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

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Appendix A: Review of Clinical Trials of Antiretroviral Interventions to Prevent Perinatal HIV Transmission (Last updated October 26, 2016; last reviewed October 26, 2016)

One of the major achievements in HIV research was the demonstration by the Pediatric AIDS Clinical Trials Group (PACTG) 076 clinical trial that administration of zidovudine to pregnant women and their infants could reduce the risk of perinatal transmission by nearly 70%.[1] Following the results of PACTG 076, researchers began to explore the development of shorter, less expensive prophylactic regimens more applicable to resource-constrained settings. In addition, a number of studies have examined optimal regimens to reduce postnatal transmission during breastfeeding. This Appendix provides a table summarizing results of major studies of antiretroviral (ARV) interventions to prevent perinatal transmission (see Supplemental Table 1) and a brief discussion of lessons learned. In many cases, the direct comparison of results from trials of these regimens is not possible because the studies involved diverse patient populations residing in different geographic locations, infected with diverse viral subtypes, and with different infant feeding practices. However, some generalizations are relevant to understanding the use of ARV drugs for prevention of perinatal transmission in both resource-limited and resource-rich countries.

Combination antenatal prophylaxis taken over a longer duration is more effective than a short-course, single-drug regimen in reducing perinatal transmission.

The use of ARV drugs to prevent transmission is highly effective, even in HIV-infected women with advanced disease.[2,3] Efficacy has been demonstrated for a number of short-course ARV regimens, including those with zidovudine alone, zidovudine plus lamivudine, single-dose nevirapine, and single-dose nevirapine combined with either short-course zidovudine or zidovudine/lamivudine.[4-13] In general, combination regimens are more effective than single-drug regimens in reducing perinatal transmission. In addition, for prevention of perinatal transmission, administration of ARV drugs during the antepartum, intrapartum, and postpartum periods is superior to administration of ARV drugs during only the antepartum and intrapartum periods or the intrapartum and postpartum periods.[5,14,15]

Almost all trials in resource-limited countries have included oral intrapartum prophylaxis, with varying durations of maternal antenatal and/or infant (and sometimes maternal) postpartum prophylaxis. Perinatal transmission is reduced by regimens with antenatal components starting as late as 36 weeks' gestation, even when lacking an infant prophylaxis component.[10-12] However, longer-duration antenatal zidovudine prophylaxis, beginning at 28 weeks' gestation, is more effective than shorter-duration zidovudine prophylaxis, beginning at 35 weeks' gestation.[13] The PHPT-5 trial demonstrated a significantly increased risk of transmission associated with less than 8 weeks of prophylaxis during pregnancy.[16] The European National Study of HIV in Pregnancy and Childhood demonstrated that each additional week of an antenatal, triple-drug regimen corresponded to a 10% reduction in risk of transmission.[17] More prolonged infant post-exposure prophylaxis does not appear to substitute for longer-duration maternal ARV prophylaxis.[13]

The PROMISE study is the first randomized clinical trial to demonstrate the superiority of antiretroviral therapy (ART) over zidovudine-based prophylaxis for prevention of *in utero* transmission in women with CD4 T lymphocyte (CD4) cell counts >350 cells/mm^3.[18] Pregnant women were randomized to one of three study arms:

- Zidovudine plus single-dose nevirapine at delivery plus postpartum tenofovir disoproxil fumarate (TDF)/emtricitabine tail
- Zidovudine plus lamivudine plus lopinavir/ritonavir
- TDF plus emtricitabine plus lopinavir/ritonavir

The rate of perinatal transmission through 14 days of life was significantly lower among women receiving triple ARV prophylaxis (0.6%, 9 infections among 1,710 infants) compared with those in the zidovudine arm (1.8%, 25 infections among 1,326 infants).

Regimens that do not include maternal ARV prophylaxis during pregnancy have been evaluated because some women may lack antenatal care and present for prenatal care for the first time when they go into labor. Regimens that include only intrapartum and postpartum drug administration also have been shown to be effective in reducing perinatal transmission.[4-6] However, without continued infant post-exposure prophylaxis, intrapartum pre-exposure prophylaxis alone with nucleoside reverse transcriptase inhibitor drugs (zidovudine/lamivudine) is not effective in reducing transmission.[5] The SAINT trial demonstrated that intrapartum/postpartum zidovudine/lamivudine and single-dose intrapartum/newborn nevirapine are similar in efficacy and safety.[6]

Combination infant ARV prophylaxis is recommended in the United States for infants whose mothers have not received antenatal ARV drugs.

In some situations, it may be impossible to administer maternal antepartum and intrapartum therapy, and only infant prophylaxis may be an option. In the absence of maternal therapy, the standard infant prophylaxis regimen of 6 weeks of zidovudine was effective in reducing HIV transmission compared with no prophylaxis, based on epidemiological data in resource-rich countries.[19] A trial in Malawi in breastfeeding infants demonstrated that adding 1 week of zidovudine therapy to infant single-dose nevirapine reduced risk of transmission by 36% compared with infant single-dose nevirapine alone.[7]

To define the optimal infant prophylaxis regimen in the absence of maternal antepartum ARV drug administration in a formula-fed population of infants such as in the United States, the NICHD-HPTN 040/P1043 (NCT00099359) clinical trial compared 3 infant ARV regimens in formula-fed infants born to mothers who did not receive ARV drugs during the current pregnancy:

- Standard 6 weeks of zidovudine alone
- 6 weeks of zidovudine plus 3 doses of nevirapine given in the first week of life (first dose birth to 48 hours, second dose 48 hours after first dose, third dose 96 hours after second dose)
- 6 weeks of zidovudine plus lamivudine and nelfinavir given from birth through age 2 weeks.[20]

The study demonstrated that both the dual- and triple-combination regimens reduced the risk of intrapartum transmission by approximately 50% compared with infant prophylaxis with zidovudine alone, although there was more hematologic toxicity with the triple regimen (see Supplemental Table 1). Based on these data, combination ARV prophylaxis is now recommended in the United States for infants born to women at increased risk for transmission including those with limited or no prenatal ART, inadequate adherence, or detectable viremia, with the dual regimen of zidovudine plus 3 doses of nevirapine in the first week of life being preferred because of lower rates of toxicity (see Infant Antiretroviral Prophylaxis).

