dose oral NVP to a standard ZDV regimen for mothers and infants [19]. For the mother, the standard ZDV regimen was oral ZDV from 28 weeks' gestation through delivery. For the infant, standard ZDV was for 1 week after birth, unless the mother received ZDV for less than 4 weeks, in which case the infant was treated for 4–6 weeks. Infants were not breastfed. The study intervention was either addition of a single-dose of NVP to the mother and the infant (nevirapine-nevirapine regimen); NVP to the mother and placebo to the infant (nevirapine-placebo regimen); or placebo to both the mother and the infant (placebo-placebo regimen). At the first interim analysis, the study's Data and Safety Monitoring Board (DSMB) stopped enrollment in the placebo-placebo group because of higher transmission rates (6.3%) compared with the nevirapine-nevirapine group (1.1%). At the completion of the trial, there was no statistically significant difference between transmission rates in the nevirapine-nevirapine group (1.9%) and the nevirapine-placebo group (2.8%). However, in resource-rich settings that used longer combination ARV regimens during pregnancy, the addition of single-dose NVP during labor or delivery and to the infant did not further reduce MTCT [20].

Infant prophylaxis perinatally, when the mother has not received prior ARV drugs

Although the results from the PHPT-1 study showed that longer maternal regimens were preferred to decrease in utero transmission, it is not always possible for women to receive antepartum or even intrapartum prophylaxis. Neonatal prophylaxis is particularly important when the mother has not received ARV medications antenatally. A retrospective analysis using data from the New York State Department of Health showed how important early initiation of neonatal prophylaxis is in this scenario [21]. HIV transmission to the infant was 6.1% when ZDV treatment was started antepartum, 10.0% when started intrapartum, 9.3% when started postnatally within the first 48 hours of life, and 18.4% when started on day 3 of life or later. The rates were all significantly lower than the rate of 26.6% in the absence of ZDV prophylaxis. Among those in whom treatment was started postnatally, ZDV showed the highest benefit, if initiated within the first 12 hours of life, with a 5.9% transmission rate

among this group of infants [22]. Because of the early success of the ZDV 076 regimen, and the subsequent studies and accumulated experience with its use, such as the study mentioned above, ZDV has been the mainstay of infant prophylaxis in the United States and Europe. Several more recent studies have investigated whether other ARV or combination regimens might offer advantages, particularly in settings with very high risk of transmission, such as when no antenatal ARV regimen had been used.

i. Among non-breastfeeding populations—HPTN 040/PACTG 1043 was a randomized, controlled trial of postpartum ARV regimens to prevent MTCT of HIV conducted in Brazil, South Africa, Argentina, and the United States [23]. Infants born to HIV-infected women who had not received ARV before labor were randomly assigned within 48 hours of birth to 1 of 3 ARV regimens: ZDV for 6 weeks; ZDV for 6 weeks plus 3 doses of NVP during the first 8 days of life; or ZDV for 6 weeks plus nelfinavir (NFV) and 3TC for 2 weeks. Intrapartum HIV transmission rates among infants who tested negative at birth were significantly lower in the ZDV plus NVP arm (2.2%) and the ZDV plus 3TC/NFV arm (2.4%) compared with the ZDV only arm (4.8%). However, the rate of neutropenia was significantly increased in the ZDV plus 3TC/NFV arm. There were no significant differences in the distribution of resistance mutations among the groups. The ZDV plus NVP regimen became the new recommended regimen in the United States for prophylaxis of infants whose mothers had not received antenatal ARV [202].

ii. Among breastfeeding populations—The NVAZ trial conducted in Malawi evaluated post-exposure prophylaxis regimens given to infants of women who presented late for delivery (i.e., within 2 hours of expected delivery) and were confirmed to be HIV-infected after delivery [24]. The study was a randomized, open label, controlled trial to determine whether prophylaxis of NVP plus ZDV given to only infants reduced transmission of HIV more than single-dose NVP alone (the standard of care for resource-limited settings at the time). All infants received NVP as soon as possible after birth. Infants randomized to the ZDV arm also received ZDV twice daily for 1 week. Overall HIV transmission rates at 6–8 weeks were 15.3% among the NVP plus ZDV group and 20.9 % among the NVP only group. Among infants who were not HIV infected at birth, transmission rates at 6–8 weeks were 7.7% among the NVP plus ZDV group and 12.1% among the NVP only group, corresponding to a 36% relative reduction in the risk of transmission to infants in the NVP plus ZDV group. This study confirmed that combination neonatal prophylaxis was more efficacious in preventing MTCT than a single agent (in this case NVP) when antenatal prophylaxis had not been received. In contrast, when the mother had presented for delivery in time to receive HIV testing and counseling and an intrapartum dose of NVP, there was no statistically significant difference in perinatal HIV transmission rates, as seen in a study of the same two regimens in Malawi [25]. 99% of infants were breastfed in these two studies.

