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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Table 1. Outline of the Guidelines Development Process

Topic	Comment
Goal of the guidelines	Provide guidance to HIV care practitioners on the optimal use of antiretroviral (ARV) agents in pregnant women for treatment of HIV infection and for prevention of mother-to-child transmission (PMTCT) of HIV in the United States.
Panel members	The Panel is composed of approximately 30 voting members who have expertise in management of pregnant HIV-infected women (such as training in either obstetrics/gynecology or women's health) and interventions for PMTCT (such as specialized training in pediatric HIV infection) as well as community representatives with knowledge of HIV infection in pregnant women and interventions for PMTCT. The U.S. government representatives, appointed by their agencies, include at least 1 representative from each of the following Department of Health and Human Services agencies: the Centers for Disease Control and Prevention, the Food and Drug Administration (FDA), the Health Resources and Services Administration (HRSA), and the National Institutes of Health (NIH). Members who do not represent U.S. government agencies are selected by Panel members after an open announcement to call for nominations. Each member serves on the Panel for a 3-year period, with an option for reappointment. A list of all Panel members can be found in the Panel Roster.
Financial disclosures	All members of the Panel submit a written financial disclosure annually reporting any association with manufacturers of ARV drugs or diagnostics used for management of HIV infections. A list of the latest disclosures is available on the AIDS*info* website (http://aidsinfo.nih.gov).
Users of the guidelines	Providers of care to HIV-infected pregnant women and to HIV-exposed infants
Developer	Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission—a working group of OARAC
Funding source	Office of AIDS Research, NIH
Evidence for recommendations	The recommendations in these guidelines are generally based on studies published in peer-reviewed journals. On some occasions, particularly when new information may affect patient safety, unpublished data presented at major conferences or prepared by the FDA and/or manufacturers as warnings to the public may be used as evidence to revise the guidelines.
Recommendation grading	See Table 2.
Method of synthesizing data	Each section of the guidelines is assigned to a small group of Panel members with expertise in the area of interest. A structured literature search is conducted by staff from the HIV/AIDS National Resource Center at the Francois-Xavier Bagnoud Center (through funding from HRSA) and provided to the Panel working group. The members review and synthesize the available data and propose recommendations to the entire Panel. The Panel discusses and votes on all proposals during monthly teleconferences. Proposals receiving endorsement from a consensus of members are included in the guidelines as official Panel recommendations.
Other guidelines	These guidelines focus on HIV-infected pregnant women and their infants. Other guidelines outline the use of ARV agents in non-pregnant HIV-infected adults and adolescents, HIV-infected children, and people who experience occupational or nonoccupational exposure to HIV. The guidelines described are also available on the AIDS*info* website (http://www.aidsinfo.nih.gov). Preconception management for non-pregnant women of reproductive age is briefly discussed in this document. However, for more detailed discussion on issues of treatment of non-pregnant adults, the Working Group defers to the designated expertise offered by Panels that have developed those guidelines.

Table 1. Outline of the Guidelines Development Process, cont'd

Topic	Comment
Update plan	The Panel meets monthly by teleconference to review data that may warrant modification of the guidelines. Updates may be prompted by new drug approvals (or new indications, new dosing formulations, or changes in dosing frequency), significant new safety or efficacy data, or other information that may have a significant impact on the clinical care of patients. In the event of significant new data that may affect patient safety, the Panel may issue a warning announcement and accompanying recommendations on the AIDS*info* website until the guidelines can be updated with appropriate changes. Updated guidelines are available at the AIDS*info* website (http://www.aidsinfo.nih.gov).
Public comments	A 2-week public comment period follows release of the updated guidelines on the AIDS*info* website. The Panel reviews comments received to determine whether additional revisions to the guidelines are indicated. The public may also submit comments to the Panel at any time at contactus@aidsinfo.nih.gov.

Table 2. Rating Scheme for Recommendations

Strength of Recommendation	Quality of Evidence for Recommendation
A: Strong recommendation for the statement **B:** Moderate recommendation for the statement **C:** Optional recommendation for the statement	**I:** One or more randomized trials with clinical outcomes and/or validated laboratory endpoints **II:** One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes **III:** Expert opinion

Table 3. Results of Major Studies on Antiretroviral Prophylaxis to Prevent Mother-to-Child Transmission of HIV (page 1 of 9)

Study Location(s) Mode of Infant Feeding	Antiretroviral (ARV) Drugs	Antepartum and Intrapartum	Postpartum	Mother-to-Child Transmission (MTCT) Rate and Efficacy
PACTG 076 United States, France[34] Formula feeding	ZDV vs. placebo	Long (from 14 weeks) IV IP	Long (6 weeks), infant only	• MTCT at 18 months was 8.3% in ZDV arm vs. 25.5% in placebo arm (68% efficacy).
CDC short-course ZDV trial Thailand[11] Formula feeding	ZDV vs. placebo	Short (from 36 weeks) Oral IP	None	• MTCT 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[10, 35] Breastfeeding	ZDV vs. placebo	Short (from 36 weeks) Oral IP	Short (1 week), mother only	• MTCT was 18.0% in ZDV arm vs. 27.5% in placebo arm at 6 months (38% efficacy) and 21.5% vs. 30.6% at 15 months (30% efficacy). • MTCT 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[9, 10] Breastfeeding	ZDV vs. placebo	Short (from 36 weeks) Oral IP	None	• MTCT was 16.5% in ZDV arm vs. 26.1% in placebo arm at 3 months (37% efficacy). • MTCT was 22.5% in ZDV arm vs. 30.2% in placebo arm in pooled analysis at 24 months (26% efficacy).

Table 3. Results of Major Studies on Antiretroviral Prophylaxis to Prevent Mother-to-Child Transmission of HIV (page 2 of 9)

Study Location(s) Mode of Infant Feeding	Antiretroviral (ARV) Drugs	Antepartum and Intrapartum	Postpartum	Mother-to-Child Transmission (MTCT) Rate and Efficacy
PETRA trial South Africa, Tanzania, and Uganda[4] Breastfeeding and formula feeding	AP/IP/PP ZDV + 3TC vs. IP/PP ZDV + 3TC vs. IP-only ZDV + 3TC vs. placebo	Short (from 36 weeks) Oral IP	Short (1 week), mother and infant	• MTCT was 5.7% at 6 weeks for AP/IP/PP ZDV + 3TC, 8.9% for IP/PP ZDV + 3TC, 14.2% for IP-only ZDV + 3TC, and 15.3% for placebo (efficacy compared with placebo: 63%, 42%, and 0%, respectively). • MTCT was 14.9% at 18 months for AP/IP/PP ZDV + 3TC, 18.1% for IP/PP ZDV + 3TC, 20.0% for IP-only ZDV + 3TC, and 22.2% for placebo (efficacy compared with placebo: 34%, 18%, and 0%, respectively).
HIVNET 012 trial Uganda[3] Breastfeeding	sdNVP vs. ZDV	No AP ARV Oral IP: sdNVP vs. oral ZDV	sdNVP within 72 hours of birth, infant only vs. ZDV (1 week), infant only	• MTCT was 11.8% in NVP arm vs. 20.0% in ZDV arm at 6–8 weeks (42% efficacy); 15.7% in NVP arm vs. 25.8% in ZDV arm at 18 months (41% efficacy).
SAINT trial South Africa[5] Breastfeeding and formula feeding	sdNVP vs. ZDV + 3TC	No AP ARV Oral IP: sdNVP vs. ZDV + 3TC	sdNVP within 48 hours of birth, mother and infant vs. ZDV + 3TC (1 week), mother and infant	• MTCT was 12.3% in sdNVP arm vs. 9.3% in ZDV + 3TC arm at 8 weeks (difference not statistically significant, $P = 0.11$).
Perinatal HIV Prevention Trial (PHPT-1) Thailand[12] 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 stopped at interim analysis (10.5%). MTCT 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%).

Table 3. Results of Major Studies on Antiretroviral Prophylaxis to Prevent Mother-to-Child Transmission of HIV (page 3 of 9)

Study Location(s) Mode of Infant Feeding	Antiretroviral (ARV) Drugs	Antepartum and Intrapartum	Postpartum	Mother-to-Child Transmission (MTCT) Rate and Efficacy
PACTG 316 trial Bahamas, Belgium, Brazil, France, Germany, Italy, Spain, Sweden, Switzerland, United Kingdom, United States[21] Formula feeding	sdNVP vs. placebo among women already receiving ZDV alone (23%) or ZDV + other ARV drugs (77% combination therapy)	Nonstudy ARV regimen Oral IP: placebo vs. sdNVP + IV ZDV	Placebo vs. sdNVP within 72 hours of birth + 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 MTCT in both arms: 1.4% in sdNVP arm vs. 1.6% in placebo arm (53% of MTCT was *in utero*).
Perinatal HIV Prevention Trial (PHPT-2) Thailand[19] Formula feeding	ZDV alone vs. ZDV + maternal and infant sdNVP vs. ZDV + maternal sdNVP	ZDV from 28 weeks Oral IP: ZDV alone or ZDV + sdNVP	ZDV for 1 week with or without sdNVP, infant only	• ZDV-alone arm was stopped because of higher MTCT than the NVP-NVP arm (6.3% vs. 1.1%). In arms in which the mother received sdNVP, MTCT rate did not differ significantly between the infant receiving or not receiving sdNVP (2.0% vs. 2.8%).
DITRAME Plus (ANRS 1201.0) trial Ivory Coast[14] Breastfeeding and formula feeding	Open label, ZDV + sdNVP	ZDV from 36 weeks Oral IP: ZDV plus sdNVP	sdNVP + ZDV for 1 week, infant only	• MTCT was 6.5% (95% CI, 3.9%–9.1%) at 6 weeks; MTCT for historical control group receiving short ZDV (98% breastfed) was 12.8%.
DITRAME Plus (ANRS 1201.1) trial Ivory Coast[14] Breastfeeding and formula feeding	Open label, ZDV + 3TC + sdNVP	ZDV + 3TC from 32 weeks (stopped at 3 days PP) Oral IP: ZDV + 3TC + sdNVP	sdNVP + ZDV for 1 week, infant only	• MTCT was 4.7% (95% CI, 2.4%–7.0%) at 6 weeks; MTCT for historical control group receiving short ZDV (98% breastfed) was 12.8%.
NVAZ trial Malawi[6] Breastfeeding	Neonatal sdNVP vs. sdNVP + ZDV	No AP or IP ARV (latecomers)	sdNVP with or without ZDV for 1 week, infant only	• MTCT was 15.3% in sdNVP + ZDV arm and 20.9% in sdNVP-only arm at 6–8 weeks. MTCT rate at 6–8 weeks among infants who were HIV uninfected at birth was 7.7% and 12.1%, respectively (36% efficacy).
Postnatal NVP + ZDV trial Malawi[7] Breastfeeding	Neonatal sdNVP vs. sdNVP + ZDV	No AP ARV Oral IP: sdNVP	sdNVP with or without ZDV for 1 week, infant only	• MTCT was 16.3% in NVP + ZDV arm and 14.1% in sdNVP-only arm at 6–8 weeks (difference not statistically significant). MTCT rate at 6–8 weeks among infants who were HIV uninfected at birth was 6.5% and 16.9%, respectively.