Adding single-dose intrapartum nevirapine is not recommended for women in the United States who are receiving standard recommended antenatal ARV prophylaxis.

PACTG 316, a clinical trial conducted in the United States, Europe, Brazil, and the Bahamas, demonstrated that for non-breastfeeding women in resource-rich countries, the addition of single-dose nevirapine did not offer significant benefit in the setting of combination ARV prophylaxis throughout pregnancy and very low viral load at the time of delivery.[21] Thus, adding single-dose intrapartum nevirapine is not recommended for women in the United States who are receiving standard recommended antenatal ARV prophylaxis (see Intrapartum Antiretroviral Therapy/Prophylaxis).

Breastfeeding by HIV-infected women is not recommended in the United States.

Breastfeeding by HIV-infected women (including those receiving ARV drugs) is not recommended in the United States, where replacement feeding is affordable, feasible, acceptable, sustainable, and safe and the risk of infant mortality due to diarrheal and respiratory infections is low.[22] Clinical trials have demonstrated that both infant prophylaxis (daily infant nevirapine, lamivudine, and ritonavir-boosted lopinavir) during breastfeeding and maternal triple-drug prophylaxis during breastfeeding decrease postnatal infection (see Supplemental Table 1).[2,23-31] Hypothetically, maternal triple-drug prophylaxis may be less effective than infant prophylaxis if the maternal regimen is first started postpartum or late in pregnancy because it takes

several weeks to months before full viral suppression in breast milk is achieved.[27,32] Importantly, although significantly lowering the risk of postnatal infection, neither infant nor maternal postpartum ARV prophylaxis completely eliminates the risk of HIV transmission through breast milk. Therefore, breastfeeding is not recommended for HIV-infected women in the United States (including those receiving combination ARV drug regimens).[22] Finally, both infant nevirapine prophylaxis and maternal triple-drug prophylaxis during breastfeeding may be associated with the development of ARV drug resistance in infants who become infected despite prophylaxis; multi-class drug resistance has been described in breastfeeding infants infected despite maternal triple-drug prophylaxis.[33-37]

Supplemental Table 1. Results of Major Studies on Antiretroviral Interventions to Prevent Perinatal HIV Transmission (page 1 of 7)

Study; Location(s); Mode of Infant Feeding	Antiretroviral Drugs	Antepartum and Intrapartum	Postpartum	Perinatal Transmission Rate and Efficacy
Pediatric AIDS Clinical Trials Group (PACTG) 076; United States, France;[1] Formula feeding	ZDV vs. placebo	Long (from 14 weeks) IV IP	Long (6 weeks); infant only	Perinatal transmission at 18 months was 8.3% in ZDV arm vs. 25.5% in placebo arm (68% efficacy).
CDC Short-Course ZDV Trial; Thailand;[12] Formula feeding	ZDV vs. placebo	Short (from 36 weeks) Oral IP	None	Perinatal transmission at 6 months was 9.4% in ZDV arm vs. 18.9% in placebo arm (50% efficacy).
DITRAME (ANRS 049a) Trial; Ivory Coast, Burkina Faso;[11,38] Breastfeeding	ZDV vs. placebo	Short (from 36 weeks) Oral IP	Short (1 week); mother only	Perinatal transmission was 18.0% in ZDV arm vs. 27.5% in placebo arm at 6 months (38% efficacy) and 21.5% vs. 30.6%, respectively, at 15 months (30% efficacy). Perinatal transmission was 22.5% in ZDV arm vs. 30.2% in placebo arm in pooled analysis at 24 months (26% efficacy).
CDC Short-Course ZDV Trial; Ivory Coast;[10,11] Breastfeeding	ZDV vs. placebo	Short (from 36 weeks) Oral IP	None	Perinatal transmission was 16.5% in ZDV arm vs. 26.1% in placebo arm at 3 months (37% efficacy). Perinatal transmission was 22.5% in ZDV arm vs. 30.2% in placebo arm in pooled analysis at 24 months (26% efficacy).
PETRA Trial; South Africa, Tanzania, Uganda;[5] Breastfeeding and formula feeding	AP/IP/PP ZDV plus 3TC vs. IP/PP ZDV plus 3TC vs. IP-only ZDV plus 3TC vs. Placebo	Short (from 36 weeks) Oral IP	Short (1 week); mother and infant	Perinatal transmission was 5.7% at 6 weeks for AP/IP/PP ZDV plus 3TC, 8.9% for IP/PP ZDV plus 3TC, 14.2% for IP-only ZDV plus 3TC, and 15.3% for placebo (efficacy compared with placebo: 63%, 42%, and 0%, respectively). Perinatal transmission was 14.9% at 18 months for AP/IP/PP ZDV plus 3TC, 18.1% for IP/PP ZDV plus 3TC, 20.0% for IP-only ZDV plus 3TC, and 22.2% for placebo (efficacy compared with placebo: 34%, 18%, and 0%, respectively).