A comparison of NVP (single-dose) and ZDV (for 6 weeks) as neonatal prophylaxis for infants of untreated mothers was performed in a randomized trial in South Africa [26]. The overall results did not show a statistically significant difference in HIV transmission between the two groups at 12 weeks (14.3% in the NVP group and 18.1% in the ZDV

group). Among infants who were not infected at birth (negative HIV PCR test result at birth), transmission rates at 12 weeks were 7.9% in the NVP arm and 13.1% in the ZDV arm. After further multivariable analysis, including adjustment for breastfeeding status, it appeared that the 6 week ZDV regimen was not as effective as single-dose NVP in reducing postnatal HIV transmission. Only about 16% of the infants breastfed in this study.

Infant prophylaxis to reduce postnatal MTCT of HIV during breastfeeding

The challenge presented by transmission of HIV during breastfeeding was addressed by a subsequent wave of important studies. Several studies evaluated administration of ARV regimens to the mother during breastfeeding [27-31]. For these studies, the neonatal regimen used was typically NVP with or without other ARV drugs for a short duration—up to 4 weeks. We focus here on those that evaluated neonatal or infant prophylaxis as peri-exposure prophylaxis (PreP).

The Mashi Study conducted in Botswana was a factorial, randomized clinical trial with peri-partum (single-dose NVP vs placebo) and postpartum infant feeding (formula vs breastfeeding with infant ZDV prophylaxis) interventions [32,33]. Infants were randomized to 6 months of breastfeeding plus ZDV or to formula feeding plus 1 month of ZDV. The HIV transmission rate among the formula-fed group was significantly lower than among the breastfed group (5.6% vs 9.0%) at 7 months, but cumulative infant mortality was significantly higher among the formula-fed infants (9.3% vs 4.9%). Both strategies had similar cumulative mortality or HIV infection rates at 18 months; 13.9% among the formula fed group and 15.1% among the breastfed group. The results of this study highlighted the importance of breastfeeding in settings where safe infant feeding alternatives are not available and, consequently, of finding effective ARV strategies for use during the breastfeeding period.

The Six Week Extended-Dose Nevirapine (SWEN) study team reported data from three separate, but coordinated, randomized clinical trials conducted in Uganda, Ethiopia, and India to assess whether daily NVP given to breastfed infants through 6 weeks of age could decrease risk of HIV transmission from breastfeeding [34]. HIV-infected women and their infants received the standard HIVNET 012 single-dose NVP regimen [11] only or the standard HIVNET 012 single-dose NVP regimen plus extended-dose NVP daily to the infants from 8 to 42 days of age. Among infants who were HIV-uninfected at birth, there was a significant reduction in the risk of HIV transmission at 6 weeks in the extended-nevirapine arm compared with the control arm, with transmission rates of 2.5% and 5.3%, respectively. At 6 months, however, there was no statistically significant difference between the two arms, with HIV transmission rates of 6.9% in the extended-nevirapine arm and 9.0% in the control arm, attributable to continued breastfeeding.

The Post-Exposure Prophylaxis of Infants (PEPI) trial conducted in Malawi also evaluated extended infant ARV prophylaxis to reduce the risk of HIV transmission from breastfeeding [35]. Infants were randomly assigned to one of three regimens: single-dose NVP plus 1 week of ZDV (control regimen); the control regimen plus daily extended prophylaxis either with NVP (extended NVP); or with NVP plus ZDV (extended dual prophylaxis) until 14 weeks of age. Mothers who presented to the clinic for delivery in time received intrapartum

single-dose NVP. The HIV transmission rate at 9 months among infants who were HIV-uninfected at birth was significantly higher among the control group (10.6%) than among the extended-nevirapine (5.2%) or the extended-dual-prophylaxis (6.4%) groups. Efficacy of the extended NVP regimen was 67% at 14 weeks and 51% at 9 months. Efficacy of the extended dual prophylaxis regimen was 66% at 14 weeks and 40% at 9 months. There were no statistically significant differences in HIV transmission rates between the two extended prophylaxis groups. The extended dual prophylaxis regimen, however, was associated with significantly more adverse events, primarily neutropenia. Results from a follow-up analysis showed that at 24 months of age, HIV transmission rates were still significantly higher among the control group (15.6%) than among the extended-nevirapine (10.8%) or the extended-dual-prophylaxis (11.2%) groups, but the protective efficacy continued to decline after stopping prophylaxis at 14 weeks [36].

The Mitra study was an open-label, non-randomized, prospective cohort study conducted in Tanzania to evaluate daily 3TC given to the infant to reduce MTCT of HIV through breastfeeding [37]. HIV-infected pregnant women were treated according to regimen A of the Petra trial [12], with ZDV and 3TC from 36 weeks' gestation to 1 week postpartum. Infants were treated with ZDV and 3TC from birth to 1 week of age, as in the Petra trial. In addition, they received 3TC during the breastfeeding period up to 6 months (median 18 weeks). The HIV transmission rate at 6 months was 4.9% overall and 1.2% among infants who were HIV-uninfected at 6 weeks. The breastfeeding population in arm A of the Petra trial was used as the comparison group, and the results showed that the HIV transmission rate was more than 50% lower during breastfeeding up to 6 months after delivery in the Mitra Study (4.0% vs 9.9%).

