APPENDIX D: REVIEW OF CLINICAL TRIALS OF ANTIRETROVIRAL INTERVENTIONS TO PREVENT PERINATAL HIV TRANSMISSION

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June 02, 2023: This Appendix was last reviewed in 2018 and no longer reflects the latest Panel recommendations. It has been maintained in the Guidelines to provide a resource for historical context of clinical trials to advance the prevention of perinatal HIV transmission.

One of the major achievements in HIV research was the demonstration by the PACTG 076 clinical trial that administering 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 that are more applicable in resource-constrained settings. In addition, multiple studies have tried to determine the optimal regimens for reducing the risk of postnatal transmission during breastfeeding. More recently, in the context of recommendations for universal antiretroviral therapy (ART), studies have also explored the efficacy of universal ART during pregnancy and breastfeeding. This Appendix provides a table summarizing the results of major studies of antiretroviral (ARV) interventions used to prevent perinatal transmission (see Supplemental Table 1) and a brief discussion of lessons learned. In many cases, a direct comparison of results from these trials is not possible because the studies involved diverse patient populations from different geographic locations, with differing viral subtypes and 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. Furthermore, these studies have provided critical information elucidating the risks, timing, and mechanisms of perinatal transmission.

ART is more effective antenatally in reducing perinatal transmission than a single-drug prophylactic regimen.

ARV drugs are highly effective at preventing perinatal transmission, even in women living with advanced HIV.[2,3] Efficacy has been demonstrated for a number of short-course ARV regimens, including 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 the risk of perinatal transmission. In addition, administering ARV drugs during the antepartum, intrapartum, and postpartum periods is a more effective approach for preventing perinatal transmission than administering 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. Regimens with antenatal components, including those starting as late as 36 weeks' gestation, can reduce the risk of perinatal transmission, even when these regimens are lacking an infant prophylaxis component.[10-12] However, longer-duration antenatal zidovudine prophylaxis that begins at 28 weeks' gestation is more effective than shorter-duration zidovudine prophylaxis that begins at 35 weeks' gestation.[13] The Perinatal HIV Prevention Trial (PHPT)-5 trial demonstrated that women who received <8 weeks of prophylaxis during pregnancy had a significantly greater risk of

perinatal transmission than women who received longer durations of prophylaxis.[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 Promoting Maternal and Infant Survival Everywhere (PROMISE) study was a large randomized clinical trial that demonstrated the superiority of 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 (LPV/r)
- TDF plus emtricitabine plus LPV/r

The rate of perinatal transmission through 1 week of life was significantly lower among women receiving ART (0.5%, 9 infections among 1,710 infants) than among those randomized to receive zidovudine plus single-dose nevirapine plus postpartum TDF/emtricitabine tail (1.8%, 25 infections among 1,386 infants).

Regimens that do not include maternal ARV therapy 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 the risk of 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 the risk of transmission.[5] The South African Intrapartum Nevirapine Trial (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 at high risk for HIV acquisition.

Delayed maternal HIV diagnosis or delayed presentation for pregnancy care may result in missing the opportunity to provide maternal ARV drugs during pregnancy or labor. In the absence of maternal therapy, the standard infant prophylaxis regimen of 6 weeks of zidovudine was effective in reducing the risk of 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 three 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 three doses of nevirapine given in the first week of life (first dose given within 48 hours of birth, second dose given 48 hours after first dose, third dose given 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 who are at increased risk for transmission (see Antiretroviral Management of Infants With *In Utero*, Intrapartum, or Breastfeeding Exposure to HIV).

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 adding single-dose nevirapine to combination antenatal ARV prophylaxis for non-breastfeeding women with very low viral loads at the time of delivery did not offer significant benefit.[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 women with HIV infection is not recommended in the United States.

Breastfeeding by women living with HIV (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 in resource-limited settings have demonstrated that both infant prophylaxis (daily infant nevirapine, lamivudine, and LPV/r) during breastfeeding and maternal triple-drug prophylaxis during breastfeeding decrease the risk of postnatal infection (see Supplemental Table 1).[2,23-31] The PROMISE trial was a large, randomized clinical trial that demonstrated that daily infant nevirapine and maternal ART have similar safety and efficacy for prevention of perinatal transmission during breastfeeding in women with CD4 cell counts ≥350 cells/mm3.[18,32] At 6 to 14 days postpartum, the study randomized participants to receive either infant nevirapine or maternal ART until 18 months after delivery or breastfeeding cessation. The rates of perinatal transmission were similar (0.58%, 5 infections among 1,211 infants receiving nevirapine vs. 0.57%, 7 infections among 1,219 infants whose mothers received ART), both strategies were safe, and infant HIV-1–free survival was high across both arms (97.7% with infant nevirapine vs. 97.1% with maternal ART at 24 months).