Supplemental Table 1. Results of Major Studies on Antiretroviral Interventions to Prevent Perinatal HIV Transmission (page 2 of 7)

Study; Location(s); Mode of Infant Feeding	Antiretroviral Drugs	Antepartum and Intrapartum	Postpartum	Perinatal Transmission Rate and Efficacy
HIVNET 012 Trial; Uganda;[4] Breastfeeding	SD NVP vs. ZDV	No AP ARV Oral IP: • SD NVP vs. oral ZDV	SD NVP within 72 hours of birth, infant only vs. ZDV (1 week); infant only	Perinatal transmission was 11.8% in NVP arm vs. 20.0% in ZDV arm at 6–8 weeks (42% efficacy) and 15.7% in NVP arm vs. 25.8% in ZDV arm at 18 months (41% efficacy).
SAINT Trial; South Africa;[6] Breastfeeding and formula feeding	SD NVP vs. ZDV plus 3TC	No AP ARV Oral IP: • SD NVP vs. ZDV plus 3TC	SD NVP within 48 hours of birth, mother and infant vs. ZDV plus 3TC (1 week); mother and infant	Perinatal transmission was 12.3% in SD NVP arm vs. 9.3% in ZDV plus 3TC arm at 8 weeks (difference not statistically significant, $P = 0.11$).
Perinatal HIV Prevention Trial (PHPT-1); Thailand;[13] Formula feeding	Four ZDV regimens with different durations of AP and infant PP administration; no placebo	Long (from 28 weeks), short (from 36 weeks) Oral IP	Long (6 weeks), short (3 days); infant only	Short-short arm was stopped at interim analysis (10.5%). Perinatal transmission was 6.5% in long-long arm vs. 4.7% in long-short arm and 8.6% in short-long arm at 6 months (no statistical difference). *In utero* transmission was significantly higher with short vs. long maternal therapy regimens (5.1% vs. 1.6%).
PACTG 316 Trial; Bahamas, Belgium, Brazil, France, Germany, Italy, Spain, Sweden, Switzerland, United Kingdom, United States;[21] Formula feeding	SD NVP vs. placebo among women already receiving ZDV alone (23%) or ZDV plus other ARV drugs (77% combination therapy)	Non-study ARV regimen Oral IP: • Placebo vs. SD NVP plus IV ZDV	Placebo vs. SD NVP within 72 hours of birth plus non-study ARV drugs (ZDV); infant only	77% of women received dual- or triple-combination ARV regimens during pregnancy. Trial stopped early because of very low perinatal transmission in both arms: 1.4% in SD NVP arm vs. 1.6% in placebo arm (53% of perinatal transmission was *in utero*).
Perinatal HIV Prevention Trial (PHPT-2); Thailand;[39] Formula feeding	ZDV alone vs. ZDV plus maternal and infant SD NVP vs. ZDV plus maternal SD NVP	ZDV from 28 weeks Oral IP: • ZDV alone, or • ZDV plus SD NVP	ZDV for 1 week with or without SD NVP; infant only	ZDV-alone arm was stopped because of higher perinatal transmission than the NVP-NVP arm (6.3% vs. 1.1%, respectively). In arms in which the mother received SD NVP, the perinatal transmission rate did not differ significantly between the infant receiving or not receiving SD NVP (2.0% vs. 2.8%, respectively).
DITRAME Plus (ANRS 1201.0) Trial; Ivory Coast;[15] Breastfeeding and formula feeding	Open label, ZDV plus SD NVP	ZDV from 36 weeks Oral IP: • ZDV plus SD NVP	SD NVP plus ZDV for 1 week; infant only	Perinatal transmission was 6.5% (95% CI, 3.9% to 9.1%) at 6 weeks; perinatal transmission for historical control group receiving short ZDV (98% breastfed) was 12.8%.
DITRAME Plus (ANRS 1201.1) Trial; Ivory Coast;[15] Breastfeeding and formula feeding	Open label, ZDV plus 3TC plus SD NVP	ZDV plus 3TC from 32 weeks (stopped at 3 days PP) Oral IP: • ZDV plus 3TC plus SD NVP	SD NVP plus ZDV for 1 week; infant only	Perinatal transmission was 4.7% (95% CI, 2.4% to 7.0%) at 6 weeks; perinatal transmission for historical control group receiving short ZDV (98% breastfed) was 12.8%.

Supplemental Table 1. Results of Major Studies on Antiretroviral Interventions to Prevent Perinatal HIV Transmission (page 3 of 7)

Study; Location(s); Mode of Infant Feeding	Antiretroviral Drugs	Antepartum and Intrapartum	Postpartum	Perinatal Transmission Rate and Efficacy
NVAZ Trial; Malawi;[7] Breastfeeding	Neonatal SD NVP vs. SD NVP plus ZDV	No AP or IP ARV (latecomers)	SD NVP with or without ZDV for 1 week; infant only	Perinatal transmission was 15.3% in SD NVP plus ZDV arm and 20.9% in SD NVP-only arm at 6–8 weeks. Perinatal transmission rates at 6–8 weeks among infants who were HIV uninfected at birth were 7.7% and 12.1%, respectively (36% efficacy).
Postnatal NVP plus ZDV Trial; Malawi;[8] Breastfeeding	Neonatal SD NVP vs. SD NVP plus ZDV	No AP ARV Oral IP: • SD NVP	SD NVP with or without ZDV for 1 week; infant only	Perinatal transmission was 16.3% in NVP plus ZDV arm and 14.1% in SD NVP-only arm at 6–8 weeks (difference not statistically significant). Perinatal transmission rates at 6–8 weeks among infants who were HIV uninfected at birth were 6.5% and 16.9%, respectively.
Post-Exposure Infant Prophylaxis; South Africa;[9] Breastfeeding and formula feeding	Neonatal SD NVP vs. ZDV for 6 weeks	No AP or IP ARV	SD NVP vs. ZDV for 6 weeks	For formula-fed infants only, perinatal transmission was 14.3% in SD NVP arm vs. 14.1% in ZDV arm at 6 weeks (not significant, $P = 0.30$). For breastfed infants only, perinatal transmission was 12.2% in SD NVP arm and 19.6% in ZDV arm ($P = 0.03$).
Mashi; Botswana;[40,41] Breastfeeding and formula feeding	Initial: • Short-course ZDV with/without maternal and infant SD NVP and with/without breastfeeding Revised: • Short-course ZDV plus infant SD NVP with/without maternal SD NVP and with/without breastfeeding; women with CD4 counts <200 cells/mm^3 receive combination therapy.	First Randomization: • ZDV from 34 weeks Oral IP: • ZDV plus either SD NVP or placebo	Second Randomization: • Breastfeeding plus ZDV (infant) 6 months plus SD NVP; infant only, vs. • Formula feeding plus ZDV (infant) 4 weeks plus SD NVP; infant only	Initial Design: • In formula-feeding arm, perinatal transmission at 1 month was 2.4% in maternal and infant SD NVP arm and 8.3% in placebo arm ($P = 0.05$). • In breastfeeding plus infant ZDV arm, perinatal transmission at 1 month was 8.4% in SD NVP arm and 4.1% in placebo arm (difference not statistically significant). Revised Design: • Perinatal transmission at 1 month was 4.3% in maternal plus infant SD NVP arm and 3.7% in maternal placebo plus infant SD NVP arm (no significant difference; no interaction with mode of infant feeding). Perinatal transmission at 7 months was 9.1% in breastfeeding plus ZDV arm and 5.6% in formula-feeding arm; mortality at 7 months was 4.9% in breastfeeding plus ZDV arm vs. 9.3% in formula-feeding arm; HIV-free survival at 18 months was 15.6% in the breastfeeding plus ZDV arm vs. 14.2% in the formula-feeding arm.