The Breastfeeding, Antiretrovirals, and Nutrition (BAN) study conducted in Malawi was a randomized, controlled trial evaluating the safety and efficacy of a maternal triple ARV regimen or infant NVP prophylaxis for 28 weeks during breastfeeding to reduce postnatal MTCT of HIV [27]. HIV-infected breastfeeding mothers and their infants were randomly assigned to receive a maternal ARV regimen, infant NVP, or no extended postnatal ARV regimen. All mothers and infants received perinatal prophylaxis with single-dose NVP and 1 week of ZDV plus 3TC. The extended regimens for mothers and infants began after delivery and continued until the cessation of breastfeeding but no longer than 28 weeks. The extended maternal ARV regimen consisted of ZDV, 3TC, and either NVP, nelfinavir (NFV), or lopinavir plus ritonavir (LPV/r). All women were counseled to exclusively breastfeed followed by rapid weaning between 24 and 28 weeks. The estimated risk of postnatal transmission at 28 weeks among infants who were HIV-uninfected at 2 weeks was significantly higher among the control group (5.7%) than among the maternal ARV (2.9%) or the infant NVP (1.7%) groups. Hypersensitivity reactions were diagnosed in 1.9% of the infants in the NVP group. The results of the 48-week follow-up showed that the cumulative risk of HIV transmission for infants HIV-uninfected at 2 weeks was still significantly higher among the control group (7%) than among the maternal-ARV (4%) or the infant NVP (4%) groups, with 30% of infections occurring after 28 weeks [38]. Preliminary analysis of NVP resistance among infants infected during the study shows development of resistance mutations in a substantial proportion of infected infants in the extended NVP group (manuscript in preparation). This trial was the only one to include a maternal and infant

ARV study arm; the results showed that the two arms had comparable efficacy. However, the study was not powered to examine this comparison and, interestingly, the infant NVP regimen was faster than the maternal ARV regimen to achieve reduction in MTCT of HIV to the infant among this population of women who had not received ARV medications antenatally.

HIV Prevention Trials Network (HPTN) 046 was a randomized, double-blind, placebo-controlled trial conducted in South Africa, Tanzania, Uganda, and Zimbabwe to assess the incremental benefit of extension of an infant NVP regimen from age 6 weeks to 6 months to reduce the risk of postnatal MTCT of HIV [39]. After receiving NVP prophylaxis from birth through 6 weeks, HIV-uninfected breastfeeding infants of HIV-infected mothers were randomized to receive extended NVP prophylaxis or placebo until 6 months of age or until breastfeeding cessation, whichever came first. The postnatal transmission rate from 6 weeks to 6 months was significantly lower among the extended NVP arm (1.1%) than among the control arm (2.4%). There were no statistical differences in postnatal transmission rates between the study arms for the remainder of the follow-up period from age 6 months through 18 months, though transmission rates at 18 months were still low (2.2% in the extended NVP arm and 3.1% in the control arm) [40].

The ANRS 12174 Trial conducted in Burkina Faso, South Africa, Uganda, and Zambia was a randomized, controlled trial comparing the efficacy and safety of prolonged infant PreP with LPV/r or 3TC to prevent postnatal MTCT of HIV during the full duration of breastfeeding [41]. HIV-uninfected breastfeeding infants born to mothers not eligible for ART for their own health (i.e., with CD4 >350 cells/mm^3) were randomly assigned to receive either LPV/r or 3TC. The median duration of breastfeeding was 42 weeks. At 50 weeks, HIV transmission rates were similar with 1.4% in the LPV/r arm and 1.5% in the 3TC arm. Both regimens were well tolerated.

WHO recommendations for prevention of MTCT of HIV

The WHO Recommendations for the use of ARV regimens for PMTCT have evolved over the years as new scientific and programmatic evidence became available. The feeding recommendations for infants of HIV-infected mothers have also changed as scientific and programmatic evidence became available, balancing the need to prevent MTCT of HIV while considering the risks associated with not breastfeeding in resource-limited settings.

