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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Guidelines Development Process

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 perinatal transmission of HIV and management of HIV-exposed infants 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 (e.g., training in obstetrics/gynecology, infectious diseases, or women's health) and interventions for prevention of perinatal transmission (e.g., specialized training in pediatric HIV infection) as well as community representatives with knowledge of HIV infection in pregnant women and interventions for prevention of perinatal transmission. The U.S. government representatives, appointed by their agencies, include at least one representative from each of the following Department of Health and Human Services agencies: the Centers for Disease Control and Prevention (CDC), 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 re-appointment. The Panel may also include liaison members from the Perinatal HIV Hotline, the American Academy of Pediatrics' Committee on Pediatric AIDS, and the American College of Obstetricians and Gynecologists. A list of all Panel members can be found on page ix of the guidelines.
Financial Disclosures	All members of the Panel submit a written financial disclosure annually reporting any association with manufacturers of antiretroviral 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 Office of AIDS Research Advisory Council (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 a representative from 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 all proposals during monthly teleconferences. Proposals are modified based on Panel discussion and then distributed, with ballots, to all Panel members for concurrence and additional comments. If there are substantive comments or votes against approval, the recommended changes and areas of disagreement are brought back to the full Panel (via email or teleconference) for additional review, discussion and further modification to reach a final version acceptable to all Panel members. The recommendations in these final versions represent endorsement from a consensus of members and are included in the guidelines as official Panel recommendations.
Other Guidelines	These guidelines focus on HIV-infected pregnant women and their infants. Other guidelines (all available on the AIDS*info* website http://www.aidsinfo.nih.gov) outline the use of ARV agents in non-pregnant HIV-infected adults and adolescents; use of ARV agents in HIV-infected infants and children; treatment and prevention of opportunistic infections (OIs) in HIV-infected adults and adolescents, including pregnant women; treatment and prevention of OIs in HIV-infected and HIV-exposed children; and treatment of people who experience occupational or non-occupational exposure to HIV). 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.

Guidelines Development Process

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

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, and/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 on 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.

Key to Acronyms: ARV = antiretroviral; FDA = Food and Drug Administration; HRSA = Health Resources and Services Administration; NIH = National Institutes of Health; OARAC = Office of AIDS Research Advisory Council

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

Note: All recommendations in the following table are based on consensus expert opinion. More details can be found in the CDC's U.S. Medical Eligibility Criteria for Contraceptive Use, 2016.

Table 3. Drug Interactions Between Antiretroviral Agents and Hormonal Contraceptives (page 1 of 8)

ARV Drug	Effect on Contraceptive Drug Levels and Contraceptive's Effects on ART and HIV	Clinical Studies	Dosing Recommendation/ Clinical Comment for COC/P/R	Dosing Recommendation/ Clinical Comment POPs	Dosing Recommendation/ Clinical Comment for DMPA[a]	Dosing Recommendation/ Clinical Comment for Etonogestrel Implants	Justification/Evidence for Recommendation
NNRTIs							
EFV	COC: • No effect on EE concentrations • ↓ active metabolites of norgestimate LN AUC ↓ 83%; norelgestromin AUC ↓ 64%[30] • Etonogestrel (in COC) C24 ↓ 61%[36] DMPA: • No effect on DMPA levels[27,29] Etonogestrel Implant: • Etonogestrel AUC ↓ 63%[45] LN Implant: • LN AUC ↓ 47%[41] • LN (emergency contraception) AUC ↓ 58%[24] Changes in ARV Levels and/or Effects on HIV: *COC:* • No effect on EFV concentrations[30] • EFV C12 ↓ 22%; was under therapeutic threshold in 3/16 subjects[36] *DMPA:* • No effect on HIV disease progression[27,46,47] • No effect on EFV concentrations[27] *LN Implant:* • No effect on HIV disease progression[41]	COC: • Pregnancy rates no difference[48] • Pregnancy rate higher (13%) in women using COCs and EFV than COCs alone[43,49] • Progesterone >3 (a surrogate for ovulation) in 3/16[50] • No ovulations[30] DMPA: • No increase in pregnancy[27,43,47,48] • Low progesterone[27,29,47] Etonogestrel Implant: • Pregnancy rate higher with EFV compared with no ART, but still lower than other hormonal methods[43] • Presumptive ovulation in 5%[45] LN Implant: • 12% pregnancy rate[37] • 15% pregnancy rate[41] • Pregnancy rate higher with EFV compared with no ART, but still lower than other hormonal methods[43] • No increase in pregnancy rate[48]	Consider an alternative method or a reliable method of barrier contraception in addition to this method.	Consider an alternative method (or a reliable method of barrier contraception) in addition to this method.	No additional contraceptive protection is needed.	Consider an alternative method (or a reliable method of barrier contraception) in addition to this method.	For COCs, some studies suggest higher pregnancy rate and ovulation and decreased progestin levels. EFV may decrease, but clinical significance unclear. For DMPA, evidence does not show effects on pregnancy rate, ovulation, or DMPA levels. Also no effect on HIV disease progression or EFV levels. For implants, some studies suggest higher pregnancy rate and decreased hormone levels.

Table 3. Drug Interactions Between Antiretroviral Agents and Hormonal Contraceptives (page 2 of 8)