Supplemental Table 1. Results of Major Studies on Antiretroviral Interventions to Prevent Perinatal HIV Transmission (page 4 of 7)

Study; Location(s); Mode of Infant Feeding	Antiretroviral Drugs	Antepartum and Intrapartum	Postpartum	Perinatal Transmission Rate and Efficacy
SWEN; Uganda, Ethiopia, India;[24] Breastfeeding	SD NVP vs. NVP for 6 weeks	No AP ARV Oral IP: • SD NVP	Infant SD NVP vs. NVP for 6 weeks	Postnatal Infection in Infants Uninfected at Birth: • Perinatal transmission at 6 weeks was 5.3% in SD NVP arm vs. 2.5% in extended NVP arm (risk ratio 0.54, *P* = 0.009). • Perinatal transmission at 6 months was 9.0% in SD NVP arm vs. 6.9% in extended NVP arm (risk ratio 0.80, *P* = 0.16). HIV-free survival was significantly lower in extended NVP arm at both 6 weeks and 6 months of age.
PEPI-Malawi Trial; Malawi;[23] Breastfeeding	SD NVP plus ZDV for 1 week (control) vs. Two extended infant regimens (NVP or NVP/ZDV) for 14 weeks	No AP ARV Oral IP: • SD NVP (if mother presents in time)	Infant SD NVP plus ZDV for 1 week (control) vs. Control plus NVP for 14 weeks vs. Control plus NVP/ZDV for 14 weeks	Postnatal Infection in Infants Uninfected at Birth: • Perinatal transmission at age 6 weeks was 5.1% in control vs. 1.7% in extended NVP (67% efficacy) and 1.6% in extended NVP/ZDV arms (69% efficacy). • Perinatal transmission at age 9 months was 10.6% in control vs. 5.2% in extended NVP (51% efficacy) and 6.4% in extended NVP/ZDV arms (40% efficacy). No significant difference in perinatal transmission between the extended prophylaxis arms; however, more hematologic toxicity with NVP/ZDV.
MITRA; Tanzania;[26] Breastfeeding	Infant 3TC for 6 months (observational)	ZDV/3TC from 36 weeks through labor	Maternal ZDV/3TC for 1 week, infant 3TC for 6 months	Perinatal transmission at age 6 months was 4.9% (postnatal perinatal transmission between ages 6 weeks and 6 months was 1.2%).
Kisumu Breastfeeding Study (KiBS); Kenya;[29] Breastfeeding	Maternal triple-drug prophylaxis (observational)	ZDV/3TC/NVP (NFV if CD4 count >250 cells/mm^3) from 34 weeks through labor	Maternal ZDV/3TC/NVP (NFV if CD4 count >250 cells/mm^3) for 6 months, infant SD NVP	Perinatal transmission at age 6 months was 5.0% (postnatal perinatal transmission between ages 7 days and 6 months was 2.6%).
MITRA-PLUS; Tanzania;[25] Breastfeeding	Maternal triple-drug prophylaxis (observational)	ZDV/3TC/NVP (NFV if CD4 count >200 cells/mm^3) from 34 weeks through labor	Maternal ZDV/3TC/NVP (NFV if CD4 count >200 cells/mm^3) for 6 months, infant ZDV/3TC for 1 week	Perinatal transmission at age 6 months was 5.0% (postnatal perinatal transmission between ages 6 weeks and 6 months was 0.9%), not significantly different from 6-month infant prophylaxis in MITRA.

Supplemental Table 1. Results of Major Studies on Antiretroviral Interventions to Prevent Perinatal HIV Transmission (page 5 of 7)