The current WHO recommendations for the use of ARV regimens for PMTCT were released in June 2013 as part of the consolidated guidelines on the use of ARV medications for treating and preventing HIV infection, which combine and harmonize guidelines for ART among adults and adolescents, among infants and children, and for treating pregnant women living with HIV and preventing HIV infection in infants [201]. One of the key recommendations is earlier initiation of ART for all populations (CD4 count < 500 cells/mm^3). Two options are recommended for PMTCT (Table 1): (a) providing lifelong ARV medications to all HIV-infected pregnant and breastfeeding women regardless of CD4 count or clinical stage (Option B+), or (b) providing ARV medications to all HIV-infected pregnant and breastfeeding women during the MTCT risk period and then continuing

lifelong ART for women eligible for treatment for their own health (Option B). For both options, the recommended infant prophylaxis regimen is once daily NVP for 6 weeks among breastfeeding infants and 4–6 weeks of once-daily NVP or twice-daily ZDV among non-breastfeeding infants. The duration of infant ARV prophylaxis may be extended to 12 weeks if the mother was diagnosed with HIV infection during labor or immediately postpartum and she plans to breastfeed, or if the infant was identified as HIV-exposed after birth and is breastfeeding. In case a mother who breastfeeds interrupts her ARV regimen (because of toxicity, stock-outs, or if she refuses to continue), infant prophylaxis with NVP is recommended until 6 weeks after the maternal ARV regimen is restarted or until 1 week after breastfeeding has ended [201]. With regard to infant feeding, the WHO guidelines recommend, (in countries where national authorities have chosen to promote breastfeeding with an ARV intervention), that infants exclusively breastfeed for 6 months, be introduced to appropriate complementary foods thereafter, and continue to breastfeed for the first 12 months of life [205]. Breastfeeding should only be stopped once a nutritionally adequate and safe diet without breast milk can be provided.

Though the WHO guidelines are based on the most up-to-date scientific and programmatic evidence, many questions remain about the long-term safety and effectiveness of the options for PMTCT. Promoting Maternal-Infant Survival Everywhere (PROMISE) is a combination of studies designed to provide answers to some of these questions [206-209]. As countries move to scale up interventions, more data about the feasibility of these options will become available.

US guidelines for the use of ARV for neonatal prophylaxis

The recommendations in resource-advantaged settings for the use of ARV for PMTCT have also changed over the years as treatment options for HIV-infected pregnant women have expanded. US guidelines will be discussed in depth as an example. There have been relatively few changes to the recommended regimen for prophylaxis provided to infants since the PACTG 076 regimen was adopted [4]. Most recently, the US guidelines were updated in March 2014 [202]. Selection of an ARV regimen for neonatal prophylaxis emphasizes the importance of classifying transmission risk by assessing maternal combination ART use and level of viral suppression. A 6-week course of twice daily ZDV, ideally started within 6–12 hours of birth, is recommended for all HIV-exposed infants. However, a shortened 4-week course may be considered for HIV-exposed infants at decreased transmission risk, (i.e., if the mother has known viral suppression before delivery and is adherent to combination ART), in line with the recommended regimen in other resource-advantaged settings [42,43]. In a 2012 survey of national PMTCT guidelines in the European region, the vast majority of these guidelines also recommended ZDV monotherapy for 4-6 weeks for HIV-exposed infants in most clinical scenarios [44]. However, there is variability among countries in the recommended dosing of ZDV. Zidovudine dosing information per US guidelines is available for both term and premature infants (Table 2); dosing is lower in premature infants per unit of body weight because the metabolic pathway to clear ZDV is immature, resulting in a longer half-life [202].

On the basis of findings from the HPTN 040/P1043 study [23], the US guidelines recommend 3 doses of NVP for HIV-exposed infants of mothers who have not received combination ART antenatally. The first is recommended to be given at birth, the second is given 48 hours after the first dose, and the final dose is given 96 hours after administration of the second dose; dosing recommendations are based on birth weight (Table 2). Of note, there is limited information about dosing of NVP in premature infants, although a pharmacokinetic study of single-dose NVP showed half-lives similar to those of term infants, and slower drug clearance in small-for-gestational age premature infants compared with those who were of average weight for gestational age [45]. Data about dosing and safety for premature infants are lacking for agents other than ZDV and NVP, and consultation with a pediatric HIV expert is recommended if their use is being considered in a high-risk premature infant [202]. Consultation with a pediatric HIV specialist is also recommended in situations where the mother may have received ARV regimens other than combination ART, be non-suppressed, or have known resistant virus.

HIV Testing of mothers with unknown HIV status

The US guidelines emphasize routine opt-out rapid HIV testing during the peripartum period if the mother's HIV status is not yet known. Most European countries also recommend routine maternal testing with an opt-out screening strategy [44]. The US guidelines specify that HIV rapid testing should be performed on the mother or infant with appropriate consent as soon as possible to allow for PMTCT interventions. The American Academy of Pediatrics recommends that rapid testing on the mother, either by saliva or blood, is preferred over rapid testing of the infant because of increased sensitivity performance. Establishing an infant's HIV exposure status in a timely fashion is the critical first step in providing effective neonatal prophylaxis [46].