ARV Drug	Effect on Contraceptive Drug Levels and Contraceptive's Effects on ART and HIV	Clinical Studies	Dosing Recommendation/ Clinical Comment for COC/P/R	Dosing Recommendation/ Clinical Comment POPs	Dosing Recommendation/ Clinical Comment for DMPA[a]	Dosing Recommendation/ Clinical Comment for Etonogestrel Implants	Justification/Evidence for Recommendation
ETR	EE AUC ↑ 22%[51] NE: • No significant effect[51]	COC: • No ovulations[51]	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	For COCs, one study found no ovulations and no significant change in progestin levels. No evidence on POCs.
NVP	EE AUC ↓ 29%;[52] EE AUC no change[53] NE AUC ↓ 18%[52] Etonogestrel (in COC) AUC decreased 22%[36] DMPA: • No significant change[27] LN Implant: • LN AUC ↑ 35%[41] Changes in ARV Levels and/or Effects on HIV *COC:* • NVP no significant effect[50,52,54] *DMPA:* • No effect on HIV disease progression[27,46,47,55] *LN Implant:* • No effect on HIV disease progression[41,56]	COC: • No increase in pregnancy rate[43,48,49,57,58] • No ovulations[50,53,58] DMPA: • No increase in pregnancy rate[43,47,48,57] • No ovulations[27] Etonogestrel Implant: • No increase in pregnancy rate[43] LN Implant: • No increase in pregnancy rate[37,41,43,48,56]	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	No additional contraceptive protection is needed	For COCs, evidence does not show effects on pregnancy rate or ovulations and demonstrated small decrease in progestin levels. Also no effect on NVP levels. For DMPA, evidence does not show effects on pregnancy rate, ovulation, or DMPA levels. Also no effect on HIV disease progression. For implants, evidence does not show effects on pregnancy rate or HIV disease progression.

Table 3. Drug Interactions Between Antiretroviral Agents and Hormonal Contraceptives (page 3 of 8)

ARV Drug	Effect on Contraceptive Drug Levels and Contraceptive's Effects on ART and HIV	Clinical Studies	Dosing Recommendation/ Clinical Comment for COC/P/R	Dosing Recommendation/ Clinical Comment POPs	Dosing Recommendation/ Clinical Comment for DMPA[a]	Dosing Recommendation/ Clinical Comment for Etonogestrel Implants	Justification/Evidence for Recommendation
RPV	EE AUC ↑ 14%[35] NE: • No significant change[35] Changes in ARV Levels and/or Effects on HIV *COC:* • No change in RPV levels compared to historical controls[35]	COC: • No change in progesterone[35]	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	For COCs, evidence does not show effects on ovulation or progestin levels. Also no change in RPV levels. No evidence on POCs.
RTV-Boosted PIs							
ATV/r	EE AUC ↓ 16%[59] Norgestimate AUC ↑ 85%[59] POP: • NE AUC ↑ 50%[60]		Can consider an alternative method (or a reliable method of barrier contraception) in addition to this method.	Can consider an alternative method (or a reliable method of barrier contraception) in addition to this method.	No additional contraceptive protection is needed.	Can consider an alternative method (or a reliable method of barrier contraception) in addition to this method.	For COCs, increase in progestin levels but only one study. For POPs, increase in progestin levels but only 1 study. RTV inhibits CYP3A4 which may increase contraceptive hormone levels. However, some PI/r cause decreases in progestin levels, so there are theoretical concerns about contraceptive effectiveness.
DRV/r	EE AUC ↓ 44%[61] NE AUC ↓ 14%[61]		Can consider an alternative method (or a reliable method of barrier contraception) in addition to this method.	Can consider an alternative method (or a reliable method of barrier contraception) in addition to this method.	No additional contraceptive protection is needed.	Can consider an alternative method (or a reliable method of barrier contraception) in addition to this method.	For COCs, small decrease in progestin levels. No evidence on POCs.

Table 3. Drug Interactions Between Antiretroviral Agents and Hormonal Contraceptives (page 4 of 8)

ARV Drug	Effect on Contraceptive Drug Levels and Contraceptive's Effects on ART and HIV	Clinical Studies	Dosing Recommendation/ Clinical Comment for COC/P/R	Dosing Recommendation/ Clinical Comment POPs	Dosing Recommendation/ Clinical Comment for DMPA[a]	Dosing Recommendation/ Clinical Comment for Etonogestrel Implants	Justification/Evidence for Recommendation
FPV/r	EE AUC ↓ 37%[62] NE AUC ↓ 34%[62] FPV/r level: no change[62]		Can consider an alternative method (or a reliable method of barrier contraception) in addition to this method.	Can consider an alternative method (or a reliable method of barrier contraception) in addition to this method.	No additional contraceptive protection is needed.	Can consider an alternative method (or a reliable method of barrier contraception) in addition to this method.	For COCs, decrease in progestin levels. No evidence on POCs.
LPV/r	EE AUC ↓ 55%%[26] NE AUC ↓ 17% Patch: • EE AUC ↓ 45%[26] • Norelgestromin AUC ↑ 83%[26] DMPA: • DMPA AUC ↑ 46%[39] Etonogestrel Implant: • Etonogestrel AUC ↑ 52%[45] Changes in ARV Levels and/or Effects on HIV Patch: • LPV/r level ↓ 19%[26] DMPA: • No effect on HIV disease progression[39] • LPV/r no change[39]	COC: • Increase pregnancy rate, but CIs overlap[43] Patch: • No ovulations[26] DMPA: • No pregnancies, no ovulations[39] • Increased pregnancy rate, but CIs overlap[43] Etonogestrel Implant: • No increase in pregnancy rate[43] LN Implant: • No increase in pregnancy rate[37,43]	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	For COCs, nonsignificant increase in pregnancy rate. Small decrease in progestin level. For patch, no ovulations and progestin levels increase. For DMPA, evidence shows no effect on pregnancy rate or ovulations and progestin levels increased. For implants, evidence shows no effect on pregnancy rate and progestin levels increased.

Table 3. Drug Interactions Between Antiretroviral Agents and Hormonal Contraceptives (page 5 of 8)

ARV Drug	Effect on Contraceptive Drug Levels and Contraceptive's Effects on ART and HIV	Clinical Studies	Dosing Recommendation/ Clinical Comment for COC/P/R	Dosing Recommendation/ Clinical Comment POPs	Dosing Recommendation/ Clinical Comment for DMPA[a]	Dosing Recommendation/ Clinical Comment for Etonogestrel Implants	Justification/Evidence for Recommendation
SQV/r	↓ EE[63] Changes in ARV Levels and/or Effects on HIV: COC: • SQV/r no change[64]		Can consider an alternative method (or a reliable method of barrier contraception) in addition to this method.	Can consider an alternative method (or a reliable method of barrier contraception) in addition to this method.	No additional contraceptive protection is needed.	Can consider an alternative method (or a reliable method of barrier contraception) in addition to this method.	No information on progestin levels for CHCs or POCs. RTV inhibits CYP3A4 which may increase contraceptive hormone levels. However, some PI/r cause decreases in progestin levels, so there are theoretical concerns about contraceptive effectiveness.
TPV/r	Ethinyl estradiol AUC ↓ 48%[65] Norethindrone: • No significant change[65] Changes in ARV Levels and/or Effects on HIV • TPV no change[65]		Can consider an alternative method (or a reliable method of barrier contraception) in addition to this method.	Can consider an alternative method (or a reliable method of barrier contraception) in addition to this method.	No additional contraceptive protection is needed.	Can consider an alternative method (or a reliable method of barrier contraception) in addition to this method.	For COCs, no significant change in progestin levels but only from product label. No evidence on POCs. RTV inhibits CYP3A4 which may increase contraceptive hormone levels. However, some PI/r cause decreases in progestin levels, so there are theoretical concerns about contraceptive effectiveness.