Study; Location(s); Mode of Infant Feeding	Antiretroviral Drugs	Antepartum and Intrapartum	Postpartum	Perinatal Transmission Rate and Efficacy
Kesho Bora; Multi-African;[28] Breastfeeding primarily	Antepartum ZDV/SD NVP with no postnatal prophylaxis vs. Maternal triple-drug prophylaxis in women with CD4 counts 200–500 cells/mm^3	Arm 1: • ZDV/3TC/LPV/r Arm 2: • ZDV plus SD NVP From 28 weeks through labor	Arm 1: • Maternal ZDV/3TC/LPV/r for 6 months, infant SD NVP plus ZDV for 1 week Arm 2: • Maternal ZDV/3TC for 1 week (no further postnatal prophylaxis), infant SD NVP plus ZDV for 1 week (no further postnatal prophylaxis)	Perinatal transmission at birth was 1.8% with maternal triple-drug prophylaxis (Arm 1) and 2.5% with ZDV/SD NVP (Arm 2), **not** significantly different. In women with CD4 counts 350–500 cells/mm^3, perinatal transmission at birth was 1.7% in both arms. Perinatal transmission at age 12 months was 5.4% with maternal triple-drug prophylaxis (Arm 1) and 9.5% with ZDV/SD NVP (with no further postnatal prophylaxis after 1 week) (Arm 2) (P = 0.029).
Mma Bana; Botswana;[2] Breastfeeding	Maternal triple-drug prophylaxis (compares 2 regimens) in women with CD4 counts >200 cells/mm^3	Arm 1: • ZDV/3TC/ABC Arm 2: • ZDV/3TC/LPV/r From 26 weeks through labor	Arm 1: • Maternal ZDV/3TC/ABC for 6 months, infant SD NVP plus ZDV for 4 weeks Arm 2: • Maternal ZDV/3TC/LPV/r for 6 months, infant SD NVP plus ZDV for 4 weeks	Perinatal transmission at age 6 months overall was 1.3%: 2.1% in ZDV/3TC/ABC Arm 1 and 0.4% in ZDV/3TC/LPV/r Arm 2 (P = 0.53).
BAN; Malawi;[27,42] Breastfeeding	Postpartum maternal triple-drug prophylaxis vs. infant NVP in women with CD4 counts ≥250 cells/mm^3	No AP drugs IP Regimens *Arm 1 (Control):* • ZDV/3TC plus SD NVP *Arm 2:* • ZDV/3TC plus SD NVP *Arm 3:* • ZDV/3TC plus SD NVP	Arm 1 (Control): • Maternal ZDV/3TC for 1 week, infant SD NVP plus ZDV/3TC for 1 week Arm 2: • Control as above, then maternal ZDV/3TC/LPV/r for 6 months Arm 3: • Control as above, then infant NVP for 6 months	Postnatal Infection in Infants Uninfected at Age 2 Weeks: • Perinatal transmission at age 28 weeks was 5.7% in control Arm 1, 2.9% in maternal triple-drug prophylaxis Arm 2 (P = 0.009 vs. control), and 1.7% in infant NVP Arm 3 (P <0.001 vs. control). • Perinatal transmission at age 48 weeks was 7.0% in control Arm 1, 4.0% in maternal triple-drug prophylaxis Arm 2 (P = 0.0273 vs. control), and 4% in infant NVP Arm 3 (P = 0.0027 vs. control). No significant difference between maternal triple-drug prophylaxis (Arm 2) and infant NVP (Arm 3) (P = 0.12 at 28 weeks and P = 0.426 at 48 weeks).

Supplemental Table 1. Results of Major Studies on Antiretroviral Interventions to Prevent Perinatal HIV Transmission (page 6 of 7)

Study; Location(s); Mode of Infant Feeding	Antiretroviral Drugs	Antepartum and Intrapartum	Postpartum	Perinatal Transmission Rate and Efficacy
HPTN 046; South Africa, Tanzania, Uganda, Zimbabwe;[37,43] **Breastfeeding**	Postpartum prophylaxis of breast milk transmission of HIV with 6 weeks vs. 6 months of infant NVP	AP drugs allowed if required for maternal health	All infants received daily NVP from birth through age 6 weeks. Arm 1: • Daily infant NVP from age 6 weeks through age 6 months Arm 2: • Daily infant placebo from age 6 weeks through age 6 months	In infants uninfected at age 6 weeks, the 6-month infant HIV infection rate was 1.1% (0.3% to 1.8%) in the extended NVP Arm 1 and 2.4% (1.3% to 3.6%) in the placebo Arm 2 (*P* = 0.048). 18-month postnatal infection rates were 2.2% (1.1% to 3.3%) in the extended NVP Arm 1 and 3.1% (1.9% to 4.4%) in the placebo Arm 2 (*P* = 0.28). HIV infection and mortality rates did not differ between arms at any age through 18 months. At infant randomization at age 6 weeks, 29% of mothers in each arm were receiving a triple-drug ARV regimen for the treatment of HIV. For mothers receiving triple-drug ARV regimens at the time of randomization, in infants uninfected at age 6 weeks, the 6-month infant HIV infection rate was 0.2% and not statistically different between the extended NVP Arm 1 (0.5%) and placebo Arm 2 (0%). For mothers with CD4 counts >350 cells/mm^3 who were not receiving triple-drug ARV regimens, in infants uninfected at age 6 weeks, the 6-month infant HIV infection rate was 0.7% (0% to 1.5%) in the extended NVP Arm 1 and 2.8% (1.3% to 4.4%) in the placebo Arm 2 (*P* = 0.014).
NICHD-HPTN 040/ PACTG 1043 Trial; Brazil, Argentina, South Africa, United States;[44] **Formula feeding**	Infant prophylaxis with 6 weeks ZDV vs. 6 weeks infant ZDV plus 3 doses of NVP in first week of life vs. 6 weeks infant ZDV plus 2 weeks 3TC/NFV	No AP drugs If mother presented early enough, IV ZDV during labor through delivery	Arm 1 (Control): • Infant ZDV for 6 weeks Arm 2: • Control as above plus NVP with first dose within 48 hours of birth, second dose 48 hours later, and third dose 96 hours after the second dose Arm 3: • Control as above, plus 3TC and NFV from birth through age 2 weeks	IP HIV transmission among infants with negative HIV test at birth: 4.8% (3.2% to 7.1%) with ZDV (Arm 1) vs. 2.2% (1.2% to 3.9%) with ZDV plus NVP (Arm 2) (*P* = 0.046 compared with Arm 1) vs. 2.4% (1.4% to 4.3%) with ZDV plus 3TC/NFV (Arm 3) (*P* = 0.046 compared with Arm 1). Overall HIV transmission rates, including *in utero* infection: 11.0% (8.7% to 14.0%) with ZDV (Arm 1) vs. 7.1% (5.2% to 9.6%) with ZDV plus NVP (Arm 2) (*P* = 0.035 compared with Arm 1) vs. 7.4% (5.4% to 9.9%) with ZDV plus 3TC/NFV (Arm 3) (*P* = 0.035 compared with Arm 1). Grade 3 or 4 neutropenia more frequent in ZDV/3TC/NFV Arm 3, 70 infants, compared with ZDV-alone Arm 1, 33 infants, or ZDV/NVP Arm 2, 32 infants (*P* <0.001).