Intensifying infant prophylaxis in cases with increased risk of HIV transmission

A recent case report of very early triple ARV initiation in an HIV-infected infant with subsequent lack of virus detection after discontinuation of therapy was believed to have resulted in a “functional cure.” While, the virus has returned to detectable levels in this child after many months of non-detection [210], the case has sparked increasing discussion about the timing of infant HIV PCR testing and triple ARV initiation and latency of the infection [47]. Clinical trials are planned to address whether administration of a three-drug regimen in therapeutic doses to HIV-exposed high-risk infants could alter the establishment and long-term persistence of HIV infection [211]. Investigation also is planned to assess the safety of such approaches in infants, particularly in the setting of preterm delivery for which pharmacokinetic data about most drugs are lacking. These investigations may inform future guidelines on neonatal prophylaxis drug selection and duration. Expert consultation on managing infants at increased risk for HIV transmission due to suboptimal viral control in the mother or high risk labor/delivery should be sought.

Safety of ARV used as neonatal and infant prophylaxis

The safety and potential toxicities of any regimen are important considerations, and safety data are reassuring for the agents most commonly used for prophylaxis among HIV-exposed infants for neonatal regimens and during breastfeeding for up to 6 months. Zidovudine (ZDV) is the ARV agent with the most safety data in the neonatal population. The most common toxicity associated with this agent is anemia or neutropenia, which usually resolves by 12 weeks of age [4].

Concerns have been raised regarding possible mitochondrial toxicity associated with nucleoside reverse transcriptase inhibitors (NRTIs), including ZDV. Some studies have found increased lactate levels, a sensitive but nonspecific marker of possible mitochondrial dysfunction, in the blood of HIV-exposed but uninfected neonates treated with ZDV [48]. Of note, neonates had been exposed in utero to varying ART regimens, but 3 infants who received postnatal ZDV only also exhibited elevated lactate levels. Most of the infants with hyperlactatemia were asymptomatic; only two infants were symptomatic, and their symptoms disappeared and lactate levels decreased after discontinuation of ZDV. In another study, which used more restrictive inclusion criteria for serum lactate measurements due to the possibility of artificially high lactate in samples taken under suboptimal conditions, 63 of 127 HIV-exposed infants on an NRTI regimen (primarily ZDV) developed benign and self-limited hyperlactatemia [49]. Compared to non-HIV exposed controls, the lactate levels in these infants were higher at each of 4 time points ($p<0.0001$), up to one year of age. However, 70% of those infants with initially elevated levels had lactate levels within the normal range by age 12 months. No symptoms consistent with hyperlactatemia were observed. Hyperlactatemia was significantly associated only with *in utero* exposure to didanosine, which is no longer included in recommended PMTCT regimens for pregnant women, and not with other ARV regimens, either during gestation or postnatally. In both studies, lactate levels trended toward normal values over time after the conclusion of 6 weeks of ZDV therapy [48,49]. A study in the Ivory Coast found that increased lactate levels were not significantly associated with *in utero* exposure to ZDV and a 7-day course of neonatal ZDV compared with a single-dose NVP regimen [50].

Data are conflicting from studies that looked into symptomatic mitochondrial toxicity among HIV-uninfected children with perinatal NRTI exposure. An analysis of the French Pediatric Cohort, which included 2644 children exposed to perinatal ARV, found an 18-month incidence of ‘established’ mitochondrial dysfunction of 0.26% among children exposed to ARV (most received either a ZDV regimen or a combined ZDV-lamivudine regimen) [51]. Established cases were shown to have a deficit in the mitochondrial respiratory chain and/or characteristic histological findings. Of note, one case was seen in an infant who was exposed to prenatal, but not neonatal, ART. No cases of possible mitochondrial dysfunction were found among the 1748 children in the cohort without perinatal ART exposure. While still a very rare outcome, the 0.26% incidence in this study is much greater than the 0.01% incidence in the general population. After a preliminary report [52] of these findings was published, a review of the US data from the Perinatal AIDS Collaborative Transmission Study (n=1954) was initiated and did not find any evidence indicating that uninfected infants exposed to perinatal NRTIs had symptoms of

mitochondrial dysfunction or that any deaths among the cohort could be attributed to this cause [53]. A review of 5 US cohorts (combined population of over 10,000 children exposed to NRTIs) also found no indication that perinatal ARV exposure was associated with death from mitochondrial dysfunction or from sudden infant death syndrome [54]. A later analysis of the data from the European Collaborative Study, which included 1008 infants exposed to ART perinatally (ZDV therapy was the most common neonatal regimen), also found no association of NRTI exposure with clinical manifestations suggestive of mitochondrial dysfunction [55].

Overall, the evidence on the possibility of mitochondrial toxicity from ZDV given postnatally is equivocal, and even supportive studies found a low absolute incidence of mitochondrial dysfunction.

There are limited safety data for multiple-agent ARV regimens for HIV-exposed infants; however, the HPTN 040/P1043 study showed that a three-agent combination of zidovudine for 6 weeks, plus nelfinavir and lamivudine for 2 weeks, had higher rates of neutropenia compared with a two-agent regimen of zidovudine for 6 weeks plus three doses of nevirapine or ZDV alone [23].