Table 3. Drug Interactions Between Antiretroviral Agents and Hormonal Contraceptives (page 6 of 8)

ARV Drug	Effect on Contraceptive Drug Levels and Contraceptive's Effects on ART and HIV	Clinical Studies	Dosing Recommendation/ Clinical Comment for COC/P/R	Dosing Recommendation/ Clinical Comment POPs	Dosing Recommendation/ Clinical Comment for DMPA[a]	Dosing Recommendation/ Clinical Comment for Etonogestrel Implants	Justification/Evidence for Recommendation
PIs without RTV							
ATV	COC: EE AUC ↑ 48%[66] NE AUC ↑ 110%[66]		Can consider an alternative method based on safety concerns (i.e., increased estrogen).	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	For COCs, increased concentrations of estrogen and progestin, but only data available are from the product label. No evidence on POCs.
ATV/ COBI	Progestin and estrogen effects unknown[67] COBI may increase steroid hormone (E/P) as COBI is a strong 3A4 inhibitor (inhibition could lead to ↑ concentrations of E and possibly P)		Can consider an alternative method based on safety concerns.	Can consider an alternative method based on safety concerns.	Can consider an alternative method based on safety concerns.	Can consider an alternative method based on safety concerns.	No evidence on POCs or COCs.
DRV/ COBI	Progestin and estrogen effects unknown[68] COBI may increase steroid hormone (E/P) as COBI is a strong 3A4 inhibitor (inhibition could lead to ↑ concentrations of E and possibly P)		Can consider an alternative method based on safety concerns.	Can consider an alternative method based on safety concerns.	Can consider an alternative method based on safety concerns.	Can consider an alternative method based on safety concerns.	No evidence on POCs or COCs.
FPV	COC: *APV:* • EE AUC no change, C_{min} ↑ 32% • NE AUC ↑ 18%, C_{min} ↑ 45%[62] FPV with EE/Norethindrone: • ↓ APV (AUC 22%, C_{min} 20%)[62]		Use alternative contraceptive method.	Can consider an alternative method (or a reliable method of barrier contraception) in addition to this method.	Can consider an alternative method (or a reliable method of barrier contraception) in addition to this method.	Can consider an alternative method (or a reliable method of barrier contraception) in addition to this method.	Use of fosamprenavir alone with ethinyl estradiol/ norethindrone may lead to loss of virologic response. No evidence on POCs.

Table 3. Drug Interactions Between Antiretroviral Agents and Hormonal Contraceptives (page 7 of 8)

ARV Drug	Effect on Contraceptive Drug Levels and Contraceptive's Effects on ART and HIV	Clinical Studies	Dosing Recommendation/ Clinical Comment for COC/P/R	Dosing Recommendation/ Clinical Comment POPs	Dosing Recommendation/ Clinical Comment for DMPA[a]	Dosing Recommendation/ Clinical Comment for Etonogestrel Implants	Justification/Evidence for Recommendation
IDV	COC: • EE AUC ↑ 22% • NE AUC ↑ 26%[69]	COCs: • No pregnancies among women taking IDV and COCs[49]	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	For COCs, small increases in EE and progestin, and one clinical study did not suggest any efficacy concerns. No evidence on POCs.
NFV	COC: • EE AUC ↓ 47%; NE AUC ↓ 18%[70] DMPA: No change[27] NFV: AUC ↓ 18%	COCs: • One small study suggested that women using COCs and NFV may have had higher pregnancy rates than those using COCs alone[49] DMPA: • No pregnancies, no ovulations[27,47] • CD4 count/HIV RNA: no change[27,47]	Can consider an alternative method (or a reliable method of barrier contraception) in addition to this method.	Can consider an alternative method (or a reliable method of barrier contraception) in addition to this method.	No additional contraceptive protection is needed.	Can consider an alternative method (or a reliable method of barrier contraception) in addition to this method.	For COCs, small decrease in progestin and decrease in estrogen; one small clinical study suggests possible higher pregnancy rate with COC and NVP use. DMPA, PK, and clinical data demonstrate no change. However, NFV AUC slightly decreased. No evidence on POPs or implants.
CCR5 Antagonist							
MVC	COC: • No significant effect on EE or LN[71]		No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	For COCs, no change in EE or progestin. No clinical data. No evidence on POCs.

Table 3. Drug Interactions Between Antiretroviral Agents and Hormonal Contraceptives (page 8 of 8)

ARV Drug	Effect on Contraceptive Drug Levels and Contraceptive's Effects on ART and HIV	Clinical Studies	Dosing Recommendation/ Clinical Comment for COC/P/R	Dosing Recommendation/ Clinical Comment POPs	Dosing Recommendation/ Clinical Comment for DMPA[a]	Dosing Recommendation/ Clinical Comment for Etonogestrel Implants	Justification/Evidence for Recommendation
Integrase Inhibitors							
RAL	COC: • EE no change • Norgestimate AUC ↑ 14%[72]		No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	For COCs, no change in EE and small increase in progestin. No clinical data. No evidence on POCs.
DTG	COC: • No significant effect on norgestimate or EE • DTG AUC no change[40]		No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	COCs, no change in EE or progestin. No clinical data No evidence on POCs.
EVG/ COBI	EVG/COBI/FTC/TDF *COC:* • Norgestimate AUC ↑ 126% EE AUC ↓ 25%		No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	When administered as the 4-drug regimen EVG/COBI/FTC/TDF, increases in P and small decrease in E was observed. No clinical data. No evidence on POCs.