Table 3. Results of Major Studies on Antiretroviral Prophylaxis to Prevent Mother-to-Child Transmission of HIV (page 4 of 9)

Study Location(s) Mode of Infant Feeding	Antiretroviral (ARV) Drugs	Antepartum and Intrapartum	Postpartum	Mother-to-Child Transmission (MTCT) Rate and Efficacy
Post-exposure Infant Prophylaxis South Africa[8] Breastfeeding and formula feeding	Neonatal sdNVP vs. ZDV for 6 weeks	No AP or IP ARV	sdNVP vs. ZDV for 6 weeks	• For formula-fed infants only, MTCT was 14.3% in sdNVP arm vs. 14.1% in ZDV arm at 6 weeks (not significant, P = 0.30). For breastfed infants only, MTCT was 12.2% in sdNVP arm and 19.6% in ZDV arm (P = 0.03).
Mashi Botswana[20, 36] Breastfeeding and formula feeding	Initial: short-course ZDV with/without maternal and infant sdNVP and with/without breastfeeding Revised: short-course ZDV + infant sdNVP with/without maternal sdNVP and with/without breastfeeding; women with CD4 T-lymphocyte (CD4-cell) counts <200 cells/mm^3 receive combination therapy	1st randomization ZDV from 34 weeks Oral IP: ZDV + either sdNVP vs. placebo	2nd randomization Breastfeeding + ZDV (infant) 6 months + sdNVP, infant only vs. Formula feeding + ZDV (infant) 4 weeks + sdNVP, infant only	• Initial design: In formula-feeding arm, MTCT at 1 month was 2.4% in maternal and infant sdNVP arm and 8.3% in placebo arm (P = 0.05). In breastfeeding + infant ZDV arm, MTCT at 1 month was 8.4% in sdNVP arm and 4.1% in placebo arm (difference not statistically significant). • Revised design: MTCT at 1 month was 4.3% in maternal + infant sdNVP arm and 3.7% in maternal placebo + infant sdNVP arm (no significant difference; no interaction with mode of infant feeding). • MTCT at 7 months was 9.1% in breastfeeding + ZDV arm and 5.6% in formula-feeding arm; mortality at 7 months was 4.9% in breastfeeding + ZDV arm vs. 9.3% in formula-feeding arm; HIV-free survival at 18 months was 15.6% breastfeeding + ZDV arm vs. 14.2% formula-feeding arm.

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Study Location(s) Mode of Infant Feeding	Antiretroviral (ARV) Drugs	Antepartum and Intrapartum	Postpartum	Mother-to-Child Transmission (MTCT) Rate and Efficacy
SWEN Uganda, Ethiopia, India[23] Breastfeeding	sdNVP vs. NVP for 6 weeks	No AP ARV Oral IP: sdNVP	Infant sdNVP vs. NVP for 6 weeks	• Postnatal infection in infants uninfected at birth: - MTCT at 6 weeks was 5.3% in sdNVP arm vs. 2.5% in extended NVP arm (risk ratio 0.54, $P = 0.009$). - MTCT at 6 months was 9.0% in sdNVP 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[22] Breastfeeding	sdNVP + ZDV for 1 week (control) vs. two extended infant regimens (NVP or NVP/ZDV) for 14 weeks	No AP ARV Oral IP: sdNVP (if mother presents in time)	Infant sdNVP + ZDV for 1 week (control) vs. control + NVP for 14 weeks vs. control + NVP/ZDV for 14 weeks	• Postnatal infection in infants uninfected at birth: - MTCT 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). - MTCT 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 MTCT between the extended prophylaxis arms; however, more hematologic toxicity with NVP/ZDV.
MITRA Tanzania[25] 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	• MTCT at age 6 months was 4.9% (postnatal MTCT between ages 6 weeks and 6 months was 1.2%).

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Study Location(s) Mode of Infant Feeding	Antiretroviral (ARV) Drugs	Antepartum and Intrapartum	Postpartum	Mother-to-Child Transmission (MTCT) Rate and Efficacy
Kisumu Breastfeeding Study (KiBS) Kenya[27] Breastfeeding	Maternal triple-drug prophylaxis (observational)	ZDV/3TC/NVP (NFV if CD4-cell count >250 cells/mm^3) from 34 weeks through labor	Maternal ZDV/3TC/NVP (NFV if CD4-cell count >250 cells/mm^3) for 6 months; infant sdNVP	• MTCT at age 6 months was 5.0% (postnatal MTCT between ages 7 days and 6 months was 2.6%).
MITRA-PLUS Tanzania[24] Breastfeeding	Maternal triple-drug prophylaxis (observational)	ZDV/3TC/NVP (NFV if CD4-cell count >200 cells/mm^3) from 34 weeks through labor	Maternal ZDV/3TC/NVP (NFV if CD4-cell count >200 cells/mm^3) for 6 months; infant ZDV/3TC for 1 week	• MTCT at age 6 months was 5.0% (postnatal MTCT between ages 6 weeks and 6 months was 0.9%), not significantly different from 6 months infant prophylaxis in MITRA.
Kesho Bora Multi-African[16] Breastfeeding primarily	Antepartum ZDV/sdNVP with no postnatal prophylaxis vs. maternal triple-drug prophylaxis in women with CD4-cell counts of 200–500 cells/mm^3	Arm 1: ZDV/3TC/LPV/r Arm 2: ZDV + sdNVP From 28 weeks through labor	Arm 1: Maternal ZDV/3TC/LPV/r for 6 months; infant sdNVP + ZDV for 1 week Arm 2: Maternal ZDV/3TC for 1 week (no further postnatal prophylaxis); infant sdNVP + ZDV for 1 week (no further postnatal prophylaxis)	• MTCT at birth was 1.8% with maternal triple-drug prophylaxis Arm 1 and 2.5% with ZDV/sdNVP Arm 2, not significantly different. In women with CD4-cell counts 350–500 cells/mm^3, MTCT at birth was 1.7% in both arms. • MTCT at age 12 months was 5.4% with maternal triple-drug prophylaxis Arm 1 and 9.5% with ZDV/sdNVP (with no further postnatal prophylaxis after 1 week) Arm 2 (P = 0.029).
Mma Bana Botswana[1] Breastfeeding	Maternal triple-drug prophylaxis (compares 2 regimens) in women with CD4-cell 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 sdNVP + ZDV for 4 weeks Arm 2: Maternal ZDV/3TC/LPV/r for 6 months; infant sdNVP + ZDV for 4 weeks	• MTCT 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).

Table 3. Results of Major Studies on Antiretroviral Prophylaxis to Prevent Mother-to-Child Transmission of HIV (page 7 of 9)

Study Location(s) Mode of Infant Feeding	Antiretroviral (ARV) Drugs	Antepartum and Intrapartum	Postpartum	Mother-to-Child Transmission (MTCT) Rate and Efficacy
BAN Malawi[26, 37] Breastfeeding	Postpartum maternal triple-drug prophylaxis vs. infant NVP in women with CD4-cell counts ≥250 cells/mm^3	No AP drugs IP regimens: Arm 1 (control): ZDV/3TC + sdNVP Arm 2: ZDV/3TC + sdNVP Arm 3: ZDV/3TC + sdNVP	Arm 1 (control): Maternal ZDV/3TC for 1 week; infant sdNVP + 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: - MTCT 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); 1.7% in infant NVP Arm 3 (P <0.001 vs. control). - MTCT at age 48 weeks was 7.0% in control Arm 1; 4% in maternal triple-drug prophylaxis Arm 2 (P = 0.0273 vs. control); 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).

Table 3. Results of Major Studies on Antiretroviral Prophylaxis to Prevent Mother-to-Child Transmission of HIV (page 8 of 9)

Study Location(s) Mode of Infant Feeding	Antiretroviral (ARV) Drugs	Antepartum and Intrapartum	Postpartum	Mother-to-Child Transmission (MTCT) Rate and Efficacy
HPTN 046 South Africa, Tanzania, Uganda, Zimbabwe[33] 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 6 weeks through 6 months of age Arm 2: Daily infant placebo from 6 weeks through age 6 months of age	• In infants uninfected at age 6 weeks, the 6-month infant HIV infection rate was 1.1% (0.3%–1.8%) in the extended NVP Arm 1 and 2.4% (1.3%–3.6%) in the placebo Arm 2 ($P = 0.048$). • At infant randomization at age 6 weeks, 29% of mothers in each arm were receiving a triple-drug ARV regimen for 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 extended NVP Arm 1 (0.5%) and placebo Arm 2 (0%). • For mothers with CD4-cell 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%–1.5%) in the extended NVP Arm 1 and 2.8% (1.3%–4.4%) in the placebo Arm 2 ($P = 0.014$).