Nevirapine has been associated with increased risk of hepatotoxicity among adults, as well as rash and hypersensitivity reactions; however, these have not been prominent among infants. In the BAN study, 6 of 39 mothers had a hypersensitivity reaction to NVP, but only 16 of 852 infants on an extended daily NVP regimen for up to 28 weeks exhibited hypersensitivity [27]. Extended dosing of nevirapine among breastfeeding infants for up to 6 months was not associated with increases in adverse events versus a 6-week regimen in HPTN 046 [39].

There is very limited or no information on neonatal safety or dosing for other ARV agents [202]; and where neonatal dosing has been studied, efficacy data are not yet available [56]. The FDA recommends that ritonavir-boosted lopinavir should not be administered before a postmenstrual age of 42 weeks and a minimum postnatal age of 14 days; this label change was in response to reports of severe toxicity among preterm neonates, including heart block and other forms of cardiac toxicity [212]. Among term infants, use of a lopinavir-ritonavir regimen was associated with asymptomatic and transient adrenal dysfunction, which was not seen among infants treated with a ZDV-based regimen; this was most pronounced among infants whose mothers had also received lopinavir-ritonavir or a similar combination therapy as ART late in their pregnancies [57].

Immunoprophylaxis

Although much progress has been made in PMTCT using ARV regimens, additional prevention methods are needed. Modeling has estimated that even with 90% coverage of recommended ARV therapy among pregnant women, a 50% reduction in HIV incidence among reproductive-age women, and the prevention of all unintended pregnancies, the goal of virtual elimination of MTCT would still not be met in the 25 countries with the largest populations of HIV-infected pregnant women [58]. In addition, a recent meta-analysis showed that only 72% of pregnant women are more than 80% adherent to their ART

regimen, and that adherence is lower during the postpartum period [59]. There is evidence that maternal adherence may be associated with correct administration of the infant's antiretrovirals. One study showed that mothers who adhered to their own ART regimens during pregnancy were more likely to have adhered to the infant's regimen after birth [60]. These and other challenges emphasize that although current strategies are making great strides, additional tools are needed [61]. One potential adjunct prevention modality is immunoprophylaxis.

Immunoprophylaxis is classified as either active, by vaccination, or passive, by infusion of antibodies. Much effort has been directed toward vaccine development, and some potential vaccines have completed trials, whereas others are currently in progress. In the United States, trials such as that of the ALVAC-HIV vCP 1452 vaccine with and without a subunit rgp 120 envelope boost showed that even in the presence of potentially attenuating maternal antibodies, infants can mount an immune response to HIV vaccine, with antibodies produced by some subjects showing neutralizing activity towards HIV homologous to the vaccine strain [62]. The first pediatric HIV vaccine trial in Africa has been completed in Uganda, and data demonstrated the safety and feasibility of the vaccine studied (ALVACHIV vCP1521) [63], although only low levels of cellular immune responses were generated, and no neutralizing antibodies were detected [64]. PedVacc001 studied the safety and immunogenicity of the MVA.HIVA vaccine in Gambia among 20-week-old infants of HIV-uninfected mothers. No severe adverse events occurred during the trial, and the vaccine did not interfere with antibody induction to the standard childhood vaccines. However, only 9% of vaccinated infants demonstrated an HIV-1-specific T cell response [65]. The most promising vaccine study so far, a trial of ALVAC-HIV vCP 1521 among adults in Thailand that incorporated boosting with 2 recombinant envelope proteins, found that the vaccine had 31% efficacy (95% CI: 1.1–51.1%; $P = .04$) [66].

Passive immunoprophylaxis is accomplished through the administration of monoclonal antibodies designed to bind to HIV and reduce its infectivity in the recipient; unlike vaccination, it does not induce the recipient to produce his or her own immune response, so the length of effect depends on the half-life of the antibody administered. In one study, HIV hyperimmune globulin (HIVIGLOB) was administered intravenously to mother-infant pairs in Uganda—to the mother at 36–38 weeks' gestation and to the infant within 18 hours of birth. Single-dose nevirapine therapy was administered both to the intervention and the control groups. Results found no difference in safety between the two groups; however, there was also no significant difference in effectiveness for the prevention of MTCT [67]. Other antibodies are under investigation, particularly broadly neutralizing antibodies, which target well-conserved sites on the HIV virus, such as the CD4 binding site [68]. One such antibody, VRC01, has been shown to protect infant macaques from oral SHIV challenge in one small study, and a phase 1 study among human infants is planned for further evaluation of this potential prophylactic treatment [69, 213].