[a] Because the hormonal levels achieved with DMPA are substantially higher than are required for contraception, any small reduction in hormonal level due to ARVs is unlikely to reduce contraceptive effectiveness.

Key to Acronyms: ART = antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; ATV/r = atazanavir/ritonavir; AUC = area under the curve; CHC = combination hormonal contraceptives; C_{min} = minimum plasma concentration; COBI = cobicistat; DMPA = depot medroxyprogesterone acetate; COC/P/R =combined oral contraceptives/patch/ring; DRV/r = darunavir/ritonavir; DTG = dolutegravir; e = estrogen; EE = ethinyl estradiol; EFV = efavirenz; ETR = etravirine; EVG = elvitegravir; FPV = fosamprenavir; FPV/r = fosamprenavir/ritonavir; FTC = IDV = indinavir; LN =levonorgestrel; LPV/r = lopinavir/ritonavir; MVC = maraviroc; NFV = nelfinavir; NVP = nevirapine; P = progestin; PI = protease inhibitor; PI/r = ritonavir boosted-protease inhibitor; POP = progesterone-only oral contraceptive pills; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SQV/r = saquinavir/ritonavir; TPV/r = tipranavir/ritonavir

Source: 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. Tables 15a, 15b, and 15d. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf. Accessed July 27, 2016.

Table 4. Clinical Trials of Pre-Exposure Prophylaxis

Trial.	Study Population	Location	Intervention	Outcome	Comments
TDF2	1,219 sexually active adults; 55% male, 45% female; 94% unmarried; approximately 90% aged 21–29	Botswana	Daily oral TDF/FTC	63% protection	>30% did not complete study; cannot draw definitive conclusions for women and men separately.
PIP	4,758 heterosexual serodiscordant couples; 38% HIV-negative female, 68% HIV-negative male partner; 98% married; median age 33	Botswana, Kenya, Rwanda, South Africa, Tanzania, Uganda, Zambia	Daily oral TDF or TDF/FTC	67% protection with TDF alone; 75% protection with TDF/FTC	Discordant couples may be a distinct, unique population.
FEM-PrEP	1,951 heterosexual women aged 18–35 at high risk of infection	Kenya, South Africa, Tanzania	Daily oral TDF/FTC	Trial discontinued for futility in April 2011.	Adherence assessment with monthly clinical samples to measure drug concentration is pending.
VOICE MTN-003	5,029 heterosexual women aged 18–45 in high-prevalence areas	Uganda, South Africa, Zimbabwe	Daily oral TDF or daily oral TDF/FTC or daily topical TFV gel	No study drug significantly reduced the risk of HIV acquisition. Estimates of effectiveness were less than 0 for TDF and TDF/FTC daily oral dosing (negative 48.8% and negative 4.2% TDF/FTC respectively), and reduced risk of HIV infection of 14.7% for TDF gel.	Adherence to study drugs was low; TFV was detected in 30% of the oral TDF arm, 29% in the oral TDF/FTC arm, and 25% in the TDF gel arm.

Key to Acronyms: TDF = tenofovir disoproxil fumarate; TFV = tenofovir; FTC = emtricitabine

Source: Adapted from: Kashuba et al., Pre-exposure prophylaxis for HIV prevention: how to predict success: Table Antiretroviral-based HIV prevention studies. *Lancet.* 2012;379(9835): 2409-2411.

Table 5. Results of Studies Assessing the Association Between Antiretroviral Regimens and Preterm Delivery (page 1 of 4)

Study Location(s); Dates of Study	Total Number of Pregnancies/ Total on ARV Drugs	Types of ARV Regimens Compared (Numbers)	Association Noted Between ARV Regimens and PTD	Notes
European Collaborative Study and Swiss Mother and Child HIV Cohort Study; 1986–2000[1]	3,920/896	• Mono (573) • Multi, no PI (215) • Multi-PI (108)	• YES (compared with no ARV) • Multi: 1.82 (1.13–2.92) • Multi-PI: 2.60 (1.43–4.7)	• Increase in PTD if ARV begun before pregnancy versus in third trimester
United States; 1990–1998[21]	3,266/2,123	• Mono (1,590) • Multi (396) • Multi-PI (137)	• NO (compared with mono) • Multi: 0.95 (0.60–1.48) • Multi-PI: 1.45 (0.81–2.50)	• 7 prospective clinical studies
European Collaborative Study; 1986–2004[32]	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 pre-pregnancy: 2.05 (1.43–2.95)	N/A
United States; 1990–2002[27]	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[3]	1,337/999	• Mono (492) • Multi (373) • Multi-PI (134)	• YES (compared with other multi) • Multi-PI: 1.8 (1.1–3.03)	• Multi-PI reserved for advanced disease, those who failed other multi-ARV regimens.
Brazil, Argentina, Mexico, Bahamas; 2002–2005[25]	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
Meta-Analysis, Europe and United States; 1986–2004[4]	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[5]	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

Table 5. Results of Studies Assessing the Association Between Antiretroviral Regimens and Preterm Delivery (page 2 of 4)

Study Location(s); Dates of Study	Total Number of Pregnancies/ Total on ARV Drugs	Types of ARV Regimens Compared (Numbers)	Association Noted Between ARV Regimens and PTD	Notes
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 LBW decreased over time.
United Kingdom, Ireland; 1990–2005[7]	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)	N/A
United States; 2002–2007[19]	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
Swiss Mother and Child HIV Cohort Study; 1985–2007[9]	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 of mono/dual with PTD compared with no ARV • No confounding by duration of ARV or maternal risk factors
Botswana; 2006–2008[10]	530/530	• LPV/r plus ZDV plus 3TC (267) • ABC plus ZDV plus 3TC (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 at 26–34 weeks for prevention of perinatal transmission • All CD4 cell counts >200 cells/mm^3
Botswana; 2007–2010[30]	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; 1986–2010[20]	519/371	• Mono/dual NRTI (73) • All multi (298) • Multi-PI (178)	• NO (compared with no ARV plus mono/dual) • Spontaneous PTD not associated with multi-ARV or multi-PI before or during pregnancy	• PTD associated with multi-ARV given in second half of pregnancy and with prior PTD
Botswana; 2009–2011[11]	9,504/7,915	• Mono (4,625) • All multi (3,290) • Multi-PI (312)	• YES (multi-ARV before and during pregnancy compared to mono) 1.2 (1.1–1.4) and 1.4 (1.2–1.8) • YES (multi-PI compared to multi-no PI before pregnancy 2.0 (1.1–3.6)	• ART group classified by initiation before and during pregnancy