Table 3. Results of Major Studies on Antiretroviral Prophylaxis to Prevent Mother-to-Child Transmission of HIV (page 9 of 9)

Study Location(s) Mode of Infant Feeding	Antiretroviral (ARV) Drugs	Antepartum and Intrapartum	Postpartum	Mother-to-Child Transmission (MTCT) Rate and Efficacy
NICHD-HPTN 040/PACTG 1043 trial Argentina, Brazil, South Africa, United States[18] Formula feeding	Infant prophylaxis with 6 weeks ZDV vs. 6 weeks infant ZDV plus three doses of NVP in first week of life vs. 6 weeks infant ZDV plus 2 weeks of 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 2 weeks of age	• IP HIV transmission among infants with negative HIV test at birth: 4.8% (3.2%–7.1%) ZDV (Arm 1) vs. 2.2% (1.2%–3.9%) in ZDV plus NVP (Arm 2) (P = 0.046 compared with Arm 1) vs. 2.4% (1.4%–4.3%) in 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%–14.0%) ZDV (Arm 1) vs. 7.1% (5.2%–9.6%) in ZDV plus NVP (Arm 2) (P = 0.035 compared with Arm 1) vs. 7.4% (5.4%–9.9%) in 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).

Key to Abbreviations: 3TC = lamivudine, ABC = abacavir, AP = antepartum, ARV = antiretroviral, CDC = Centers for Disease Control and Prevention, CI = confidence interval, IP = intrapartum, IV = intravenous, LPV/r = lopinavir/ritonavir, MTCT = mother-to-child transmission, NFV = nelfinavir, NVP = nevirapine, PP = postpartum, sd = single-dose, ZDV = zidovudine

Table 4: Drug Interactions Between Antiretroviral Agents and Hormonal Contraceptives (page 1 of 2)

Data on drug interactions between antiretroviral (ARV) agents and hormonal contraceptives primarily come from drug labels and the clinical implications have not been well studied. The magnitude of changes in contraceptive drug levels that may reduce contraceptive efficacy or increase contraceptive-associated adverse effects is unknown. Hormonal contraceptives can be used with antiretroviral therapy (ART) in women without other contraindications. Additional or alternative methods of contraception may be recommended when drug interactions are known.

Antiretroviral Drug	Effect on Drug Levels	Dosing Recommendation/ Clinical Comment
Non-nucleoside Reverse Transcriptase Inhibitor (NNRTI)		
Efavirenz (EFV)	Oral ethinyl estradiol/norgestimate: No effect on ethinyl estradiol concentrations; ↓ active metabolites of norgestimate (levonorgestrel AUC ↓83%; norelgestromin AUC ↓64%)	A reliable method of barrier contraception must be used in addition to hormonal contraceptives. Efavirenz had no effect on ethinyl estradiol concentrations, but progestin levels (norelgestromin and levonorgestrel) were markedly decreased. No effect of ethinyl estradiol/norgestimate on efavirenz plasma concentrations was observed.
	Implant: ↓ etonogestrel	A reliable method of barrier contraception must be used in addition to hormonal contraceptives. The interaction between etonogestrel and efavirenz has not been studied. Decreased exposure of etonogestrel may be expected. In postmarketing reports, contraceptive failure with etonogestrel has been noted in efavirenz-exposed patients.
	Levonorgestrel AUC ↓58%	Effectiveness of emergency postcoital contraception may be diminished.
Etravirine (ETR)	Ethinyl estradiol AUC ↑22% Norethindrone: no significant effect	No dosage adjustment needed.
Nevirapine (NVP)	Ethinyl estradiol AUC ↓20% Norethindrone AUC ↓19%	Additional methods recommended; alternative methods can be considered.
	DMPA: no significant change	No dosage adjustment needed.
Rilpivirine (RPV)	Ethinyl estradiol AUC ↑14% Norethindrone: no significant change	No dose adjustment needed.
Ritonavir (RTV)-boosted Protease Inhibitor (PI)		
Atazanavir/ritonavir (ATV/r)	↓ Ethinyl estradiol ↑ Norgestimate	Oral contraceptive should contain ≥35 mcg ethinyl estradiol. Oral contraceptives containing progestins other than norethindrone or norgestimate have not been studied.

Table 4: Drug Interactions Between Antiretroviral Agents and Hormonal Contraceptives (page 2 of 2)

Antiretroviral Drug	Effect on Drug Levels	Dosing Recommendation/ Clinical Comment
Darunavir/ritonavir (DRV/r)	Ethinyl estradiol AUC ↓44% Norethindrone AUC ↓14%	Additional methods recommended; alternative methods can be considered.
Fosamprenavir/ritonavir (FPV/r)	Ethinyl estradiol AUC ↓37% Norethindrone AUC ↓34%	Alternative methods of nonhormonal contraception are recommended.
Lopinavir/ritonavir (LPV/r)	Ethinyl estradiol AUC ↓42% Norethindrone AUC ↓17%	Additional methods recommended; alternative methods can be considered.
Saquinavir/ritonavir (SQV/r)	↓Ethinyl estradiol	Additional methods recommended; alternative methods can be considered.
Tipranavir/ritonavir (TPV/r)	Ethinyl estradiol AUC ↓48% Norethindrone: no significant change	Additional methods recommended; alternative methods can be considered.
PI without RTV		
Atazanavir (ATV)	Ethinyl estradiol AUC ↑48% Norethindrone AUC ↑110%	Oral contraceptive should contain ≤30 mcg of ethinyl estradiol or use alternative method. Oral contraceptives containing <25 mcg ethinyl estradiol or progestins other than norethindrone or norgestimate have not been studied.
Fosamprenavir (FPV)	Amprenavir: ↑ Ethinyl estradiol and ↑ norethindrone Fosamprenavir with ethinyl estradiol/norethindrone: ↓ Amprenavir (AUC 22%, C_{min} 20%)	Use alternative method. Use of fosamprenavir alone with ethinyl estradiol/norethindrone may lead to loss of virologic response.
Indinavir (IDV)	Ethinyl estradiol AUC ↑25% Norethindrone AUC ↑26%	No dose adjustment needed.
Nelfinavir (NFV)	Ethinyl estradiol AUC ↓47% Norethindrone AUC ↓18%	Additional methods recommended; alternative methods may be considered.
CCR5 Antagonist		
Maraviroc (MVC)	No significant effect on ethinyl estradiol or levonorgestrel	No dose adjustment needed.
Integrase Inhibitor		
Raltegravir (RAL)	No significant effect	No dose adjustment needed.

Key to Abbreviations: AUC = area under the curve, C_{min} = minimum plasma concentration, DMPA = depot medroxyprogesterone acetate

Table 4 derived from: Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf. Tables 15a, 15b, and 15d. Accessed June 7, 2012.

Table 5. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy (page 1 of 16)

(See also Safety and Toxicity of Individual Antiretroviral Drugs in Pregnancy supplement for additional toxicity data and *Guidelines for the Use of Antiretroviral Agents in HIV-1-infected Adults and Adolescents* for detailed guidelines regarding treatment options.)

ARV Drug Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations[a]	Recommendations for Use in Pregnancy	PKs in Pregnancy[b]	Concerns in Pregnancy
NRTIs			NRTIs are recommended for use as part of combination regimens, usually including two NRTIs with either an NNRTI or one or more PIs. Use of single or dual NRTIs alone is not recommended for treatment of HIV infection.		See text for discussion of potential maternal and infant mitochondrial toxicity.
Preferred Agents					
Lamivudine (3TC) Epivir	Epivir 150-, 300-mg tablets or 10-mg/mL oral solution	Epivir 150 mg BID or 300 mg once daily Take without regard to meals.	Because of extensive experience with 3TC in pregnancy in combination with ZDV, 3TC plus ZDV is a recommended dual-NRTI backbone for pregnant women.	PK not significantly altered in pregnancy; no change in dose indicated.[24] High placental transfer to fetus.	No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects).[25] Well tolerated; short-term safety demonstrated for mothers and infants. If hepatitis B coinfected, possible hepatitis B flare if drug stopped postpartum; see Special Situations: Hepatitis B Virus Coinfection.
	Combivir 3TC 150 mg + ZDV 300 mg	Combivir 1 tablet BID			
	Epzicom 3TC 300 mg + ABC 600 mg	Epzicom 1 tablet once daily			
	Trizivir[c] 3TC 150 mg + ZDV 300 mg + ABC 300 mg	Trizivir 1 tablet BID			

Table 5. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy (page 2 of 16)

ARV Drug Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations[a]	Recommendations for Use in Pregnancy	PKs in Pregnancy[b]	Concerns in Pregnancy
Zidovudine (AZT, ZDV) Retrovir	Retrovir 100-mg capsules, 300-mg tablets, 10-mg/mL IV solution, 10-mg/mL oral solution	Retrovir 300 mg BID or 200 mg TID Take without regard to meals.	Because of extensive experience with ZDV in pregnancy in combination with 3TC, ZDV plus 3TC is a recommended dual-NRTI backbone for pregnant women.	PK not significantly altered in pregnancy; no change in dose indicated.[26] High placental transfer to fetus.	No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects).[25] Well tolerated; short-term safety demonstrated for mothers and infants.
	Combivir ZDV 300 mg + 3TC 150 mg	Combivir 1 tablet BID			
	Trizivir[c] ZDV 300 mg + 3TC 150 mg + ABC 300 mg	Trizivir 1 tablet BID			
Alternative Agents					
Abacavir (ABC) Ziagen	Ziagen 300-mg tablets or 20-mg/mL oral solution	Ziagen 300 mg BID or 600 mg once daily Take without regard to meals.	Alternative NRTI for dual-NRTI backbone of combination regimens. See footnote regarding use in triple-NRTI regimen.[c]	PK not significantly altered in pregnancy; no change in dose indicated.[27] High placental transfer to fetus.	No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects).[25] Hypersensitivity reactions occur in ~5%–8% of non-pregnant individuals; a much smaller percentage are fatal and are usually associated with re-challenge. Rate in pregnancy unknown. Testing for HLA-B*5701 identifies patients at risk of reactions [28, 29] and should be done and documented as negative before starting ABC. Patients should be educated regarding symptoms of hypersensitivity reaction.
	Epzicom ABC 600 mg + 3TC 300 mg	Epzicom 1 tablet once daily			
	Trizivir[c] ABC 300 mg + ZDV 300 mg + 3TC 150 mg	Trizivir 1 tablet BID			