Expert commentary & five-year view

There has been a great deal of progress and many developments in the field of preventing MTCT of HIV; the use of extended ARV prophylaxis during gestation, labor and delivery,

and, for resource-limited settings, during breastfeeding has certainly transformed the field. Now, envisioning elimination of pediatric HIV infection has become possible. However, even with the use of best approaches, including extended combination ARV regimens and optimal infant delivery practices, a residual small risk of transmission exists (approximately 1% for perinatal transmission, 3%–5% for breastfeeding transmission). Several questions and areas for research remain. The short- and long-term safety of ARV regimens for mothers and infants during gestation and breastfeeding, including drugs of newer ARV classes, needs to be continuously monitored. It is perhaps surprising that there is still very limited pharmacokinetic and dosing information for most ARV drugs for infants, (including widely used agents, such as nevirapine and protease inhibitors), particularly infants who are premature or of low-birth weight; such studies are urgently needed. Development of resistance (incidence and patterns) among infants who become HIV-infected despite prophylaxis also needs to be carefully monitored, as it may affect their treatment options. The role of new ARV drugs needs to be investigated; such agents may offer distinct advantages for PMTCT, either by acting on different stages of the viral cycle, or because of unique pharmacokinetic and pharmacodynamic properties (e.g., integrase inhibitors). Pharmacogenetic studies are another area that will develop during the next few years, as it appears that genetic polymorphisms may underlie individual differences in the metabolism of some ARV drugs (e.g., nonnucleoside reverse transcriptase inhibitors (NNRTI), as well as hypersensitivity reactions to others (e.g., abacavir and possibly NNRTI). Single nucleotide genetic polymorphisms may also underlie increased susceptibility to HIV infection for some infants. In the future, genome-wide association studies will pave the way for personalized pharmacotherapy and dosing, and for identification of infants at higher risk who can be targeted for intensified prophylaxis. Whether combined maternal *and* infant prophylaxis for the duration of breastfeeding is advantageous for reducing residual transmission, when balanced against risks of ARV exposure, and whether such an approach might also be acceptable in a resource-rich setting, offers a new research direction. More research on the immune aspects of protection needs to be pursued; indeed we still do not understand why a majority of exposed infants escape HIV infection. Such research could pave the way for immune strategies of protection (passive immunoprophylaxis or a vaccine) that could be given in combination with ARV strategies to maximize benefit and minimize duration of ARV exposure. Addressing other maternal and infant co-infections should not be overlooked as they contribute to maternal and infant morbidity and mortality and increase the risk of infant HIV infection; (such infections include herpes simplex virus, cytomegalovirus, or malaria) [70]. In addition, approaches to promote infant intestinal health (exclusive breastfeeding, use of rotavirus vaccine, and possibly probiotics) might be beneficial in further reducing HIV transmission through breastfeeding because damage to the mucosal barrier, either caused by food insults, gastrointestinal infections, or receipt of broad-spectrum antibiotics, is correlated with increased risk of immune activation and infant HIV infection [71]. Whether breastfeeding with ARV prophylaxis is an acceptable strategy in resource-rich settings for the HIV-infected women who strongly wish to breastfeed their infants has not been evaluated; a formal assessment of its risk-benefit ratio deserves more study. Finally, the role of early aggressive treatment for all HIV-exposed infants in interrupting establishment of infection is an avenue that holds promise for the future of pediatric HIV infection and may well transform the concept of neonatal prophylaxis.

Translating research into successful implementation is still challenging in many parts of the world. Limited access to ARV medications in many settings because of costs and lack of resources or political will, poor health infrastructure, lack of integration of HIV prevention and treatment with maternal and reproductive health services, and social reasons, such as stigma, are still major obstacles to ARV scale-up among pregnant women. Even more challenging is implementation of neonatal ARV prophylaxis. Data from WHO show that worldwide, less than half of infants born to HIV-infected mothers received ARV prophylaxis in 2011 [214]. Now that plans are in place for Option B+ roll out in many parts of the world, it is important to evaluate women's long-term acceptance of and adherence to life-long ART, particularly for those who are at earlier stages of their HIV disease, as well as to examine the effects of ARV and adherence on maternal and infant outcomes. Linking HIV prevention, care and treatment services with family planning, antenatal and child and maternal health services, and building the health infrastructure required for such programs, can aid in achieving prophylaxis and treatment goals and lead to the elimination of pediatric HIV infection worldwide.