Table 5. Results of Studies Assessing the Association Between Antiretroviral Regimens and Preterm Delivery (page 3 of 4)

Study Location(s); Dates of Study	Total Number of Pregnancies/ Total on ARV Drugs	Types of ARV Regimens Compared (Numbers)	Association Noted Between ARV Regimens and PTD	Notes
France; ANRS French Perinatal Cohort 1990–2009[12]	8,696/8,491	• Mono (950) • Dual (590) • Multi-PI (2,414)	• YES (multi-ARV compared to mono) 1.69 (1.38–2.07) • YES (before conception compared to during pregnancy) 1.31 (1.11–1.55)	• Patients on ART before and during pregnancy had increased rates of PTD
United States; 2000–2011[29]	183/183	• Multi-PI (183)	• NO (no control group without ART) • Rate of PTD 18.6%	• SGA rate 31.2% • NNRTI-based ART less likely to have SGA 0.28 (0.1–0.75)
United States; 2007–2010[13]	1,869/1,810	• Mono/dual (138) • Multi-NRTI (193) • Multi-NNRTI (160) • Multi-PI (1,319)	• YES (compared with no ARV in first trimester) • Multi-PI in first trimester vs. none in first trimester • PTD 1.55 (1.16–2.07); spontaneous PTD 1.59 (1.10–2.30)	N/A
Latin America; 2002–2012[14]	1,512/1,446	• Multi-PI (907) • Multi-non-PI (409) • Mono/dual (130) • No ART or ART <28 days (66)	• YES (when on ARVs at conception), PTD 1.53 (1.11–2.09)	• ART for treatment rather than prophylaxis associated with increased rates of LBW (<2,500 gm) infants, LBW 1.8 (1.26–2.56) • Multi-non-PI associated with decreased risk of LBW 0.33 (0.14–0.74) and stillbirth 0.11 (0.04–0.34) • Multi-PI associated with decreased risk of stillbirth 0.14 (0.05–0.34)
Uganda; 2009–2012[33]	356/356	• Multi-PI (LPV/r) (179) • Multi-non-PI (EFV) (177)	• NO (no control group without ART)	• Trend in increased PTD among women starting ART 24–28 week GA was NS, aOR 1.76 (0.96–3.23)
Italy; 1997–2013[34]	158/158	• Mono/dual (27) • Multi-PI (114) • Multi-non-PI (17)	• NO (no control group without ART)	• PTD rate was 17% for this cohort, trend towards association with longer duration of ART 2.82 (0.35–8.09)
Canada; 1988–2011[15]	589/530	• Multi-non-boosted PI (220) • Multi-boosted PI with ritonavir (144) • Multi-non-PI (166) • Mono (77) • No ART (59)	• YES (compared to multi-non boosted PI) 2.01 (1.02–3.97) • NO (non-PI compared to non-boosted PI) 0.81 (0.4–1.66)	• Highest risk of PTD among women not taking ART compared to non-boosted PI group, 2.7 (1.2–6.09)

Table 5. Results of Studies Assessing the Association Between Antiretroviral Regimens and Preterm Delivery (page 4 of 4)

Study Location(s); Dates of Study	Total Number of Pregnancies/ Total on ARV Drugs	Types of ARV Regimens Compared (Numbers)	Association Noted Between ARV Regimens and PTD	Notes
United Kingdom; 2007–2012[22]	493/493	• Multi-PI LPV/r • Multi-PI ATV/r	• NO (comparing two PI-based regimens) aOR 1.87 (0.93–3.75)	• Rate of PTD 13% among women who conceived on ART and 14% among women who started ART during pregnancy. • In multivariate analysis, a history of PTD was associated with recurrent PTD, aOR 5.23 (1.91–14.34)
Republic of the Congo; 2007–2012[26]	188/188	• Multi-non-PI, EFV-based (31) • Multi-non-PI, NVP-based (146)	• NO (comparing EFV 13% vs NPV 10%)	• Rate of PTD 11%, no difference between study groups • LBW increased in EFV group (33% vs 16%, *P* = 0.04). • Stillbirth rate 4% (8/188)
Tanzania; 2004–2011[16]	3,314/2,862	• Multi (1,094) • Mono (1,768) • No ART (452-excluded)	• YES (Multi before pregnancy vs Mono, 1.24 (1.05–1.47)) • VPTD, YES (Multi before pregnancy vs Mono, 1.42 (1.02–1.99) • NO (Multi during pregnancy compared to Mono, 0.85 (0.7–1.02)	• Rate of PTD 29%; women who conceived on ART more likely to have PTD compared to women on AZT monotherapy. • Pregnancy-induced hypertension associated with PTD, 1.25 (1.03–1.51)

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; BMI = body mass index; dual = two ARV drugs; LBW = low birth weight; mono = single ARV drug; multi = three or more ARV drugs; multi-PI = combination ARV with PI; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; PTD = preterm delivery; VPTD= very preterm delivery

Table 6. What to Start: Initial Combination Regimens for Antiretroviral-Naive Pregnant Women (page 1 of 2)

These recommendations are for pregnant women who have never received antiretroviral therapy (ART) previously (i.e., antiretroviral-naive) and who have no evidence of significant resistance to regimen components. See Table 8 for more information on specific drugs and dosing in pregnancy. Within each drug class and recommendation category, regimens are listed alphabetically, and the order does not indicate a ranking of preference. It is recommended that women who become pregnant while on a stable ART regimen with viral suppression remain on that same regimen, with the exception of regimens containing didanosine, stavudine, or treatment-dose ritonavir.

