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  

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%. 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. 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. 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.

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. However, longer-duration antenatal zidovudine prophylaxis, beginning at 28 weeks’ gestation, is more effective than shorter-duration zidovudine prophylaxis, beginning at 35 weeks’ gestation. The PHPT-5 trial demonstrated a significantly increased risk of transmission associated with less than 8 weeks of prophylaxis during pregnancy. 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. More prolonged infant post-exposure prophylaxis does not appear to substitute for longer-duration maternal ARV prophylaxis.

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/mm³. 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.\(^6\) 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 diarrhea 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).\(^23\) 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.\textsuperscript{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).\textsuperscript{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.\textsuperscript{33-37}

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

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<th>Study; Location(s); Mode of Infant Feeding</th>
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<tr>
<td>Pediatric AIDS Clinical Trials Group (PACTG) 076; United States, France;\textsuperscript{1} Formula feeding</td>
<td>ZDV vs. placebo</td>
<td>Long (from 14 weeks) IV IP</td>
<td>Long (6 weeks); infant only</td>
<td>Perinatal transmission at 18 months was 8.3% in ZDV arm vs. 25.5% in placebo arm (68% efficacy).</td>
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<tr>
<td>CDC Short-Course ZDV Trial; Thailand;\textsuperscript{12} Formula feeding</td>
<td>ZDV vs. placebo</td>
<td>Short (from 36 weeks) Oral IP</td>
<td>None</td>
<td>Perinatal transmission at 6 months was 9.4% in ZDV arm vs. 18.9% in placebo arm (50% efficacy).</td>
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<tr>
<td>DITRAME (ANRS 049a) Trial; Ivory Coast, Burkina Faso;\textsuperscript{11,38} Breastfeeding</td>
<td>ZDV vs. placebo</td>
<td>Short (from 36 weeks) Oral IP</td>
<td>Short (1 week); mother only</td>
<td>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).</td>
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<tr>
<td>CDC Short-Course ZDV Trial; Ivory Coast;\textsuperscript{10,11} Breastfeeding</td>
<td>ZDV vs. placebo</td>
<td>Short (from 36 weeks) Oral IP</td>
<td>None</td>
<td>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).</td>
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<tr>
<td>PETRA Trial; South Africa, Tanzania, Uganda;\textsuperscript{4} Breastfeeding and formula feeding</td>
<td>AP/IP/PP ZDV plus 3TC vs. IP/PP ZDV plus 3TC vs. IP-only ZDV plus 3TC vs. Placebo</td>
<td>Short (from 36 weeks) Oral IP</td>
<td>Short (1 week); mother and infant</td>
<td>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).</td>
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<td>HIVNET 012 Trial; Uganda; Breastfeeding</td>
<td>SD NVP vs. ZDV</td>
<td>No AP ARV</td>
<td>SD NVP within 72 hours of birth, infant only vs. ZDV (1 week); infant only</td>
<td>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).</td>
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<tr>
<td>SAINT Trial; South Africa; Breastfeeding and formula feeding</td>
<td>SD NVP vs. ZDV plus 3TC</td>
<td>No AP ARV</td>
<td>SD NVP within 48 hours of birth, mother and infant vs. ZDV plus 3TC (1 week); mother and infant</td>
<td>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 )).</td>
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<tr>
<td>Perinatal HIV Prevention Trial (PHPT-1); Thailand; Formula feeding</td>
<td>Four ZDV regimens with different durations of AP and infant PP administration; no placebo</td>
<td>Long (from 28 weeks), short (from 36 weeks) Oral IP</td>
<td>Long (6 weeks), short (3 days); infant only</td>
<td>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). <em>In utero</em> transmission was significantly higher with short vs. long maternal therapy regimens (5.1% vs. 1.6%).</td>
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<td>PACTG 316 Trial; Bahamas, Belgium, Brazil, France, Germany, Italy, Spain, Sweden, Switzerland, United Kingdom, United States; Formula feeding</td>
<td>SD NVP vs. placebo among women already receiving ZDV alone (23%) or ZDV plus other ARV drugs (77% combination therapy)</td>
<td>Non-study ARV regimen Oral IP: Placebo vs. SD NVP plus IV ZDV</td>
<td>Placebo vs. SD NVP within 72 hours of birth plus non-study ARV drugs (ZDV); infant only</td>
<td>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 <em>in utero</em>).</td>
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<td>Perinatal HIV Prevention Trial (PHPT-2); Thailand; Formula feeding</td>
<td>ZDV alone vs. ZDV plus maternal and infant SD NVP vs. ZDV plus maternal SD NVP</td>
<td>ZDV from 28 weeks Oral IP: ZDV alone, or ZDV plus SD NVP</td>
<td>ZDV for 1 week with or without SD NVP; infant only</td>
<td>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).</td>
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<td>DITRAME Plus (ANRS 1201.0) Trial; Ivory Coast; Breastfeeding and formula feeding</td>
<td>Open label, ZDV plus SD NVP</td>
<td>ZDV from 36 weeks Oral IP: ZDV plus SD NVP</td>
<td>SD NVP plus ZDV for 1 week; infant only</td>
<td>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%.</td>
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<tr>
<td>DITRAME Plus (ANRS 1201.1) Trial; Ivory Coast; Breastfeeding and formula feeding</td>
<td>Open label, ZDV plus 3TC plus SD NVP</td>
<td>ZDV plus 3TC from 32 weeks (stopped at 3 days PP) Oral IP: ZDV plus 3TC plus SD NVP</td>
<td>SD NVP plus ZDV for 1 week; infant only</td>
<td>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%.</td>
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<td>NVAZ Trial; Malawi; Breastfeeding</td>
<td>Neonatal SD NVP vs. SD NVP plus ZDV</td>
<td>No AP or IP ARV (latecomers)</td>
<td>SD NVP with or without ZDV for 1 week; infant only</td>
<td>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).</td>
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<td>Postnatal NVP plus ZDV Trial; Malawi; Breastfeeding</td>
<td>Neonatal SD NVP vs. SD NVP plus ZDV</td>
<td>No AP ARV Oral IP: • SD NVP</td>
<td>SD NVP with or without ZDV for 1 week; infant only</td>
<td>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.</td>
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<td>Post-Exposure Infant Prophylaxis; South Africa; Breastfeeding and formula feeding</td>
<td>Neonatal SD NVP vs. ZDV for 6 weeks</td>
<td>No AP or IP ARV</td>
<td>SD NVP vs. ZDV for 6 weeks</td>
<td>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 )).</td>
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<tr>
<td>Mashi; Botswana; Breastfeeding and formula feeding</td>
<td>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 &lt;200 cells/mm(^2) receive combination therapy.</td>
<td>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</td>
<td>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.</td>
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Supplemental Table 1. Results of Major Studies on Antiretroviral Interventions to Prevent Perinatal HIV Transmission (page 4 of 7)