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 to achieve full viral suppression in breast milk.[27,33] Importantly, although prophylaxis significantly lowers the risk of postnatal infection, neither infant nor maternal postpartum ARV prophylaxis eliminates the risk of HIV transmission through breast milk. Therefore, breastfeeding is not recommended for women living in the United States (including those receiving combination ARV drug regimens).[22] Finally, both infant nevirapine prophylaxis and maternal ART during breastfeeding may be associated with the development of ARV drug resistance in infants who

acquire HIV despite prophylaxis; multiclass drug resistance has been described in breastfeeding infants with HIV despite maternal triple-drug prophylaxis.[34-38]

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

Study Name; Location(s); Mode of Infant Feeding	Antiretroviral Drugs	Antepartum and Intrapartum Interventions	Postpartum Interventions	Perinatal Transmission Rate and Efficacy
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;[11,39] Breastfeeding	ZDV vs. placebo	Short (from 36 weeks) Oral IP	Short (1 week); mother only	Perinatal transmission at 6 months was 18.0% in ZDV arm vs. 27.5% in placebo arm (38% efficacy). Perinatal transmission at 15 months was 21.5% in ZDV arm vs. 30.6% in placebo arm (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 at 3 months was 16.5% in ZDV arm vs. 26.1% in placebo arm (37% efficacy). Perinatal transmission was 22.5% in ZDV arm vs. 30.2% in placebo arm in pooled analysis at 24 months (26% efficacy).

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Study Name; Location(s); Mode of Infant Feeding	Antiretroviral Drugs	Antepartum and Intrapartum Interventions	Postpartum Interventions	Perinatal Transmission Rate and 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 at 6 weeks was 5.7% 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 at 18 months was 14.9% 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).
HIVNET 012 Trial; Uganda;[4] Breastfeeding	SD NVP vs. ZDV	No AP ARV drugs Oral IP • SD NVP vs. oral ZDV	SD NVP within 72 hours of birth; infant only vs. ZDV for 1 week; infant only	Perinatal transmission at 6–8 weeks was 11.8% in NVP arm vs. 20.0% in ZDV arm (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 drugs Oral IP • SD NVP vs. ZDV plus 3TC	SD NVP within 48 hours of birth; mother and infant vs. ZDV plus 3TC for 1 week; mother and infant	Perinatal transmission at 8 weeks was 12.3% in SD NVP arm vs. 9.3% in ZDV plus 3TC arm (difference not statistically significant, $P = 0.11$).
PHPT-1; Thailand;[13] Formula feeding	4 ZDV regimens with different durations of AP	Long (from 28 weeks) or short (from 36 weeks)	Long (6 weeks) or short (3 days); infant only	Perinatal transmission rate was 10.5% in the short-short arm. This

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Study Name; Location(s); Mode of Infant Feeding	Antiretroviral Drugs	Antepartum and Intrapartum Interventions	Postpartum Interventions	Perinatal Transmission Rate and Efficacy
	and infant PP administration; no placebo	Oral IP		arm was stopped at interim analysis. Perinatal transmission at 6 months was 6.5% in long-long arm vs. 4.7% in long-short arm and 8.6% in short-long arm (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)	Nonstudy ARV regimen Oral IP • Placebo vs. SD NVP plus IV ZDV	Placebo vs. SD NVP within 72 hours of birth plus nonstudy 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*).
PHPT-2; Thailand;[40] 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 the rate of perinatal transmission was higher in this arm than in the ZDV/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 whether the infant received SD NVP or not (2.0% vs. 2.8%, respectively).

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Study Name; Location(s); Mode of Infant Feeding	Antiretroviral Drugs	Antepartum and Intrapartum Interventions	Postpartum Interventions	Perinatal Transmission Rate and Efficacy
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 at 6 weeks was 6.5% (95% CI, 3.9% to 9.1%); perinatal transmission for historical control group receiving short ZDV (98% of whom were 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 at 6 weeks was 4.7% (95% CI, 2.4% to 7.0%); perinatal transmission for historical control group receiving short ZDV (98% of whom were breastfed) was 12.8%.
NVAZ Trial; Malawi;[7] Breastfeeding	Neonatal SD NVP vs. SD NVP plus ZDV	No AP or IP ARV drugs	SD NVP with or without ZDV for 1 week; infant only	Perinatal transmission at 6–8 weeks was 15.3% in SD NVP plus ZDV arm vs. 20.9% in SD NVP-only arm. Perinatal transmission rates at 6–8 weeks among infants without HIV 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 at 6–8 weeks was 16.3% in NVP plus ZDV arm vs. 14.1% in SD NVP-only arm (difference not statistically significant). Perinatal transmission rates at 6–8 weeks among infants without HIV at birth were 6.5% and 16.9%, respectively.