Drug	Comments
Preferred Initial Regimens in Pregnancy: • Drugs or drug combinations are designated as Preferred for initiating ART in ARV-naive pregnant women when clinical trial data in adults have demonstrated optimal efficacy and durability with acceptable toxicity and ease of use; pregnancy-specific PK data are available to guide dosing; and no established association with teratogenic effects (from animal and/or human studies) or clinically significant adverse outcomes for mothers, fetuses, or newborns have been reported.	
Preferred Two-NRTI Backbones	
ABC/3TC	Available as FDC. Can be administered once daily. ABC **should not be used** in patients who test positive for HLA-B*5701 because of risk of hypersensitivity reaction. ABC/3TC with ATV/r or with EFV is not recommended if pretreatment HIV RNA is >100,000 copies/mL.
TDF/FTC or TDF/3TC	TDF/FTC available as FDC. Either TDF/FTC (coformulated) or TDF with separate 3TC can be administered once daily. TDF has potential renal toxicity, thus TDF-based dual NRTI combinations should be used with caution in patients with renal insufficiency.
Preferred PI Regimens	
ATV/r plus a Preferred Two-NRTI Backbone	Once-daily administration. Extensive experience in pregnancy. Maternal hyperbilirubinemia; no clinically significant neonatal hyperbilirubinemia or kernicterus reported, but neonatal bilirubin monitoring recommended.
DRV/r plus a Preferred Two-NRTI Backbone	Better tolerated than LPV/r. PK data available. Increasing experience with use in pregnancy. Must be used twice daily in pregnancy.
Preferred Integrase Inhibitor Regimen	
RAL plus a Preferred Two-NRTI Backbone	PK data available and increasing experience in pregnancy. Rapid viral load reduction (potential role for women who present for initial therapy late in pregnancy). Useful when drug interactions with PI regimens are a concern. Twice-daily dosing required. If there are concerns about adherence or medication discontinuation postpartum, a PI regimen is preferred instead of an integrase inhibitor regimen, to minimize the risk of resistance.
Alternative Initial Regimens in Pregnancy: • Regimens with clinical trial data demonstrating efficacy in adults but one or more of the following apply: experience in pregnancy is limited, data are lacking or incomplete on teratogenicity, or regimen is associated with dosing, formulation, toxicity, or interaction issues.	
Alternative Two-NRTI Backbones	
ZDV/3TC	Available as FDC. NRTI combination with most experience for use in pregnancy but has disadvantages of requirement for twice-daily administration and increased potential for hematologic toxicities.
PI Regimens	
LPV/r plus a Preferred Two-NRTI Backbone	Abundant experience and established PK in pregnancy. More nausea than with preferred agents. Twice-daily administration. Dose increase recommended in third trimester (see Table 8). Once-daily LPV/r is not recommended for use in pregnant women.
NNRTI Regimen	
EFV plus a Preferred Two-NRTI Backbone	Concern because of birth defects seen in primate study; data not borne out in human studies, but cautionary text remains in package insert (see Teratogenicity and Table 8). Preferred regimen in women who require coadministration of drugs with significant interactions with PIs or the convenience of coformulated, single-tablet, once-daily regimen. Screening for antenatal and postpartum depression is recommended.
RPV/TDF/FTC (or RPV plus a Preferred Two-NRTI Backbone)	RPV not recommended with pretreatment HIV RNA >100,000 copies/mL or CD4 cell count <200 cells/mm^3. Do not use with PPIs. PK data available in pregnancy but relatively little experience with use in pregnancy. Available in coformulated single-pill, once-daily regimen.

Table 6. What to Start: Initial Combination Regimens for Antiretroviral-Naive Pregnant Women (page 2 of 2)

Drug	Comments
Insufficient Data in Pregnancy to Recommend Routine Use in Initial Regimens for ART-Naive Women: • Drugs that are approved for use in adults but lack adequate pregnancy-specific PK or safety data	
COBI	Limited data on use of COBI (including coformulations with ATV or DRV) in pregnancy.
DTG	Limited data on use of DTG in pregnancy.
EVG/COBI/TDF/FTC Fixed Drug Combination	Limited data on use of EVG/COBI component in pregnancy.
FPV	Limited data on use in pregnancy.
MVC	MVC requires tropism testing before use. Few case reports of use in pregnancy.
EVG/COBI/TAF/FTC Fixed Drug Combination	Limited data on use of EVG/COBI; no data on use of TAF in pregnancy
TAF/FTC Fixed Drug Combination	No data on use of TAF in pregnancy.
RPV/TAF/FTC Fixed Drug Combination	No data on use of TAF in pregnancy.
Not Recommended for Initial ART in Pregnancy: • Drugs whose use is not recommended as part of initial regimens in pregnancy because of toxicity, lower rate of viral suppression or because not recommended in ART-naive populations.	
Note: Drugs not recommended for initial use because of toxicity (stavudine [d4T], didanosine [ddI], treatment-dose ritonavir [RTV]) should also be stopped in women who present during pregnancy while taking these medications. Other medications listed below may be continued in women who present during pregnancy, as long as they are well tolerated and result in sustained virologic suppression.	
ABC/3TC/ZDV	Generally not recommended due to inferior virologic efficacy.
d4T*	Not recommended due to toxicity.
ddI*	Not recommended due to toxicity.
IDV/r	Nephrolithiasis, maternal hyperbilirubinemia.
NFV	Lower rate of viral suppression with NFV compared to LPV/r or EFV in adult trials.
RTV*	RTV as a single PI is not recommended because of inferior efficacy and increased toxicity.
SQV/r	Not recommended based on potential toxicity and dosing disadvantages. Baseline ECG is recommended before initiation of SQV/r because of potential PR and QT prolongation; contraindicated with preexisting cardiac conduction system disease. Limited data in pregnancy. Large pill burden. Twice-daily dosing required.
ETR	Not recommended in ART-naive populations.
NVP	Not recommended because of greater potential for adverse events, complex lead-in dosing, and low barrier to resistance. NVP should be used with caution when initiating ART in women with CD4 cell count >250 cells/mm^3. Use NVP and ABC together with caution; both can cause hypersensitivity reactions within the first few weeks after initiation.
T20	Not recommended in ART-naive populations.
TPV/r	Not recommended in ART-naive populations.