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<td>SWEN; Uganda, Ethiopia, India; Breastfeeding</td>
<td>SD NVP vs. NVP for 6 weeks</td>
<td>No AP ARV Oral IP: • SD NVP</td>
<td>Infant SD NVP vs. NVP for 6 weeks</td>
<td>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.</td>
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<tr>
<td>PEPI-Malawi Trial; Malawi; Breastfeeding</td>
<td>SD NVP plus ZDV for 1 week (control) vs. Two extended infant regimens (NVP or NVP/ZDV) for 14 weeks</td>
<td>No AP ARV Oral IP: • SD NVP (if mother presents in time)</td>
<td>Infant SD NVP plus ZDV for 1 week (control) vs. Control plus NVP for 14 weeks vs. Control plus NVP/ZDV for 14 weeks</td>
<td>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.</td>
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<td>MITRA; Tanzania; Breastfeeding</td>
<td>Infant 3TC for 6 months (observational)</td>
<td>ZDV/3TC from 36 weeks through labor</td>
<td>Maternal ZDV/3TC for 1 week, infant 3TC for 6 months</td>
<td>Perinatal transmission at age 6 months was 4.9% (postnatal perinatal transmission between ages 6 weeks and 6 months was 1.2%).</td>
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<tr>
<td>Kisumu Breastfeeding Study (KIBS); Kenya; Breastfeeding</td>
<td>Maternal triple-drug prophylaxis (observational)</td>
<td>ZDV/3TC/NVP (NFV if CD4 count &gt;250 cells/mm(^3)) from 34 weeks through labor</td>
<td>Maternal ZDV/3TC/NVP (NFV if CD4 count &gt;250 cells/mm(^3)) for 6 months, infant SD NVP</td>
<td>Perinatal transmission at age 6 months was 5.0% (postnatal perinatal transmission between ages 7 days and 6 months was 2.6%).</td>
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<tr>
<td>MITRA-PLUS; Tanzania; Breastfeeding</td>
<td>Maternal triple-drug prophylaxis (observational)</td>
<td>ZDV/3TC/NVP (NFV if CD4 count &gt;200 cells/mm(^3)) from 34 weeks through labor</td>
<td>Maternal ZDV/3TC/NVP (NFV if CD4 count &gt;200 cells/mm(^3)) for 6 months, infant ZDV/3TC for 1 week</td>
<td>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.</td>
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<td>Kesho Bora; Multi-African; breastfeeding primarily</td>
<td>Antepartum ZDV/SD NVP with no postnatal prophylaxis vs. Maternal triple-drug prophylaxis in women with CD4 counts 200–500 cells/mm³</td>
<td>Arm 1: • ZDV/3TC/LPV/r</td>
<td>Arm 1: • Maternal ZDV/3TC/LPV/r for 6 months, infant SD NVP plus ZDV for 1 week</td>
<td>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/mm³, 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) ($P = 0.029$).</td>
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<td>Mma Bana; Botswana; breastfeeding</td>
<td>Maternal triple-drug prophylaxis (compares 2 regimens) in women with CD4 counts &gt;200 cells/mm³</td>
<td>Arm 1: • ZDV/3TC/ABC</td>
<td>Arm 1: • Maternal ZDV/3TC/ABC for 6 months, infant SD NVP plus ZDV for 4 weeks</td>
<td>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 ($P = 0.53$).</td>
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<tr>
<td>BAN; Malawi; breastfeeding</td>
<td>Postpartum maternal triple-drug prophylaxis vs. infant NVP in women with CD4 counts ≥250 cells/mm³</td>
<td>No AP drugs</td>
<td>Arm 1 (Control): • Maternal ZDV/3TC for 1 week, infant SD NVP plus ZDV for 4 weeks</td>
<td>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 ($P &lt;0.001$ 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).</td>
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<td>HPTN 046; South Africa, Tanzania, Uganda, Zimbabwe; Breastfeeding</td>
<td>Postpartum prophylaxis of breast milk transmission of HIV with 6 weeks vs. 6 months of infant NVP</td>
<td>AP drugs allowed if required for maternal health</td>
<td>All infants received daily NVP from birth through age 6 weeks.</td>
<td>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 &gt;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)).</td>
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<tr>
<td>NICHD-HPTN 040/PACTG 1043 Trial; Brazil, Argentina, South Africa, United States; Formula feeding</td>
<td>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</td>
<td>No AP drugs If mother presented early enough, IV ZDV during labor through delivery</td>
<td>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</td>
<td>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 &lt; 0.001)).</td>
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</table>
### Supplemental Table 1. Results of Major Studies on Antiretroviral Interventions to Prevent Perinatal HIV Transmission (page 7 of 7)