Supplemental Table 1. Results of Major Studies on Antiretroviral Interventions to Prevent Perinatal HIV Transmission (page 7 of 7)

Study; Location(s); Mode of Infant Feeding	Antiretroviral Drugs	Antepartum and Intrapartum	Postpartum	Perinatal Transmission Rate and Efficacy
ANRS 12174 Trial; Burkina Faso, South Africa, Uganda, Zambia;[30,31] Breastfeeding	Compared 2 infant ARV prophylaxis regimens during breastfeeding; infants testing PCR-negative at birth, born to mothers with CD4 counts >350 cells/mm^3	As per standard of care	Arm 1: • Daily infant LPV/r from 1 week through 50 weeks of age Arm 2: • Daily infant 3TC from 1 week through 50 weeks of age	Postnatal Infection in Infants Uninfected at Birth: • Postnatal transmission at age 50 weeks was 1.4% (0.70–2.76) in Arm 1 and 1.5% (0.80–2.91) in Arm 2 (*P* = 0.83). • HIV-free survival was 96.5% (84.6–97.7) in Arm 1 and 96.3% (94.4–975) in Arm 2 (*P* = 0.85).
PROMOTE; Uganda;[45] Breastfeeding	Compared 2 triple-ARV regimens; no CD4 restriction	Arm 1: • AZT/3TC/LPV/r Arm 2: • AZT/3TC/EFV • ARVs started at 12–28 weeks' gestation and continued through labor	Randomized regimen continued postpartum through 1 year of breastfeeding	HIV-free survival was 92.9% in the LPV/r arm vs. 97.2% in the EFV arm (*P* = 0.10). Only 2 of 374 liveborn infants acquired infection, both in the LPV/r arm.
PROMISE; India, Malawi, South Africa, Tanzania, Uganda, Zambia, Zimbabwe;[18] Breastfeeding and formula feeding (antepartum component)	Compared 2 ARV regimens during pregnancy among women >14 weeks gestation and CD4 counts ≥350 cells/mm^3	Arm 1: • ZDV during pregnancy plus SD NVP plus TDF plus FTC at delivery Arm 2: • ZDV plus 3TC plus LPV/r Arm 3: • TDF plus FTC plus LPV/r	Arm 1: • TDF/FTC tail continued for 6–14 days postpartum Arms 2 and 3: • Triple-drug regimen continued for 6–14 days postpartum Infants received once-daily NVP for 6 weeks.	Infant HIV Infection Rates by Age 14 Days *Arm 1:* • 1.8% (25/1,386) *Arm 2:* • 0.5% (7/1,385) *Arm 3:* • 0.6% (2/325) Combined triple-ARV arms vs. Arm 1 difference in perinatal transmission risk: -1.28% (95% CI, -2.11% to -0.44%)

Key to Abbreviations: 3TC = lamivudine; ABC = abacavir; AP = antepartum; ARV = antiretroviral; CD4 = CD4 T lymphocyte; CDC = Centers for Disease Control and Prevention; CI = confidence interval; EFV = efavirenz; FTC = emtricitabine; IP = intrapartum; IV = intravenous; LPV/r = lopinavir/ritonavir; NFV = nelfinavir; NVP = nevirapine; PCR = polymerase chain reaction; PP = postpartum; SD = single-dose; TDF = tenofovir disoproxil fumarate; ZDV = zidovudine

References

1. Connor EM, Sperling RS, Gelber R, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. *N Engl J Med*. 1994;331(18):1173-1180. Available at http://www.ncbi.nlm.nih.gov/pubmed/7935654.
2. Shapiro RL, Hughes MD, Ogwu A, et al. Antiretroviral regimens in pregnancy and breast-feeding in Botswana. *N Engl J Med*. 2010;362(24):2282-2294. Available at http://www.ncbi.nlm.nih.gov/pubmed/20554983.
3. Kesho Bora Study Group. Eighteen-month follow-up of HIV-1-infected mothers and their children enrolled in the Kesho Bora study observational cohorts. *J Acquir Immune Defic Syndr*. 2010;54(5):533-541. Available at http://www.ncbi.nlm.nih.gov/pubmed/20543706.
4. Jackson JB, Musoke P, Fleming T, et al. Intrapartum and neonatal single-dose nevirapine compared with zidovudine

for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: 18-month follow-up of the HIVNET 012 randomised trial. *Lancet*. 2003;362(9387):859-868. Available at http://www.ncbi.nlm.nih.gov/pubmed/13678973.