Table 5. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy (page 3 of 16)

ARV Drug Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations[a]	Recommendations for Use in Pregnancy	PKs in Pregnancy[b]	Concerns in Pregnancy
Alternative Agents, continued					
Emtricitabine (FTC) Emtriva	Emtriva 200-mg capsule or 10-mg/mL oral solution	Emtriva 200-mg capsule once daily or 240-mg (24-mL) oral solution once daily Take without regard to meals.	Alternative NRTI for dual-NRTI backbone of combination regimens.	PK study shows slightly lower levels in third trimester, compared with postpartum.[30] No clear need to increase dose. High placental transfer to fetus.	No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects).[25] If hepatitis B coinfected, possible hepatitis B flare if drug stopped postpartum; see Special Situations: Hepatitis B Virus Coinfection.
	Truvada FTC 200 mg + TDF 300 mg	Truvada 1 tablet once daily			
	Atripla FTC 200 mg + EFV[d] 600 mg + TDF 300 mg	Atripla 1 tablet at or before bedtime Take on an empty stomach to reduce side effects.			
Tenofovir Disoproxil Fumarate (TDF) Viread	Viread 300-mg tablet	Viread 1 tablet once daily Take without regard to meals.	Alternative NRTI for dual-NRTI backbone of combination regimens. TDF would be a preferred NRTI in combination with 3TC or FTC in women with chronic HBV infection. Because of potential for renal toxicity, renal function should be monitored.	AUC lower in third trimester than postpartum but trough levels adequate.[31] High placental transfer to fetus.[7, 32-35]	No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects).[25] Studies in monkeys at doses approximately 2-fold higher than that for human therapeutic use show decreased fetal growth and reduction in fetal bone porosity within 2 months of starting maternal therapy.[36] Clinical studies in humans (particularly children) show bone demineralization with chronic use; clinical significance unknown.[37, 38] If hepatitis B coinfected, possible hepatitis B flare if drug stopped postpartum; see Special Situations: Hepatitis B Virus Coinfection.
	Truvada TDF 300 mg + FTC 200 mg	Truvada 1 tablet once daily			
	Atripla TDF 300 mg + EFV[d] 600 mg + FTC 200 mg	Atripla 1 tablet at or before bedtime Take on an empty stomach to reduce side effects.			

Table 5. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy (page 4 of 16)

ARV Drug Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations[a]	Recommendations for Use in Pregnancy	PKs in Pregnancy[b]	Concerns in Pregnancy
Use in Special Circumstances					
Didanosine (ddI) Videx EC, generic didanosine (dose same as Videx EC)	Videx EC 125-, 200-, 250-, 400-mg capsules Buffered tablets (non-EC) no longer available Videx 10-mg/mL oral solution	**Body weight ≥60kg:** 400 mg once daily; with TDF, 250 mg once daily **Body weight <60kg:** 250 mg once daily; with TDF, 200 mg once daily Take 1/2 hour before or 2 hours after a meal. Preferred dosing with oral solution is BID (total daily dose divided into 2 doses).	Because of the need to administer on empty stomach and potential toxicity, ddI should be used only in special circumstances where preferred or alternative NRTIs cannot be used. ddI should not be used with d4T.	PK not significantly altered in pregnancy; no change in dose indicated.[39] Moderate placental transfer to fetus.	In the APR, an increased rate of birth defects with ddI compared to general population was noted after both first trimester (19/409, 4.6%, 95% CI, 2.8–7.2) and later exposure (20/460, 4.3%, 95% CI 2.7–6.6). This difference may have been due to maternal characteristics such as older age or more advanced disease among women using ddI. No specific pattern of defects was noted and clinical relevance is uncertain. Lactic acidosis, sometimes fatal, has been reported in pregnant women receiving ddI and d4T together.[40, 41]
Stavudine (d4T) Zerit	Zerit 15-, 20-, 30-, 40-mg capsules or 1-mg/mL oral solution	**Body weight ≥60 kg:** 40 mg BID **Body weight <60 kg:** 30 mg BID Take without regard to meals. WHO recommends 30-mg BID dosing regardless of body weight.	Because of potential toxicities, d4T should be used only in special circumstances where preferred or alternative NRTIs cannot be used. d4T should not be used with ddI or ZDV.	PKs not significantly altered in pregnancy; no change in dose indicated.[9] High placental transfer.	No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects).[25] Lactic acidosis, sometimes fatal, has been reported in pregnant women receiving ddI and d4T together.[40, 41]

Table 5. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy (page 5 of 16)

ARV Drug Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations[a]	Recommendations for Use in Pregnancy	PKs in Pregnancy[b]	Concerns in Pregnancy
NNRTIs			NNRTIs are recommended for use in combination regimens with 2 NRTI drugs.		Hypersensitivity reactions, including hepatic toxicity, and rash more common in women; unclear if increased in pregnancy.
Preferred Agents					
Nevirapine (NVP) Viramune	200-mg tablets or 50-mg/5-mL oral suspension	200 mg once daily for 14 days (lead-in period); thereafter, 200 mg BID Take without regard to meals. Repeat lead-in period if therapy is discontinued for >7 days. In patients who develop mild-to-moderate rash without constitutional symptoms during lead-in, continue lead-in dosing until rash resolves, but ≤28 days total.	NVP should be initiated in pregnant women with CD4 T-lymphocyte (CD4-cell) counts >250 cells/mm^3 only if benefit clearly outweighs risk because of the increased risk of potentially life-threatening hepatotoxicity in women with high CD4-cell counts. Elevated transaminase levels at baseline also may increase the risk of NVP toxicity. Women who become pregnant while taking NVP-containing regimens and are tolerating them well can continue therapy, regardless of CD4-cell count.	PK not significantly altered in pregnancy; no change in dose indicated.[42-44] High placental transfer to fetus.	No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects).[25] Increased risk of symptomatic, often rash-associated, and potentially fatal liver toxicity among women with CD4-cell counts >250/mm^3 when first initiating therapy; [45, 46] unclear if pregnancy increases risk.

Table 5. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy (page 6 of 16)

ARV Drug Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations[a]	Recommendations for Use in Pregnancy	PKs in Pregnancy[b]	Concerns in Pregnancy
Use in Special Circumstances					
Efavirenz[d] (EFV) Sustiva	50-, 200-mg capsules or 600-mg tablets	600 mg once daily at or before bedtime Take on an empty stomach to reduce side effects.	Non-pregnant women of childbearing potential should undergo pregnancy testing before initiation of EFV and counseling about the potential risk to the fetus and desirability of avoiding pregnancy while on EFV-containing regimens. Alternate ARV regimens that do not include EFV should be strongly considered in women who 1) are planning to become pregnant or 2) are sexually active and not using effective contraception, assuming these alternative regimens are acceptable to the provider and are not thought to compromise the health of the woman. Because the risk of neural tube defects is restricted to the first 5–6 weeks of pregnancy and pregnancy is rarely recognized before 4–6 weeks of pregnancy, and unnecessary ARV drug changes during pregnancy may be associated with loss of viral control and increased risk of perinatal transmission, EFV may be continued in pregnant women receiving an EFV-based regimen who present for antenatal care in the first trimester, provided there is virologic suppression on the regimen (see HIV-Infected Pregnant Women Who are Currently Receiving Antiretroviral Treatment).	AUC decreased during third trimester, compared with postpartum, but nearly all third-trimester subjects exceeded target exposure and no change in dose is indicated.[47] Moderate placental transfer to fetus.	FDA Pregnancy Class D; significant malformations (anencephaly, anophthalmia, cleft palate) were observed in 3 of 20 infants (15%) born to cynomolgus monkeys receiving EFV during the first trimester at a dose resulting in plasma levels comparable to systemic human therapeutic exposure. There are 4 retrospective case reports and 1 prospective case report of neural tube defects in humans with first-trimester exposure and 1 prospective case of anophthalmia with facial clefts; [25, 48, 49] relative risk unclear.
	Atripla EFV[d] 600 mg + FTC 200 mg + TDF 300 mg	Atripla 1 tablet once daily at or before bedtime			

Table 5. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy (page 7 of 16)

ARV Drug Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations[a]	Recommendations for Use in Pregnancy	PKs in Pregnancy[b]	Concerns in Pregnancy
Insufficient Data to Recommend Use					
Etravirine (ETR) Intelence	100-, 200-mg tablets	200 mg BID Take following a meal.	Safety and PK data in pregnancy are insufficient to recommend use during pregnancy.	Limited PK data in pregnancy; in 4 pregnant women, drug levels and AUC similar to those in non-pregnant adults, suggesting no dose modification needed.[50]	Limited experience in human pregnancy. Only 23 first-trimester exposures have been reported to APR. No evidence of teratogenicity in rats and rabbits.
Rilpivirine (RPV) Endurant	25-mg tablets	25 mg once daily with a meal.	Safety and PK data in pregnancy are insufficient to recommend use during pregnancy.	No PK studies in human pregnancy, placental transfer rate unknown.	No published experience in human pregnancy. No evidence of teratogenicity in rats or rabbits.
	Complera RPV 25 mg + TDF 300 mg + FTC 200 mg	Complera 1 tablet once daily			
PIs			PIs are recommended for use in combination regimens with 2 NRTI drugs.		Hyperglycemia, new onset or exacerbation of diabetes mellitus, and diabetic ketoacidosis reported with PI use; unclear if pregnancy increases risk. Conflicting data regarding preterm delivery in women receiving PIs (see text).