<table>
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<tr>
<th>Study; Location(s); Mode of Infant Feeding</th>
<th>Antiretroviral Drugs</th>
<th>Antepartum and Intrapartum</th>
<th>Postpartum</th>
<th>Perinatal Transmission Rate and Efficacy</th>
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<tbody>
<tr>
<td>ANRS 12174 Trial; Burkina Faso, South Africa, Uganda, Zambia; Breastfeeding</td>
<td>Compared 2 infant ARV prophylaxis regimens during breastfeeding; infants testing PCR-negative at birth, born to mothers with CD4 counts &gt;350 cells/mm³</td>
<td>As per standard of care</td>
<td>Arm 1: • Daily infant LPV/r from 1 week through 50 weeks of age</td>
<td>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).</td>
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<tr>
<td>PROMOTE; Uganda; Breastfeeding</td>
<td>Compared 2 triple-ARV regimens; no CD4 restriction</td>
<td>Arm 1: • AZT/3TC/LPV/r Arm 2: • AZT/3TC/EFV • ARVs started at 12–28 weeks' gestation and continued through labor</td>
<td>Randomized regimen continued postpartum through 1 year of breastfeeding</td>
<td>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.</td>
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<tr>
<td>PROMISE; India, Malawi, South Africa, Tanzania, Uganda, Zambia, Zimbabwe; Breastfeeding and formula feeding (antepartum component)</td>
<td>Compared 2 ARV regimens during pregnancy among women ≥14 weeks gestation and CD4 counts ≥350 cells/mm³</td>
<td>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</td>
<td>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.</td>
<td>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%).</td>
</tr>
</tbody>
</table>

**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 ditroproxil fumarate; ZDV = zidovudine

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