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Study Name; Location(s); Mode of Infant Feeding	Antiretroviral Drugs	Antepartum and Intrapartum Interventions	Postpartum Interventions	Perinatal Transmission Rate and Efficacy
Post-Exposure Infant Prophylaxis; South Africa;[9] Breastfeeding and formula feeding	Neonatal SD NVP vs. ZDV for 6 weeks	No AP or IP ARV drugs	SD NVP vs. ZDV for 6 weeks	For formula-fed infants only, perinatal transmission at 6 weeks was 14.3% in SD NVP arm vs. 14.1% in ZDV arm (not significant, *P* = 0.30). For breastfed infants only, perinatal transmission was 12.2% in SD NVP arm vs. 19.6% in ZDV arm (*P* = 0.03).
Mashi; Botswana;[41,42] 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 received 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 vs. 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 vs. 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 vs. 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

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Study Name; Location(s); Mode of Infant Feeding	Antiretroviral Drugs	Antepartum and Intrapartum Interventions	Postpartum Interventions	Perinatal Transmission Rate and Efficacy
				breastfeeding plus ZDV arm vs. 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.
SWEN; Uganda, Ethiopia, India;[24] Breastfeeding	SD NVP vs. NVP for 6 weeks	No AP ARV drugs Oral IP • SD NVP	Infant SD NVP vs. NVP for 6 weeks	Postnatal Infection in Infants Without HIV 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. 2 extended infant regimens (NVP or NVP/ZDV) for 14 weeks	No AP ARV drugs 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.	Postnatal Infection in Infants Without HIV at Birth • Perinatal transmission at 6 weeks was 5.1% in control arm vs. 1.7% in extended NVP arm (67% efficacy) and 1.6% in

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Study Name; Location(s); Mode of Infant Feeding	Antiretroviral Drugs	Antepartum and Intrapartum Interventions	Postpartum Interventions	Perinatal Transmission Rate and Efficacy
			Control plus NVP/ZDV for 14 weeks	extended NVP/ZDV arm (69% efficacy). • Perinatal transmission at 9 months was 10.6% in control arm vs. 5.2% in extended NVP arm (51% efficacy) and 6.4% in extended NVP/ZDV arm (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 6 months was 4.9% (postnatal perinatal transmission between 6 weeks and 6 months was 1.2%).
Kisumu Breastfeeding Study; 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 6 months was 5.0% (postnatal perinatal transmission between 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 6 months was 5.0% (postnatal perinatal transmission between 6 weeks and 6 months was 0.9%), not significantly different from 6-month infant prophylaxis in MITRA.

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Study Name; Location(s); Mode of Infant Feeding	Antiretroviral Drugs	Antepartum and Intrapartum Interventions	Postpartum Interventions	Perinatal Transmission Rate and Efficacy
Kesho Bora; Multi-African;[28] Breastfeeding primarily	AP 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) vs. 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 12 months was 5.4% with maternal triple-drug prophylaxis (Arm 1) vs. 9.5% with ZDV/SD NVP (with no further postnatal prophylaxis after 1 week) (Arm 2) (P = 0.029).
Mma Bana; Botswana;[2] Breastfeeding	Compared 2 maternal triple-drug prophylaxis 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 6 months overall was 1.3%: 2.1% in ZDV/3TC/ABC Arm 1 vs. 0.4% in ZDV/3TC/LPV/r Arm 2 (P = 0.53).
BAN; Malawi;[27,43] 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 1 (Control) • Maternal ZDV/3TC for 1 week; infant SD NVP plus ZDV/3TC for 1 week	Postnatal Infection in Infants Without HIV at 2 Weeks • Perinatal transmission at 28 weeks was 5.7% in control Arm 1, 2.9% in maternal triple-drug prophylaxis