Table 5. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy (page 8 of 16)

ARV Drug Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations[a]	Recommendations for Use in Pregnancy	PKs in Pregnancy[b]	Concerns in Pregnancy
Preferred Agents					
Atazanavir (ATV) Reyataz (combined with low-dose RTV boosting)	100-, 150-, 200-, 300-mg capsules	ATV 300 mg + RTV 100 mg once daily Second and third trimester: Some experts recommend increased dose (ATV 400 mg + RTV 100 mg once daily) in all pregnant women in the second and third trimesters ATV package insert recommends increased dose (ATV 400 mg + RTV 100 mg once daily) in the following situations: - With TDF or H_2-receptor antagonist (not both; use of both with ATV not recommended) in ARV-experienced pregnant patients - With EFV[d] in ARV-naive patients (Concurrent use of ATV with EFV in ARV-experienced patients is not recommended because of decreased ATV levels.) Take with food.	Preferred PI for use in combination regimens in pregnancy. Should give as low-dose RTV-boosted regimen, may use once-daily dosing. Several studies have shown decreased ATV plasma concentrations with standard dosing during pregnancy.[32, 51, 52] Use of an increased dose during the second and third trimesters resulted in plasma concentrations equivalent to those in non-pregnant adults on standard dosing.[53] Although some experts recommend increased ATV dosing in all women during the second and third trimesters, the package insert recommends increased ATV dosing only for ARV-experienced pregnant women in the second and third trimesters also receiving either TDF or an H_2-receptor antagonist or ARV-naive pregnant women receiving EFV. ATV should not be used in patients receiving both TDF and H_2 receptor antagonists or in ARV-experienced patients also taking EFV.	Two of three intensive PK studies of ATV with RTV boosting during pregnancy and the PK study described in the recently approved product label suggest that standard dosing in pregnancy results in decreased plasma concentrations, compared with non-pregnant adults.[32, 35, 51, 52] ATV concentrations further reduced ~25% with concomitant TDF use.[32, 35] Low placental transfer to fetus.[32, 51]	No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects).[25] Theoretical concern regarding increased indirect bilirubin levels causing significant exacerbation in physiologic hyperbilirubinemia in neonates has not been observed in clinical trials to date.[32, 35, 51, 52, 54]

Table 5. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy (page 9 of 16)

ARV Drug Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations[a]	Recommendations for Use in Pregnancy	PKs in Pregnancy[b]	Concerns in Pregnancy
Preferred Agents, continued					
Lopinavir + Ritonavir (LPV/r) Kaletra	Tablets: (LPV 200 mg + RTV 50 mg) or (LPV 100 mg + RTV 25 mg) Oral solution: Each 5 mL contains LPV 400 mg + RTV 100 mg Oral solution contains 42% alcohol and therefore may not be optimal for use in pregnancy.	LPV/r 400 mg/100 mg BID Second and third trimester: Some experts recommend increased dose (LPV/r 600 mg/150 mg BID) in second and third trimesters. With EFV[d] or NVP (PI-naive or PI-experienced patients): LPV/r 500 mg/125 mg tablets BID (Use a combination of two LPV/r 200 mg/50 mg tablets + one LPV/r 100 mg/25 mg tablet to make a total dose of LPV/r 500 mg/125 mg) or LPV/r 533 mg/133 mg oral solution (6.5mL) BID. Tablets: Take without regard to meals. Oral solution: Take with food. Not used in pregnancy: Adult dosage of LPV/r 800 mg/200 mg once daily is not recommended for use in pregnancy.	PK studies suggest dose should be increased to 600 mg/150 mg BID in second and third trimesters, especially in PI-experienced patients. If standard dosing is used, monitor virologic response and LPV drug levels, if available. Once-daily LPV/r dosing is not recommended during pregnancy because there are no data to address whether drug levels are adequate with such administration.	AUC decreased in second and third trimesters with standard dosing.[55-57] AUC with dose of LPV/r 600 mg/150 mg twice daily in third trimester in U.S. women resulted in AUC similar to that in non-pregnant adults taking LPV/r 400 mg/100 mg dose twice daily.[30] Low placental transfer to fetus.	No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects).[25] Well tolerated; short-term safety demonstrated in Phase I/II studies.

Table 5. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy (page 10 of 16)

ARV Drug Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations[a]	Recommendations for Use in Pregnancy	PKs in Pregnancy[b]	Concerns in Pregnancy
Preferred Agents, continued					
Ritonavir (RTV) Norvir When used as low-dose booster with other PIs	100-mg capsules 100-mg tablets 80-mg/mL oral solution Oral solution contains 43% alcohol and therefore may not be optimal for use in pregnancy.	As PK booster for other PIs: 100–400 mg per day in 1–2 divided doses (Refer to other PIs for specific dosing recommendations.) Tablets: Take with food. Capsule and oral solution: Take with food if possible, which may improve tolerability.	Should only be used in combination with second PI as low-dose RTV "boost" to increase levels of second PI because of low drug levels in pregnant women when used as a sole PI and poor tolerance when given as full dose.	Phase I/II study in pregnancy showed lower levels during pregnancy compared with postpartum.[58] Minimal placental transfer to fetus.	No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects).[25] Limited experience at full dose in human pregnancy; should be used as low-dose RTV boosting with other PIs.
Alternative Agents					
Darunavir (DRV) Prezista (must be combined with low-dose RTV boosting)	75-, 150-, 400-, 600-mg tablets	ARV-naive patients: (DRV 800 mg + RTV 100 mg) once daily ARV-experienced patients: (DRV 800 mg + RTV 100 mg) once daily if no DRV resistance mutations (DRV 600 mg + RTV 100 mg) BID if any DRV resistance mutations Some experts recommend use of only twice-daily dosing (DRV 600 mg + RTV 100 mg BID) during pregnancy. Unboosted DRV is **not** recommended. Take with food.	Safety and PK data in pregnancy are limited. DRV may be considered when preferred and alternative agents cannot be used. Must give as low-dose RTV-boosted regimen.	In PK study of women in the third trimester and postpartum, third-trimester DRV average plasma concentrations were decreased by 23%–28% with once- and twice-daily dosing and third-trimester DRV trough concentrations were low, especially with once-daily dosing.[59] Some experts recommend use of only twice-daily dosing during pregnancy and investigation of use of an increased twice-daily dose is under way. Low placental transfer to fetus.[59]	Insufficient data to assess for teratogenicity in humans. No evidence of teratogenicity in mice, rats, or rabbits but low bioavailability limited exposure. Limited experience in human pregnancy.

Table 5. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy (page 11 of 16)

ARV Drug Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations[a]	Recommendations for Use in Pregnancy	PKs in Pregnancy[b]	Concerns in Pregnancy
Alternative Agents, continued					
Saquinavir (SQV) Invirase (available as capsules and tablets. SQV must be combined with low-dose RTV boosting.)	500-mg tablets or 200-mg capsules	(SQV 1000 mg + RTV 100 mg) BID Unboosted SQV is **not** recommended. Take with meals or within 2 hours after a meal.	PK data on SQV capsules and the tablet formulation in pregnancy are limited. RTV-boosted SQV capsules or SQV tablets are alternative PIs for combination regimens in pregnancy and are alternative initial ARV recommendations for non-pregnant adults. Must give as low-dose RTV-boosted regimen.	Limited PK data on capsules and the 500-mg tablet formulation suggest that 1000-mg SQV capsules /100 mg RTV given twice daily achieves adequate SQV drug levels in pregnant women.[60] Minimal placental transfer to fetus.	Insufficient data to assess for teratogenicity in humans. No evidence of teratogenicity in rats or rabbits but low bioavailability limited exposure. Well tolerated; short-term safety demonstrated for mothers and infants for SQV in combination with low-dose RTV. Baseline ECG recommended before starting because PR and/or QT interval prolongations have been observed and drug is contraindicated in patients with pre-existing cardiac conduction system disease.
Use in Special Circumstances					
Indinavir (IDV) Crixivan (combined with low-dose RTV boosting)	100-, 200-, 400-mg capsules	With RTV: (IDV 800 mg + RTV 100–200 mg) BID Take without regard to meals. Not used in pregnancy: Adult dosage of IDV (without RTV) 800 mg every 8 hours is not recommended for use in pregnancy.	Because of twice-daily dosing, pill burden, and potential for renal stones, IDV should only be used when preferred and alternative agents cannot be used. Must give as low-dose RTV-boosted regimen.	Two studies including 18 women receiving IDV 800 mg TID showed markedly lower levels during pregnancy compared with postpartum, although suppression of HIV RNA levels was seen.[61, 62] In a study of RTV-boosted IDV (400 mg IDV/100 mg RTV twice daily), 82% of women met the target trough level.[63] Minimal placental transfer to fetus.	No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects).[25] Theoretical concern regarding increased indirect bilirubin levels, which may exacerbate physiologic hyperbilirubinemia in neonates, but minimal placental passage. Use of unboosted IDV during pregnancy is not recommended.