Key to Abbreviations: 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; ATV/r = atazanavir/ritonavir; CD4 = CD4 T lymphocyte cell; COBI = cobicistat; d4T = stavudine; ddI = didanosine; DRV/r = darunavir/ritonavir; DTG = dolutegravir; ECG = electrocardiogram; EFV = efavirenz; ETR = etravirine; EVG = elvitegravir; FDC = fixed-drug combination; FPV = fosamprenavir; FTC = emtricitabine; IDV/r = indinavir/ritonavir; LPV/r = lopinavir/ritonavir; MVC = maraviroc; NFV = nelfinavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; PK = pharmacokinetic; PPI = proton pump inhibitor; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SQV/r = saquinavir/ritonavir; T20 = enfuvirtide; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TPV = tipranavir; TPV/r = tipranavir/ritonavir; ZDV = zidovudine

Neonatal Antiretroviral Drug Dosing

Table 7. Neonatal Dosing for Prevention of Perinatal Transmission of HIV

<table>
<tr><th colspan="3">All HIV-Exposed Infants
Initiated as soon after delivery as possible</th></tr>
<tr><th>Regimen</th><th>Dosing</th><th>Duration</th></tr>
<tr><td rowspan="3">ZDV
Note:
Twice-daily dosing prophylaxis should be started as soon after birth as possible, preferably within 6–12 hours of delivery
For infants unable to tolerate oral agents, the IV dose is 75% of the oral dose while maintaining the same dosing interval.</td><td>≥35 Weeks' Gestation at Birth:
Birth to Age 6 Weeks:
• 4 mg/kg orally twice daily
Simplified Weight-Band Dosing for Infants ≥35 Weeks:
<table><tr><th>Weight Band (kg)</th><th>* Volume (mL) ZDV 10 mg/mL Oral Syrup Twice Daily</th></tr><tr><td>2 to <3 kg</td><td>1 mL</td></tr><tr><td>3 to <4 kg</td><td>1.5 mL</td></tr><tr><td>4 to <5 kg</td><td>2 mL</td></tr></table></td><td>Birth through 4–6 weeks[a]</td></tr>
<tr><td>≥30 to <35 Weeks' Gestation at Birth:
Birth to Age 2 Weeks:
• 2 mg/kg orally twice daily
Age 2 Weeks to 4–6 Weeks:
• 3 mg/kg orally twice daily</td><td>Birth through 6 weeks</td></tr>
<tr><td><30 weeks' Gestation at Birth:
Birth to Age 4 Weeks:
• 2 mg/kg orally twice daily
Age 4 Weeks to 6 Weeks:
• 3 mg/kg orally twice daily</td><td>Birth through 6 weeks</td></tr>
<tr><th colspan="3">Additional Antiretroviral Prophylaxis Agents for HIV-Exposed Infants Who are at High Risk of HIV Acquisition
Initiated as soon after delivery as possible</th></tr>
<tr><td colspan="3">NICHD-HPTN 040/PACTG 1043 Study Regimen</td></tr>
<tr><td rowspan="2">NVP
In addition to ZDV as shown above</td><td>Birth Weight 1.5–2 kg:
• 8 mg dose PO (Note: No calculation is required for this dose; this is the actual dose, not a mg/kg dose.)</td><td rowspan="2">Three Doses in the First Week of Life:
1. Within 48 hours of birth
2. 48 hours after first dose
3. 96 hours after second dose</td></tr>
<tr><td>Birth Weight >2 kg:
• 12 mg dose PO (Note: No calculation is required for this dose; this is the actual dose, not a mg/kg dose.)</td></tr>
<tr><th colspan="3">Three-Drug Infant Combination Antiretroviral Prophylaxis Regimen
This regimen is under investigation, but is already used in clinical practice by some experts</th></tr>
<tr><td>3TC
In addition to ZDV as shown above</td><td>≥32 Weeks' Gestation at Birth:
Birth to Age 4 Weeks:
• 2 mg/kg PO twice daily
Aged 4 Weeks to 6 Weeks:
• 4 mg/kg PO twice daily</td><td>Birth through 2–6 weeks</td></tr>
<tr><td rowspan="2">NVP
In addition to ZDV as shown above</td><td>≥37 Weeks' Gestation at Birth:
Birth to Age 6 Weeks:
• 6 mg/kg PO twice daily</td><td>Birth through 2–6 weeks[b]</td></tr>
<tr><td>34 to <37 Weeks' Gestation at Birth:
Birth to Age 1 Week:
• 4 mg/kg PO twice daily
Age 1 Week to Age 6 Weeks:
• 6 mg/kg PO twice daily</td><td>Birth through 2–6 weeks[b]</td></tr>
</table>

[a] A 4-week neonatal ZDV prophylaxis regimen may be used when the mother has received standard ART during pregnancy with sustained viral suppression and there are no concerns related to maternal adherence. All other infants should receive a 6-week course of ZDV.

[b] The optimal duration of NVP is unknown. Some experts recommend continuation of NVP for a 6-week course while others recommend discontinuation after 2 weeks of life if HIV nucleic acid amplification test is negative.