5. Petra Study T. Efficacy of three short-course regimens of zidovudine and lamivudine in preventing early and late transmission of HIV-1 from mother to child in Tanzania, South Africa, and Uganda (Petra study): a randomised, double-blind, placebo-controlled trial. *Lancet*. 2002;359(9313):1178-1186. Available at http://www.ncbi.nlm.nih.gov/pubmed/11955535.
6. Moodley D, Moodley J, Coovadia H, et al. A multicenter randomized controlled trial of nevirapine versus a combination of zidovudine and lamivudine to reduce intrapartum and early postpartum mother-to-child transmission of human immunodeficiency virus type 1. *J Infect Dis*. 2003;187(5):725-735. Available at http://www.ncbi.nlm.nih.gov/pubmed/12599045.
7. Taha TE, Kumwenda NI, Gibbons A, et al. Short postexposure prophylaxis in newborn babies to reduce mother-to-child transmission of HIV-1: NVAZ randomised clinical trial. *Lancet*. 2003;362(9391):1171-1177. Available at http://www.ncbi.nlm.nih.gov/pubmed/14568737.
8. Taha TE, Kumwenda NI, Hoover DR, et al. Nevirapine and zidovudine at birth to reduce perinatal transmission of HIV in an African setting: a randomized controlled trial. *JAMA*. 2004;292(2):202-209. Available at http://www.ncbi.nlm.nih.gov/pubmed/15249569.
9. Gray GE, Urban M, Chersich MF, et al. A randomized trial of two postexposure prophylaxis regimens to reduce mother-to-child HIV-1 transmission in infants of untreated mothers. *AIDS*. 2005;19(12):1289-1297. Available at http://www.ncbi.nlm.nih.gov/pubmed/16052084.
10. Wiktor SZ, Ekpini E, Karon JM, et al. Short-course oral zidovudine for prevention of mother-to-child transmission of HIV-1 in Abidjan, Cote d'Ivoire: a randomised trial. *Lancet*. 1999;353(9155):781-785. Available at http://www.ncbi.nlm.nih.gov/pubmed/10459958.
11. Leroy V, Karon JM, Alioum A, et al. Twenty-four month efficacy of a maternal short-course zidovudine regimen to prevent mother-to-child transmission of HIV-1 in West Africa. *AIDS*. 2002;16(4):631-641. Available at http://www.ncbi.nlm.nih.gov/pubmed/11873008.
12. Shaffer N, Chuachoowong R, Mock PA, et al. Short-course zidovudine for perinatal HIV-1 transmission in Bangkok, Thailand: a randomised controlled trial. Bangkok Collaborative Perinatal HIV Transmission Study Group. *Lancet*. 1999;353(9155):773-780. Available at http://www.ncbi.nlm.nih.gov/pubmed/10459957.
13. Lallemant M, Jourdain G, Le Coeur S, et al. A trial of shortened zidovudine regimens to prevent mother-to-child transmission of human immunodeficiency virus type 1. Perinatal HIV Prevention Trial (Thailand) Investigators. *N Engl J Med*. 2000;343(14):982-991. Available at http://www.ncbi.nlm.nih.gov/pubmed/11018164.
14. Leroy V, Sakarovitch C, Cortina-Borja M, et al. Is there a difference in the efficacy of peripartum antiretroviral regimens in reducing mother-to-child transmission of HIV in Africa? *AIDS*. 2005;19(16):1865-1875. Available at http://www.ncbi.nlm.nih.gov/pubmed/16227795.
15. Dabis F, Bequet L, Ekouevi DK, et al. Field efficacy of zidovudine, lamivudine and single-dose nevirapine to prevent peripartum HIV transmission. *AIDS*. 2005;19(3):309-318. Available at http://www.ncbi.nlm.nih.gov/pubmed/15718842.
16. Lallemant M, Le Coeur S, Sirirungsi W, et al. Randomized noninferiority trial of two maternal single-dose nevirapine-sparing regimens to prevent perinatal HIV in Thailand. *AIDS*. 2015;29(18):2497-2507. Available at http://www.ncbi.nlm.nih.gov/pubmed/26372485.
17. Townsend CL, Cortina-Borja M, Peckham CS, de Ruiter A, Lyall H, Tookey PA. Low rates of mother-to-child transmission of HIV following effective pregnancy interventions in the United Kingdom and Ireland, 2000-2006. *AIDS*. 2008;22(8):973-981. Available at http://www.ncbi.nlm.nih.gov/pubmed/18453857.
18. Fowler M, Qin M, Shapiro D, et al. PROMISE: Efficacy and safety of 2 strategies to prevent perinatal HIV transmission. Presented at: 22nd Conference on Retroviruses and Opportunistic Infections. 2015. Seattle, WA.
19. Wade NA, Birkhead GS, Warren BL, et al. Abbreviated regimens of zidovudine prophylaxis and perinatal transmission of the human immunodeficiency virus. *N Engl J Med*. 1998;339(20):1409-1414. Available at http://www.ncbi.nlm.nih.gov/pubmed/9811915.
20. Nielsen-Saines K, Watts DH, Veloso VG, et al. Three postpartum antiretroviral regimens to prevent intrapartum HIV infection. *N Engl J Med*. 2012;366(25):2368-2379. Available at http://www.ncbi.nlm.nih.gov/pubmed/22716975.
21. Dorenbaum A, Cunningham CK, Gelber RD, et al. Two-dose intrapartum/newborn nevirapine and standard antiretroviral therapy to reduce perinatal HIV transmission: a randomized trial. *JAMA*. 2002;288(2):189-198. Available at http://www.ncbi.nlm.nih.gov/pubmed/12095383.

22. Committee on Pediatric AIDS. Infant feeding and transmission of human immunodeficiency virus in the United States. *Pediatrics*. 2013;131(2):391-396. Available at http://www.ncbi.nlm.nih.gov/pubmed/23359577.

23. Kumwenda NI, Hoover DR, Mofenson LM, et al. Extended antiretroviral prophylaxis to reduce breast-milk HIV-1 transmission. *N Engl J Med*. 2008;359(2):119-129. Available at http://www.ncbi.nlm.nih.gov/pubmed/18525035.

24. Six Week Extended-Dose Nevirapine Study T, Bedri A, Gudetta B, et al. Extended-dose nevirapine to 6 weeks of age for infants to prevent HIV transmission via breastfeeding in Ethiopia, India, and Uganda: an analysis of three randomised controlled trials. *Lancet*. 2008;372(9635):300-313. Available at http://www.ncbi.nlm.nih.gov/pubmed/18657709.

25. Kilewo C, Karlsson K, Ngarina M, et al. Prevention of mother-to-child transmission of HIV-1 through breastfeeding by treating mothers with triple antiretroviral therapy in Dar es Salaam, Tanzania: the Mitra Plus study. *J Acquir Immune Defic Syndr*. 2009;52(3):406-416. Available at http://www.ncbi.nlm.nih.gov/pubmed/19730269.

26. 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. *J Acquir Immune Defic Syndr*. 2008;48(3):315-323. Available at http://www.ncbi.nlm.nih.gov/pubmed/18344879.