Table 5. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy (page 12 of 16)

ARV Drug Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations[a]	Recommendations for Use in Pregnancy	PKs in Pregnancy[b]	Concerns in Pregnancy
Use in Special Circumstances, continued					
Nelfinavir (NFV) Viracept	250-, 625-mg tablets 50-mg/g oral powder	1250 mg BID Take with food. Not used in pregnancy: Adult dosage of NFV 750 mg TID is not recommended for use in pregnancy.	Given PK data and extensive experience with use in pregnancy, NFV might be considered in special circumstances for prophylaxis of transmission in women in whom therapy would not otherwise be indicated when alternative agents are not tolerated. In clinical trials of initial therapy in non-pregnant adults, NFV-based regimens had a lower rate of viral response compared with LPV/r- or EFV-based regimens but similar viral response to ATV- or NVP-based regimens.	Adequate drug levels are achieved in pregnant women with NFV 1250 mg given twice daily, although levels are variable in late pregnancy.[43, 64, 65] In a study of women in their second and third trimesters dosed at 1250 mg twice daily, women in the third trimester had lower concentration of NFV than those in the second trimester.[65] In a study of the new 625-mg tablet formulation dosed at 1250 mg twice daily, lower AUC and peak levels were observed during the third trimester than postpartum.[66] Minimal to low placental transfer to fetus.	No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects).[25] Well tolerated; short-term safety demonstrated for mothers and infants.

Table 5. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy (page 13 of 16)

ARV Drug Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations[a]	Recommendations for Use in Pregnancy	PKs in Pregnancy[b]	Concerns in Pregnancy
Insufficient Data to Recommend Use					
Fosamprenavir (FPV) Lexiva (a prodrug of amprenavir) (recommended to be combined with low-dose RTV boosting)	700-mg tablet or 50-mg/mL oral suspension	ARV-naive patients: • FPV 1400 mg BID or • (FPV 1400 mg + RTV 100–200 mg) once daily or • (FPV 700 mg + RTV 100 mg) BID PI-experienced patients (once-daily dosing **not** recommended): • (FPV 700 mg + RTV 100 mg) BID With EFV: • (FPV 700 mg + RTV 100 mg) BID or • (FPV 1400 mg + RTV 300 mg) once daily Tablet: Take without regard to meals (if not boosted with RTV tablet). Suspension: Take without food. FPV with RTV tablet: Take with meals.	Safety and PK data in pregnancy are insufficient to recommend routine use during pregnancy in ARV-naive patients. Recommended to be given as low-dose RTV-boosted regimen.	With RTV boosting, AUC is reduced during the third trimester. However, exposure is greater during the third trimester with boosting than in non-pregnant adults without boosting and trough concentrations achieved during the third trimester were adequate for patients without PI resistance mutations.[67] Low placental transfer to fetus.	Insufficient data to assess for teratogenicity in humans. Increased fetal loss in rabbits but no increase in defects in rats and rabbits. Limited experience in human pregnancy.

Table 5. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy (page 14 of 16)

ARV Drug Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations[a]	Recommendations for Use in Pregnancy	PKs in Pregnancy[b]	Concerns in Pregnancy
Insufficient Data to Recommend Use, continued					
Tipranavir (TPV) Aptivus (must be combined with low-dose RTV boosting)	250-mg capsules or 100-mg/mL oral solution	(TPV 500 mg + RTV 200 mg) BID Unboosted TPV is **not** recommended. TPV taken with RTV tablets: Take with meals. TPV taken with RTV capsules or solution: Take without regard to meals.	Safety and PK data in pregnancy are insufficient to recommend routine use during pregnancy in ARV-naive patients. Must give as low-dose RTV-boosted regimen.	Limited PK studies in human pregnancy. Moderate placental transfer to fetus reported in one patient.[68]	Insufficient data to assess for teratogenicity in humans. No teratogenicity in rats or rabbits. Limited experience in human pregnancy.
Entry Inhibitors					
Insufficient Data to Recommend Use					
Enfuvirtide (T20) Fuzeon	• Injectable—supplied as lyophilized powder • Each vial contains 108 mg of T20; reconstitute with 1.1 mL of sterile water for injection for delivery of approximately 90 mg/1 mL.	90 mg (1mL) SQ BID	Safety and PK data in pregnancy are insufficient to recommend use during pregnancy in ARV-naive patients.	Limited PK studies in human pregnancy. No placental transfer to fetus, based on very limited data.[68,69]	Insufficient data to assess for teratogenicity in humans. No evidence of teratogenicity in rats or rabbits. Minimal data in human pregnancy.[68, 70]

Table 5. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy (page 15 of 16)

ARV Drug Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations[a]	Recommendations for Use in Pregnancy	PKs in Pregnancy[b]	Concerns in Pregnancy
Entry Inhibitors, continued					
Insufficient Data to Recommend Use, continued					
Maraviroc (MVC) Selzentry	150-, 300-mg tablets	• **150 mg BID** when given with strong CYP3A inhibitors (with or without CYP3A inducers) including PIs (except TPV/r) • **300 mg BID** when given with NRTIs, NVP, RAL, T-20, TPV/r, and other drugs that are not strong CYP3A inhibitors or inducers • **600 mg BID** when given with CYP3A inducers, including EFV, ETR (without a CYP3A inhibitor) Take without regard to meals.	Safety and PK data in pregnancy are insufficient to recommend use during pregnancy in ARV-naive patients.	No PK studies in human pregnancy. Unknown placental transfer rate to fetus.	Insufficient data to assess for teratogenicity in humans. No evidence of teratogenicity in rats or rabbits. Limited experience in human pregnancy.
Integrase Inhibitors					
Use in Special Circumstances					
Raltegravir (RAL) Isentress	400-mg tablets	400 mg BID With rifampin: 800 mg BID Take without regard to meals.	Safety and PK data in pregnancy are limited; can be considered for use in special circumstances when preferred and alternative agents cannot be used.	During third trimester, RAL PK showed extensive variability but RAL exposure was not consistently altered compared with postpartum and historical data. The standard dose appears appropriate during pregnancy.[71] Variable but high placental transfer to fetus.[71, 72]	Insufficient data to assess for teratogenicity in humans. Increased skeletal variants in rats, no increase in defects in rabbits. Limited experience in human pregnancy.

Table 5. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy (page 16 of 16)

Key to Abbreviations: APR = Antiretroviral Pregnancy Registry, ARV = antiretroviral, AUC = area under the curve, BID = twice daily, CI = confidence interval, CYP = cytochrome P, EC = enteric coated, ECG = electrocardiogram, FDA = Food and Drug Administration, HBV = hepatitis B virus, IV = intravenous, NNRTI = non-nucleoside reverse transcriptase inhibitor, NRTI = nucleoside/nucleotide reverse transcriptase inhibitor, PI = protease inhibitor, PK = pharmacokinetic, PPI = proton pump inhibitor, SQ = subcutaneous injection, TID = three times daily, WHO = World Health Organization

[a] Dosage should be adjusted in renal or hepatic insufficiency (see *Adult Guidelines, Appendix B, Table 7*).

[b] Placental transfer categories—Mean or median cord blood/maternal delivery plasma drug ratio:

High: >0.6
Moderate: 0.3–0.6
Low: 0.1–0.3
Minimal: <0.1

[c] Triple-NRTI regimens including abacavir have been less potent virologically compared with PI-based combination ARV drug regimens. Triple-NRTI regimens should be used only when an NNRTI- or PI-based combination regimen cannot be used, such as because of significant drug interactions.

[d] See Teratogenicity for discussion of efavirenz and risks in pregnancy.

Table 6. Clinical Scenario Summary Recommendations for Antiretroviral Drug Use by Pregnant HIV-Infected Women and Prevention of Perinatal Transmission of HIV-1 in the United States (page 1 of 4)

Clinical Scenario	Recommendations
Non-pregnant HIV-infected women of childbearing potential (sexually active and not using contraception) who have indications for initiating antiretroviral therapy (ART)	Initiate combination antiretroviral (ARV) drug therapy as per adult treatment guidelines. When feasible, include one or more nucleoside reverse transcriptase inhibitors (NRTIs) with good placental passage as a component of the ARV regimen. • Exclude pregnancy and ensure access to effective contraception for sexually active women before starting treatment with efavirenz; alternative ART regimens that do not include efavirenz should be strongly considered in women who are planning to become pregnant. Emphasize need for women on efavirenz to review their regimens with their providers before discontinuing contraception.
HIV-infected women on ART who become pregnant	**Women:** • In general, in women who require treatment, ARV drugs should not be stopped during the first trimester or during pregnancy. • Continue current combination ARV regimen, assuming the regimen is tolerated and effective in successfully suppressing viremia. • Perform HIV ARV drug-resistance testing in women on therapy who have detectable viremia (that is, >500–1,000 copies/mL). • Continue the ART regimen during the intrapartum period (if oral zidovudine is part of the antepartum regimen, and a woman's viral load is >400 copies/mL, the oral zidovudine component of her regimen should be stopped while she receives zidovudine as an intravenous continuous infusion[a] during labor and other ARV agents are continued orally) and postpartum. • Schedule cesarean delivery at 38 weeks if plasma HIV RNA remains >1,000 copies/mL near the time of delivery. **Infants:** • Start zidovudine as soon as possible after birth and administer for 6 weeks.[b]

Table 6. Clinical Scenario Summary Recommendations for Antiretroviral Drug Use by Pregnant HIV-Infected Women and Prevention of Perinatal Transmission of HIV-1 in the United States (page 2 of 4)