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Study Name; Location(s); Mode of Infant Feeding	Antiretroviral Drugs	Antepartum and Intrapartum Interventions	Postpartum Interventions	Perinatal Transmission Rate and Efficacy
		Arm 2 • ZDV/3TC plus SD NVP *Arm 3* • ZDV/3TC plus SD NVP	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	Arm 2 (P = 0.009 vs. control), and 1.7% in infant NVP Arm 3 (P < 0.001 vs. control). • Perinatal transmission at 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).
HPTN 046; South Africa, Tanzania, Uganda, Zimbabwe;[38,44] Breastfeeding	Postpartum prophylaxis to prevent breast milk transmission of HIV with 6 weeks of infant NVP 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 6 weeks through 6 months Arm 2 • Daily infant placebo from 6 weeks through 6 months	In infants without HIV at age 6 weeks, the 6-month infant HIV infection rate was 1.1% (0.3% to 1.8%) in the extended NVP arm vs. 2.4% (1.3% to 3.6%) in the placebo arm (P = 0.048). 18-month postnatal infection rates were 2.2% (1.1% to 3.3%) in the extended NVP arm vs. 3.1% (1.9% to 4.4%) in the placebo arm (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

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Study Name; Location(s); Mode of Infant Feeding	Antiretroviral Drugs	Antepartum and Intrapartum Interventions	Postpartum Interventions	Perinatal Transmission Rate and Efficacy
				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 without HIV at age 6 weeks, the 6-month infant HIV infection rate was 0.2% and not statistically different from the rates seen in the extended NVP arm (0.5%) and placebo arm (0%). For mothers with CD4 counts >350 cells/mm^3 who were not receiving triple-drug ARV regimens, in infants without HIV at age 6 weeks, the 6-month infant HIV infection rate was 0.7% (0% to 1.5%) in the extended NVP arm vs. 2.8% (1.3% to 4.4%) in the placebo arm (P = 0.014).
NICHD-HPTN 040/PACTG 1043 Trial; Brazil, Argentina, South Africa, United States;[45] Formula feeding	Infant prophylaxis with 6 weeks of ZDV vs. 6 weeks of infant ZDV plus 3 doses of NVP in first week of life vs. 6 weeks of 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	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).

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Study Name; Location(s); Mode of Infant Feeding	Antiretroviral Drugs	Antepartum and Intrapartum Interventions	Postpartum Interventions	Perinatal Transmission Rate and Efficacy
			after second dose Arm 3 • Control as above, plus 3TC and NFV from birth through age 2 weeks	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) than in ZDV-alone Arm 1 (33 infants) or ZDV/NVP Arm 2 (32 infants) (P < 0.001).
ANRS 12174 Trial; Burkina Faso, South Africa, Uganda, Zambia;[30,31] Breastfeeding	Compared 2 infant ARV prophylaxis regimens during breastfeeding; infants tested PCR-negative at birth and were 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 Without HIV at Birth • Postnatal transmission at age 50 weeks was 1.4% (0.70–2.76) in Arm 1 vs. 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 vs. 96.3% (94.4–97.5) in Arm 2 (P = 0.85).
PROMOTE; Uganda;[46] Breastfeeding	Compared 2 triple-ARV regimens; no CD4 restriction	Arm 1 • ZDV/3TC/LPV/r Arm 2 • ZDV/3TC/EFV • ARVs started at 12–28 weeks'	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.

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

Study Name; Location(s); Mode of Infant Feeding	Antiretroviral Drugs	Antepartum and Intrapartum Interventions	Postpartum Interventions	Perinatal Transmission Rate and Efficacy
		gestation and continued through labor		
PROMISE; India, Malawi, South Africa, Tanzania, Uganda, Zambia, Zimbabwe;[18] Breastfeeding and formula feeding (antepartum component)	Compared ZDV prophylaxis and 2 ART regimens during pregnancy among women at >14 weeks' gestation and with 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 • ART 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 ART arms vs. ZDV arm difference in perinatal transmission risk: • -1.3% (95% CI, -2.1% to -0.4%)
PROMISE; India, Malawi, South Africa, Tanzania, Uganda, Zambia, Zimbabwe;[18] Breastfeeding (postpartum component)	Compared infant NVP and maternal ART during breastfeeding among infants born to women with CD4 counts ≥350 cells/mm3	This was a postpartum study. intervention only. Eligible women included women enrolled in PROMISE antepartum (see above) and women who received no ARV drugs during pregnancy.	Arm 1 • Mothers received TDF plus FTC plus LPV/r Arm 2 • Once-daily infant NVP Regimens were continued until 42 days after last breastmilk exposure or age 18 months, whichever came first.	Infant Infection Rates *Arm 1* • 0.57% (7/1,219) *Arm 2* • 0.58% (7/1,211) Rates of Infant HIV-1–Free Survival at 24 Months *Arm 1* • 97.1% *Arm 2* • 97.7%

Key: 3TC = lamivudine; ABC = abacavir; AP = antepartum; ARV = antiretroviral; ART = antiretroviral therapy; CD4 = CD4 T lymphocyte; CDC = Centers for Disease Control and Prevention; CI = confidence interval; EFV = efavirenz; FTC = emtricitabine;

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

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

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