27. Chasela CS, Hudgens MG, Jamieson DJ, et al. Maternal or infant antiretroviral drugs to reduce HIV-1 transmission. *N Engl J Med*. 2010;362(24):2271-2281. Available at http://www.ncbi.nlm.nih.gov/pubmed/20554982.

28. Kesho Bora Study Group, de Vincenzi I. Triple antiretroviral compared with zidovudine and single-dose nevirapine prophylaxis during pregnancy and breastfeeding for prevention of mother-to-child transmission of HIV-1 (Kesho Bora study): a randomised controlled trial. *Lancet Infect Dis*. 2011;11(3):171-180. Available at http://www.ncbi.nlm.nih.gov/pubmed/21237718.

29. Thomas TK, Masaba R, Borkowf CB, et al. Triple-antiretroviral prophylaxis to prevent mother-to-child HIV transmission through breastfeeding--the Kisumu Breastfeeding Study, Kenya: a clinical trial. *PLoS Med*. 2011;8(3):e1001015. Available at http://www.ncbi.nlm.nih.gov/pubmed/21468300.

30. Kankasa C, Nagot N, Meda N. Infant Lopinavir/r Versus 3TC to Prevent Postnatal HIV-1 Transmission: The ANRS 12174 Trial. 21st Conference on Retroviruses and Opportunistic Infections (CROI 2014); 2014; Boston, MA.

31. Nagot N, Kankasa C, Tumwine JK, et al. Extended pre-exposure prophylaxis with lopinavir-ritonavir versus lamivudine to prevent HIV-1 transmission through breastfeeding up to 50 weeks in infants in Africa (ANRS 12174): a randomised controlled trial. *Lancet*. 2016;387(10018):566-573. Available at http://www.ncbi.nlm.nih.gov/pubmed/26603917.

32. Mofenson LM. Protecting the next generation—eliminating perinatal HIV-1 infection. *N Engl J Med*. 2010;362(24):2316-2318. Available at http://www.ncbi.nlm.nih.gov/pubmed/20554987.

33. 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(1):e4096. Available at http://www.ncbi.nlm.nih.gov/pubmed/19119321.

34. Lidstrom J, Guay L, Musoke P, et al. Multi-class drug resistance arises frequently in HIV-infected breastfeeding infants whose mothers initiate HAART postpartum. 17th Conference on Retroviruses and Opportunistic Infections. 2010. San Francisco, CA.

35. Zeh C, Weidle PJ, Nafisa L, et al. HIV-1 drug resistance emergence among breastfeeding infants born to HIV-infected mothers during a single-arm trial of triple-antiretroviral prophylaxis for prevention of mother-to-child transmission: a secondary analysis. *PLoS Med*. 2011;8(3):e1000430. Available at http://www.ncbi.nlm.nih.gov/pubmed/21468304.

36. Fogel J, Li Q, Taha TE, et al. Initiation of antiretroviral treatment in women after delivery can induce multiclass drug resistance in breastfeeding HIV-infected infants. *Clin Infect Dis*. 2011;52(8):1069-1076. Available at http://www.ncbi.nlm.nih.gov/pubmed/21460326.

37. Coovadia HM, Brown ER, Fowler MG, et al. Efficacy and safety of an extended nevirapine regimen in infant children of breastfeeding mothers with HIV-1 infection for prevention of postnatal HIV-1 transmission (HPTN 046): a randomised, double-blind, placebo-controlled trial. *Lancet*. 2012;379(9812):221-228. Available at http://www.ncbi.nlm.nih.gov/pubmed/22196945.

38. Dabis F, Msellati P, Meda N, et al. 6-month efficacy, tolerance, and acceptability of a short regimen of oral zidovudine to reduce vertical transmission of HIV in breastfed children in Cote d'Ivoire and Burkina Faso: a double-blind placebo-controlled multicentre trial. DITRAME Study Group. Diminution de la Transmission Mere-Enfant. *Lancet*. 1999;353(9155):786-792. Available at http://www.ncbi.nlm.nih.gov/pubmed/10459959.

39. 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(3):217-228. Available at http://www.ncbi.nlm.nih.gov/pubmed/15247338.

40. Shapiro RL, Thior I, Gilbert PB, et al. Maternal single-dose nevirapine versus placebo as part of an antiretroviral strategy to prevent mother-to-child HIV transmission in Botswana. *AIDS*. 2006;20(9):1281-1288. Available at http://www.ncbi.nlm.nih.gov/pubmed/16816557.

41. 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(7):794-805. Available at http://www.ncbi.nlm.nih.gov/pubmed/16905785.

42. Jamieson DJ, Chasela CS, Hudgens MG, et al. Maternal and infant antiretroviral regimens to prevent postnatal HIV-1 transmission: 48-week follow-up of the BAN randomised controlled trial. *Lancet*. 2012. Available at http://www.ncbi.nlm.nih.gov/pubmed/22541418.

43. Fowler MG, Coovadia H, Herron CM, et al. Efficacy and safety of an extended nevirapine regimen in infants of breastfeeding mothers with HIV-1 infection for prevention of HIV-1 transmission (HPTN 046): 18-month results of a randomized, double-blind, placebo-controlled trial. *J Acquir Immune Defic Syndr*. 2014;65(3):366-374. Available at http://www.ncbi.nlm.nih.gov/pubmed/24189151.

44. Nielsen-Saines K, al. Tenofovir disoproxil fumarate (TDF) pharmacokinetics (PK) with daily dosing in the first week of life (HPTN 057). Abstract no. TUAB0201. Presented at: 19th International AIDS Conference. 2012. Washington, DC.

45. Cohan D, Natureeba P, Koss CA, et al. Efficacy and safety of lopinavir/ritonavir versus efavirenz-based antiretroviral therapy in HIV-infected pregnant Ugandan women. *AIDS*. 2015;29(2):183-191. Available at http://www.ncbi.nlm.nih.gov/pubmed/25426808.