Clinical Scenario	Recommendations
HIV-infected pregnant women who are ARV naive	**Women:** Perform HIV ARV drug-resistance testing before initiating combination ARV drug therapy and repeat after initiating therapy if viral suppression is suboptimal (<1 log drop after 4 weeks on ARVs). If HIV is diagnosed late in pregnancy, the ARV regimen should be initiated promptly without waiting for the results of resistance testing. • Initiate combination ARV regimen. - Delayed initiation of ARVs until after the first trimester can be considered in women with high CD4 T-lymphocyte (CD4-cell) counts and low HIV RNA levels, but earlier initiation may be more effective in reducing perinatal transmission of HIV. Benefits of first trimester use must be weighed against potential fetal effects of first-trimester exposure. - Avoid initiation of efavirenz or other potentially teratogenic drugs in the first trimester and drugs with known adverse potential for mother throughout the pregnancy. - When feasible, include one or more NRTIs with good placental passage (zidovudine, lamivudine, emtricitabine, tenofovir, or abacavir) in the ARV regimen. - Use nevirapine as a component of the ARV regimen only in women who have CD4-cell counts ≤250 cells/mm^3. Because of the increased risk of severe hepatic toxicity, use nevirapine in women with CD4-cell counts >250 cells/mm^3 only if the benefit clearly outweighs the risk. • Continue the combination regimen intrapartum. Continuous infusion zidovudine[a] should be administered to HIV-infected women with HIV RNA >400 copies/mL (or unknown HIV RNA) near delivery, regardless of antepartum regimen or mode of delivery. If oral zidovudine is part of the antepartum regimen, and a woman's viral load is >400 copies/mL, the oral zidovudine component of her regimen should be stopped while she receives zidovudine as an intravenous continuous infusion[a] during labor while other ARV agents are continued orally and postpartum. • Schedule cesarean delivery at 38 weeks if plasma HIV RNA remains >1,000 copies/mL near the time of delivery. • Evaluate need for continuing the combination regimen postpartum. Following delivery, considerations for continuation of the mother's ARV regimen are the same as in other non-pregnant individuals (see General Principles Regarding Use of Antiretroviral Drugs in Pregnancy). If treatment is to be stopped and the regimen includes a drug with a long half-life, such as a non-nucleoside reverse transcriptase inhibitor [NNRTI]), continue NRTIs for at least 7 days after stopping NNRTI (see Stopping Antiretroviral Therapy and Prevention of Antiretroviral Drug Resistance). **Infants:** • Start zidovudine as soon as possible after birth and administer for 6 weeks.[b]

Table 6. Clinical Scenario Summary Recommendations for Antiretroviral Drug Use by Pregnant HIV-Infected Women and Prevention of Perinatal Transmission of HIV-1 in the United States (page 3 of 4)

Clinical Scenario	Recommendations
HIV-infected pregnant women who are ARV experienced but not currently receiving ARV drugs	**Women:** • Obtain full ARV drug history, including prior resistance testing, and evaluate need for ART for maternal health. • Test for HIV ARV drug resistance before reinitiating ARV prophylaxis or therapy and retest after initiating combination ARV regimen if viral suppression is suboptimal (<1 log drop after 4 weeks on ARVs). If HIV is diagnosed late in pregnancy, the ARV regimen should be initiated promptly without waiting for the results of resistance testing. • Initiate a combination ARV regimen (that is, at least three drugs), with the regimen chosen based on results of resistance testing and history of prior therapy. - Delayed initiation of ARVs until after the first trimester can be considered in women with high CD4-cell counts and low HIV RNA levels, but earlier initiation of prophylaxis may be more effective in reducing perinatal transmission of HIV. Benefits of first trimester use must be weighed against potential fetal effects of first-trimester exposure. - Avoid initiation of efavirenz or other potentially teratogenic drugs in the first trimester and drugs with known adverse potential for the mother throughout the pregnancy. - When feasible, include one or more NRTIs with good transplacental passage (zidovudine, lamivudine, emtricitabine, tenofovir, or abacavir) as a component of the ARV regimen. - Use nevirapine as a component of therapy in women who have CD4-cell counts >250 cells/mm^3 only if the benefit clearly outweighs the risk because of the drug's association with an increased risk of severe hepatic toxicity. • Continue the combination regimen intrapartum. Continuous infusion zidovudine[a] should be administered to HIV-infected women with HIV RNA >400 copies/mL (or unknown HIV RNA) near delivery, regardless of antepartum regimen or mode of delivery. If oral zidovudine is part of the antepartum regimen, and a woman's viral load is >400 copies/mL, the oral zidovudine component of her regimen should be stopped while she receives zidovudine as an intravenous continuous infusion[a] during labor while other ARV agents are continued orally. • Evaluate need for continuing the combination regimen postpartum. Following delivery, considerations for continuation of the mother's ARV regimen are the same as in other non-pregnant adults (see General Principles Regarding Use of Antiretroviral Drugs in Pregnancy). If treatment is to be stopped and the regimen includes a drug with a long half-life, such as NNRTIs, continue NRTIs for at least 7 days after stopping NNRTIs (see Stopping Antiretroviral Therapy and Prevention of Antiretroviral Drug Resistance). • Schedule cesarean delivery at 38 weeks if plasma HIV RNA remains >1,000 copies/mL near the time of delivery. **Infant:** • Start zidovudine as soon as possible after birth and administer for 6 weeks.[b]

Table 6. Clinical Scenario Summary Recommendations for Antiretroviral Drug Use by Pregnant HIV-Infected Women and Prevention of Perinatal Transmission of HIV-1 in the United States (page 4 of 4)

Clinical Scenario	Recommendations
HIV-infected women who have received no ARV before labor	**Women:** Give zidovudine as continuous infusion[a] during labor. **Infants:** Infants born to HIV-infected women who have not received antepartum ARV drugs should receive prophylaxis with a combination ARV drug regimen started as close to the time of birth as possible. Zidovudine[b] given for 6 weeks combined with three doses of nevirapine in the first week of life (at birth, 48 hours later, and 96 hours after the second dose) has been shown to be effective in a randomized controlled trial and less toxic than a three-drug regimen with nelfinavir and lamivudine for 2 weeks and 6 weeks of zidovudine. The two-drug regimen is preferred because of lower toxicity and because nelfinavir powder is no longer available in the United States (see Infant Antiretroviral Prophylaxis and Table 9). • Evaluate need for initiation of maternal therapy postpartum.
Infants born to HIV-infected women who have received no ARV before or during labor	• Infants born to HIV-infected women who have not received antepartum ARV drugs should receive prophylaxis with a combination ARV drug regimen started as close to the time of birth as possible. Zidovudine[b] given for 6 weeks combined with three doses of nevirapine in the first week of life (at birth, 48 hours later, and 96 hours after the second dose) has been shown to be effective in a randomized controlled trial and less toxic than a three-drug regimen with nelfinavir and lamivudine for 2 weeks and 6 weeks of zidovudine. The two-drug regimen is preferred because of lower toxicity and because nelfinavir powder is no longer available in the United States (see Infant Antiretroviral Prophylaxis and Table 9). • Evaluate need for initiation of maternal therapy postpartum.

Key to Abbreviations: ARV = antiretroviral; ART = antiretroviral therapy; IV = intravenously; NRTI = nucleoside reverse transcriptase inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor

[a] Zidovudine continuous infusion: 2 mg/kg zidovudine IV over 1 hour, followed by continuous infusion of 1 mg/kg/hour until delivery.

[b] Zidovudine dosing for infants varies by gestational age – see Table 9.

Table 7. Results of Studies Assessing Association Between Antiretroviral Regimens and Preterm Delivery (page 1 of 3)

Study Location(s)/ Dates of Study/ Reference	Total Number of Pregnancies/ Total on ARV Drugs	Types of ARV Regimens Compared (Numbers)	Association Noted Between PI-Containing or Other Multi-ARV Regimens and PTD	Special Notes
European Collaborative + Swiss Mother and Child HIV Cohort Study 1986–2000[1]	3,920/896	Mono (573) Multi, no PI (215) PI-multi (108)	YES (compared with no ARV) Multi: 1.82 (1.13–2.92) PI-multi: 2.60 (1.43–4.7)	• Increase in PTD if ARV begun before pregnancy versus in third trimester
United States 1990–1998[3]	3,266/2,123	Mono (1,590) Multi (396) PI-multi (137)	NO (compared with mono) Multi: 0.95 (0.60–1.48) PI-multi: 1.45 (0.81–2.50)	• 7 prospective clinical studies
European Collaborative Study 1986–2004[2]	4,372/2,033	Mono (704) Dual (254) Multi (1,075)	YES (compared with mono/dual) Multi in pregnancy: 1.88 (1.34–2.65) Multi prepregnancy: 2.05 (1.43–2.95)	
United States 1990–2002[4]	2,543/not given	Early (<25 weeks): Mono (621) Multi (≥2 without PI or NNRTI) (198) Multi (with PI or NNRTI) (357) Late (≥32 weeks): Mono (932) Multi (≥2 without PI or NNRTI) (258) Multi (with PI or NNRTI) (588)	NO (compared with mono) No association between any ARV and PTD	• PTD decreased with ARV compared with no ARV
United States 1990–2002[21]	1,337/999	Mono (492) Multi (373) PI-multi (134)	YES (compared with other multi) PI-multi: 1.8 (1.1–3.03)	• PI-multi reserved for advanced disease, those who failed other multi-ARV regimens
Brazil, Argentina, Mexico, Bahamas 2002–2005[22]	681/681	Mono/dual NRTI (94) Multi-NNRTI (257) Multi-PI (330)	NO (compared with mono/dual NRTI) No association between any ARV regimen and PTD	• All on ARV for at least 28 days during pregnancy • Preeclampsia/ eclampsia, cesarean delivery, diabetes, low BMI associated with PTD

Table 7. Results of Studies Assessing Association Between Antiretroviral Regimens and Preterm Delivery (page 2 of 3)