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Key issues

- Significant reductions in the rate of mother-to-child transmission of HIV have been achieved with the use of ARV regimens during pregnancy, labor and delivery, and postnatally to the infant. However, in less advantaged settings, pediatric HIV infection is an ongoing epidemic caused by challenges in identifying HIV-infected mothers and implementing preventive strategies.
- Neonatal prophylaxis is an important component of PMTCT of HIV when the mother has received ARV medications antenatally, and it's absolutely critical when the mother has not received ARV prophylaxis before delivering the infant.
- The recommended regimen for neonatal prophylaxis in the United States is 4–6 weeks of ZDV depending on gestational age at birth and maternal ART status. In addition, three doses of NVP in the first week of life are recommended if the mother did not receive antepartum combination ART.
- The WHO recommendation for neonatal prophylaxis is 6 weeks of NVP for breastfed infants and 4–6 weeks of NVP or ZDV for non-breastfed infants. The recommended duration of infant ARV prophylaxis is extended on the basis of varying clinical scenarios. For mothers who are not on lifelong ART and are breastfeeding, the recommendation is to continue ART until 1 week after breastfeeding ends.
- ARV prophylaxis regimens provided to the mother or to the infant during breastfeeding are effective at reducing the risk of postnatal transmission of HIV and are key strategies in settings where breastfeeding is the safest infant feeding option.
- Current WHO guidelines focus on strategies for use of ARV regimens by the mother throughout the duration of pregnancy, labor and delivery, and breastfeeding, but there are many questions about the long-term safety, effectiveness, and acceptability of these options.
- The short- and long-term safety of ARV regimens for mothers and infants during gestation and breastfeeding, including drugs of newer ARV classes, needs to be continuously monitored.
- Although much progress has been made in identifying effective ARV regimens for PMTCT, additional prevention methods are needed to eliminate pediatric HIV infections worldwide: prevention of HIV infection in women, prevention of unintended pregnancies, provision of appropriate ARV regimens, and care to all mothers and infants, and, hopefully, the development of immunoprophylaxis as an adjunct strategy (active or passive immunization).

Table 1

WHO Programme Options for ART for PMTCT, 2013

National PMTCT programme option	Pregnant and breastfeeding women with HIV		HIV-exposed infant	
Use lifelong ART for all pregnant and breastfeeding women ("Option B+")	Regardless of WHO clinical stage or CD4 cell count		Breastfeeding	Replacement feeding
	Initiate ART and maintain after delivery and cessation of breastfeeding		6 weeks of infant prophylaxis with once-daily NVP	4-6 weeks of infant prophylaxis with once-daily NVP (or twice-daily AZT)
Use lifelong ART only for pregnant and breastfeeding women eligible for treatment ("Option B")	Eligible for treatment [a]	Not eligible for treatment [a]		
	Initiate ART and maintain after delivery and cessation of breastfeeding [b]	Initiate ART and stop after delivery and cessation of breastfeeding [b c]		

Reproduced, with the permission of the publisher, from the *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Recommendations for a public health approach June 2013.* Geneva, World Health Organization, 2013 (Table 7.3, Page 101 http://apps.who.int/iris/bitstream/10665/85321/1/9789241505727_eng.pdf, accessed 07 March 2014)"

Abbreviations: PMTCT: Prevention of Mother-to-Child Transmission of HIV; ART: Antiretroviral Therapy; WHO: World Health Organization; NVP: Nevirapine; AZT: Zidovudine

[a] CD4 count ≤500 cells/mm^3 or clinical stage 3 or 4 disease at the time of ART initiation or in accordance with national guidelines.

[b] Patients who develop clinical or laboratory criteria indicating failure during pregnancy or the breastfeeding period should be assessed for second-line therapy.

[c] In the case of breastfeeding, stop ART one week after breastfeeding ends. In the case of replacement feeding, stop ART after delivery.

Table 2

US Guidelines for dosing neonatal prophylaxis in infants born to HIV-infected mothers

Zidovudine (ZDV) dosing for neonates for the prevention of perinatal transmission of HIV*

Gestational age at birth	Dosing	Duration
>35 weeks	PO: 4mg/kg/dose twice daily IV: 3mg/kg/dose every 12 hours	Birth through 4-6 weeks**
≥30 to <35 weeks	PO: 2 mg/kg/dose every 12 hours, advanced to 3 mg/kg/dose every 12 hours at age 15 days IV: 1.5mg/kg/dose every 12 hours, advanced to 2.3 mg/kg/dose every 12 hours at age 15 days	Birth through 6 weeks
<30 weeks	PO: 2 mg/kg/dose every 12 hours, advanced to 3 mg/kg/dose every 12 hours after age 4 weeks IV: 1.5 mg/kg/dose IV every 12 hours, advanced to 2.3 mg/kg/dose IV every 12 hours after age 4 weeks	Birth through 6 weeks

Nevirapine (NVP) dosing for neonates (recommended in addition to ZDV, as shown above, for HIV-exposed infants of women who did not receive antepartum combination ART)

Birth weight	Dosing	Duration
1.5-2 kg	8 mg/dose PO	3 doses within the first week of life Dose 1: Administer as soon as possible after delivery, within 48 hours of birth
>2 kg	12 mg/dose PO	Dose 2: 48 hours after dose 1 Dose 3: 96 hours after dose 2

Adapted from 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. p. E-12 “Recommended Neonatal Dosing for Prevention of Perinatal Transmission of HIV” [202].

*For all infants, give first dose as soon as possible after birth, preferably within 6-12 hours of delivery. Use IV dosing if infant is unable to tolerate PO medication.

**A 6-week course of neonatal ZDV is generally recommended. A 4-week course may be considered for infants born at ≥35 weeks when the mother has received standard ART during pregnancy with consistent viral suppression, and there are no concerns regarding maternal adherence.