Study Location(s)/ Dates of Study/ Reference	Total Number of Pregnancies/ Total on ARV Drugs	Types of ARV Regimens Compared (Numbers)	Association Noted Between PI-Containing or Other Multi-ARV Regimens and PTD	Special Notes
Meta-analysis, Europe and United States 1986–2004[12]	11,224/not given	Multi-no PI [including dual] or multi-PI (2,556)	YES (only comparing PI with multi) PI versus multi no PI: 1.35 (1.08–1.70)	• 14 studies, 5 in PTD-ARV comparison • No overall increase in PTD with antepartum ARV • PTD increased in those on ARV pre-pregnancy and in first trimester compared with later use
Italy 2001–2006[7]	419/366	Multi-PI second trimester (97) Multi-PI third trimester (146)	YES Multi-PI second trimester: 2.24 (1.22–4.12) Multi-PI third trimester: 2.81 (1.46–5.39)	• Multivariate association also with hepatitis C
United States 1989–2004[6]	8,793/6,228	Mono (2,621) Dual (1,044) Multi-no PI (1,781) Multi-PI (782)	YES (compared with dual) Multi-PI associated with PTD 1.21 (1.04–1.40)	• Lack of antepartum ARV also associated with PTD • PTD and low birth weight decreased over time
United Kingdom, Ireland 1990–2005[5]	5,009/4,445	Mono/dual (1,061) Multi-NNRTI or Multi-PI (3,384)	YES (compared with mono/dual) Multi: 1.51 (1.19–1.93)	• Similar increased risk with PI or no-PI multi • No association with duration of use
Germany, Austria 1995–2001[8]	183/183	Mono (77) Dual (31) Multi-PI (21) Multi-NNRTI (54)	YES (compared with mono) Multi-PI: 3.40 (1.13–10.2)	
United States 2002–2007[16]	777/777	Mono (6) Dual (11) Multi, no PI (202) Multi-PI (558)	NO (compared PI with all non-PI) Multi-PI: 1.22 (0.70–2.12)	• All started ARV during pregnancy • Analyzed only spontaneous PTD

Table 7. Results of Studies Assessing Association Between Antiretroviral Regimens and Preterm Delivery (page 3 of 3)

Study Location(s)/ Dates of Study/ Reference	Total Number of Pregnancies/ Total on ARV Drugs	Types of ARV Regimens Compared (Numbers)	Association Noted Between PI-Containing or Other Multi-ARV Regimens and PTD	Special Notes
Swiss Mother and Child HIV Cohort Study 1985–2007[13]	1,180/941	Mono (94) Dual (53) Multi (PI or no PI) (409) Multi-PI (385)	YES (compared with no ARV) Multi: 2.5 (1.4–4.3)	• No association mono/dual with PTD compared with no ARV • No confounding by duration of ARV or maternal risk factors
Botswana 2006–2008[19]	530/530	Lopinavir/ritonavir +zidovudine +lamivudine (267) Abacavir +zidovudine +lamivudine (263)	YES Multi-PI versus multi-NRTI: 2.03 (1.26–3.27)	• Secondary analysis of data from randomized, controlled clinical trial of ARV begun 26–34 weeks for MTCT prevention • All CD4-cell counts >200 cells/mm^3
Botswana 2007–2010[20]	4,347/3,659	ARV, regimen unspecified (70) Mono (2,473) Multi, 91% NNRTI (1,116)	NO No association between multi-ART and very PTD (<32 weeks gestation)	• Observational multi-ART before conception associated with very small for gestational age and maternal hypertension during pregnancy
Spain 2000–2008[10]	803/739	Mono/dual (32) Multi-no PI (281) Multi-PI (426)	NO No association between ARV and PTD	• Greatest PTD risk if no antepartum ARV received
Spain 1986–2010[17]	519/371	Mono/dual NRTI (73) All multi (298) Multi-PI (178)	NO (compared with no ARV + mono/dual) • Spontaneous PTD not associated with multi-ARV or multi-PI before or during pregnancy	• Iatrogenic PTD associated with multi-ARV given in second half of pregnancy and prior PTD

Key to Abbreviations: ARV = antiretroviral, BMI = body mass index, dual = two ARV drugs, mono = single ARV drug, MTCT = mother-to-child transmission, multi = three or more ARV drugs, multi-PI = combination ARV with PI, NNRTI = non-nucleoside analogue reverse transcriptase inhibitor, NRTI = nucleoside analogue reverse transcriptase inhibitor, PI = protease inhibitor, PTD = preterm delivery

Table 8. Clinical Scenarios and Recommendations Regarding Mode of Delivery to Reduce Perinatal Transmission of HIV (page 1 of 2)

Clinical Scenario	Recommendations
HIV-infected women presenting late in pregnancy (after about 36 weeks' gestation), known to be HIV infected but not receiving ARV medications, and who have HIV RNA level and CD4 T-lymphocyte (CD4-cell) counts pending but unlikely to be available before delivery.	• Start antiretroviral (ARV) medications as per Table 6. • Provide counseling on the likelihood that scheduled cesarean delivery will reduce the risk of mother-to-child transmission, if viral suppression cannot be documented before 38 weeks. Include information on increased maternal risks of cesarean delivery, including risks related to anesthesia and surgery and increased rates of postoperative infection. • When the delivery method selected is scheduled cesarean, perform the procedure at 38 weeks' gestation, as determined by best obstetrical dating. • Administer a 1-hour intraveneous (IV) loading dose followed by continuous IV zidovudine for 2 hours (3 hours total) before scheduled cesarean. • Continue other ARV medications on schedule, as much as possible, before and after surgery. • All standard cesarean delivery management should be recommended, including use of prophylactic antibiotics.

Table 8. Clinical Scenarios and Recommendations Regarding Mode of Delivery to Reduce Perinatal Transmission of HIV (page 2 of 2)

Clinical Scenario	Recommendations
HIV-infected women who began prenatal care early in the third trimester, are receiving combination ARV drug regimens, and have an initial virologic response but have HIV RNA levels that remain substantially >1,000 copies/mL at 36 weeks' gestation.	• Continue the current combination ARV regimen if response in HIV RNA level is appropriate. • Consult an expert in HIV infection to determine the appropriateness of additional ARV agents to rapidly further decrease viral load. • Recommend scheduled cesarean delivery if viral load suppression is not achieved by 38 weeks because of the potential additional benefit in preventing intrapartum HIV transmission. Inform woman about the increased maternal risks associated with cesarean delivery, including risks related to anesthesia and surgery and increased rates of postoperative infection. • When the delivery method selected is scheduled cesarean, perform the procedure at 38 weeks' gestation by best obstetrical dating. • When the delivery method selected is scheduled cesarean delivery, administer a 1-hour loading dose and continuous IV zidovudine for 2 hours (3 hours total) before scheduled cesarean. • Continue other ARV medications on schedule, as much as possible, before and after surgery. • All standard cesarean delivery management should be recommended, including the use of prophylactic antibiotics.
HIV-infected women on combination ARV drug regimens with undetectable HIV RNA levels at 36 weeks' gestation.	• Provide counseling on risk of perinatal transmission of HIV with a persistently undetectable HIV RNA level, which is 1% or less, even with vaginal delivery. No evidence currently exists to show that this risk can be lowered further by performing scheduled cesarean delivery. • Risk of complications is increased with cesarean delivery compared with vaginal delivery, and the risks must be balanced against the uncertain benefits of cesarean delivery in women with undetectable viral load.
HIV-infected women with HIV RNA level >1,000 copies/mL who have elected scheduled cesarean delivery but present after rupture of membranes or onset of labor at >37 weeks' gestation.	• Start IV zidovudine immediately. • Individualize the decision regarding mode of delivery based on clinical factors at presentation including duration of rupture and/or labor, plasma RNA level, and current ARV regimen. Management of vaginal delivery, if chosen, should be individualized. Some clinicians may consider administration of oxytocin, if clinically appropriate, in order to expedite delivery. Scalp electrodes and other invasive monitoring and operative delivery should be avoided, if possible, unless there are clear obstetric indications. • When cesarean delivery is chosen, administration of the loading dose of IV zidovudine ideally should be completed before the procedure.

Table 9. Recommended Neonatal Dosing for Prevention of Mother-to-Child Transmission of HIV

All HIV-Exposed Infants (initiated as soon after delivery as possible)		
Zidovudine (ZDV)	**Dosing**	**Duration**
ZDV	**≥35 weeks' gestation at birth:** 4 mg/kg/dose PO twice daily, started as soon after birth as possible and preferably within 6–12 hours of delivery (or, if unable to tolerate oral agents, 3 mg/kg/dose IV, beginning within 6–12 hours of delivery, then every 12 hours)	Birth through 6 weeks
ZDV	**≥30 to <35 weeks' gestation at birth:** 2 mg/kg/dose PO (or 1.5 mg/kg/dose IV), started as soon after birth as possible, preferably within 6–12 hours of delivery, then every 12 hours, advanced to 3 mg/kg/dose PO (or 2.3 mg/kg/dose IV) every 12 hours at age 15 days	Birth through 6 weeks
ZDV	**<30 weeks' gestation at birth:** 2 mg/kg body weight/dose PO (or 1.5 mg/kg/dose IV) started as soon after birth as possible, preferably within 6–12 hours of delivery, then every 12 hours, advanced to 3 mg/kg/dose PO (or 2.3 mg/kg/dose IV) every 12 hours after age 4 weeks	Birth through 6 weeks
Additional Antiretroviral Prophylaxis Agents for HIV-Exposed Infants of Women who Received No Antepartum Antiretroviral Prophylaxis (initiated as soon after delivery as possible)		
In addition to ZDV as shown above, administer **Nevirapine (NVP)**	**Weight Band Dosing** **Birth weight 1.5-2 kg: 8 mg TOTAL for each dose** **Birth weight >2 kg: 12 mg TOTAL for each dose**	3 doses in the first week of life • 1st dose within 48 hours of birth (birth–48 hours) • 2nd dose 48 hours after 1st • 3rd dose 96 hours after 2nd

Key to Abbreviations: IV = intravenously; NVP = nevirapine; PO = orally; ZDV = zidovudine