Key to Abbreviations: 3TC=lamivudine; IV = intravenously; NVP = nevirapine; PO = orally; ZDV = zidovudine

Table 8. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy[a] (page 1 of 19)

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations	Use in Pregnancy	Last Reviewed
NNRTIs 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.				
Abacavir (ABC) *Ziagen* (ABC/3TC) *Epzicom* (ABC/3TC/ZDV) *Trizivir* (ABC/DTG/3TC) *Triumeq*	ABC (Ziagen): *Tablet:* • 300 mg *Solution:* • 20 mg/mL Epzicom: • ABC 600 mg plus 3TC 300-mg tablet Trizivir: • ABC 300 mg plus 3TC 150 mg plus ZDV 300-mg tablet Triumeq: • ABC 600 mg plus DTG 50 mg plus 3TC 300-mg tablet	Standard Adult Doses: *ABC (Ziagen):* • 300 mg twice daily or 600 mg once daily, without regard to food *Epzicom:* • 1 tablet once daily without regard to food *Trizivir:* • 1 tablet twice daily without regard to food *Triumeq:* • 1 tablet daily without regard to food PK in Pregnancy: • PK not significantly altered in pregnancy. Dosing in Pregnancy: • No change in dose indicated.	High placental transfer to fetus.[b] No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects). Hypersensitivity reactions occur in approximately 5% to 8% of non-pregnant individuals; a much smaller percentage are fatal and are usually associated with re-challenge. Rate in pregnancy is unknown. Testing for HLA-B*5701 identifies patients at risk of reactions and should be done and documented as negative before starting ABC. Patients should be educated regarding symptoms of hypersensitivity reaction.	April 29, 2016
Didanosine (ddI) *Videx* *Videx EC*	ddI (Videx) *Buffered Tablets (Non-EC):* • No longer available *Solution:* • 10 mg/mL oral solution Videx EC (EC Beadlets) Capsules: • 125 mg • 200 mg • 250 mg • 400 mg Generic Delayed-Release Capsules: • 200 mg • 250 mg • 400 mg	Standard Adult Doses *Body Weight ≥60 kg:* • 400 mg once daily *With TDF:* • 250 mg once daily; take 1/2 hour before or 2 hours after a meal. *Body Weight <60kg:* • 250 mg once daily *With TDF:* • 200 mg once daily; take 1/2 hour before or 2 hours after a meal. **Note:** Preferred dosing with oral solution is twice daily (total daily dose divided into 2 doses); take 1/2 hour before or 2 hours after a meal.	Low-moderate placental transfer to fetus.[b] In the Antiretroviral Pregnancy Registry, an increased rate of birth defects with ddI compared to general population was noted after both first-trimester (20/423, 4.7%; 95% CI, 2.9% to 7.2%) and later exposure (20/461, 4.3%; 95% CI 2.7% to 6.6%). No specific pattern of defects was noted and clinical relevance is uncertain. ddI **should not be used** with d4T. Lactic acidosis, sometimes fatal, has been reported in pregnant women receiving ddI and d4T together.	April 29, 2016

Table 8. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy[a] (page 2 of 19)

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations	Use in Pregnancy	Last Reviewed
		PK in Pregnancy: • PK not significantly altered in pregnancy. Dosing in Pregnancy: • No change in dose indicated.		
Emtricitabine (FTC) *Emtriva* (FTC/TDF) *Truvada* (FTC/TDF/EFV) *Atripla* (FTC/TDF/RPV) *Complera* (FTC/TDF/EVG/COBI) *Stribild* (FTC/TAF/RPV) *Odefsey* (FTC/TAF/EVG/COBI) *Genvoya*	Emtriva (FTC) *Capsules:* • 200 mg *Oral Solution:* • 10 mg/mL Truvada: • FTC 200 mg plus TDF 300 mg tablet Atripla: • FTC 200 mg plus TDF 300 mg plus EFV[c] 600 mg tablet Complera: • FTC 200 mg plus TDF 300 mg plus RPV 25 mg tablet Stribild: • FTC 200 mg plus TDF 300 mg plus EVG 150 mg plus COBI 150 mg tablet Odefsey: • FTC 200 mg plus TAF 25 mg plus RPV 25 mg tablet Genvoya: • FTC 200 mg plus TAF 10 mg plus EVG 150 mg plus COBI 150 mg tablet	Standard Adult Dose(s) *Emtriva (FTC)* *Capsule:* • 200 mg once daily without regard to food *Oral Solution:* • 240 mg (24 mL) once daily without regard to food *Truvada:* • 1 tablet once daily without regard to food *Atripla:* • 1 tablet once daily at or before bedtime. Take on an empty stomach to reduce side effects. *Complera:* • 1 tablet once daily with food *Stribild:* • 1 tablet once daily with food *Odefsey:* • 1 tablet once daily with food *Genvoya:* • 1 tablet once daily with food PK in Pregnancy: • PK of FTC not significantly altered in pregnancy. Dosing in Pregnancy: • No change in FTC dose indicated.	High placental transfer to fetus.[b] No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects). If HBV-coinfected, it is possible that a HBV flare may occur if the drug is stopped; see HIV/Hepatitis B Virus Coinfection.	June 7, 2016

Table 8. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy[a] (page 3 of 19)

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations	Use in Pregnancy	Last Reviewed
Lamivudine (3TC) *Epivir* (3TC/ZDV) *Combivir* (3TC/ABC) *Epzicom* (3TC/ZDV/ABC) *Trizivir* (3TC/ABC/DTG) *Triumeq*	3TC (Epivir) *Tablets:* • 150 mg • 300 mg *Oral Solution:* • 10 mg/mL Combivir: • 3TC 150 mg plus ZDV 300 mg tablet Epzicom: • 3TC 300 mg plus ABC 600 mg tablet Trizivir: • 3TC 150 mg plus ZDV 300 mg plus ABC 300 mg tablet Triumeq: • 3TC 300 mg plus ABC 600 mg plus DTG 50-mg tablet	Standard Adult Dose(s) *3TC (Lamivudine):* • 150 mg twice daily or 300 mg once daily, without regard to food *Combivir:* • 1 tablet twice daily without regard to food *Epzicom:* • 1 tablet once daily without regard to food *Trizivir:* • 1 tablet twice daily without regard to food *Triumeq:* • 1 tablet once daily without regard to food PK in Pregnancy: • PK not significantly altered in pregnancy. Dosing in Pregnancy: • No change in dose indicated.	High placental transfer to fetus.[b] No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects). If HBV-coinfected, it is possible that an HBV flare may occur if the drug is stopped; see HIV/Hepatitis B Virus Coinfection.	June 7, 2016
Stavudine (d4T) *Zerit*	d4T (Zerit) *Capsules:* • 15 mg • 20 mg • 30 mg • 40 mg *Oral Solution:* • 1 mg/mL following reconstitution	Standard Adult Dose(s)[d] *Body Weight ≥60 kg:* • 40 mg twice daily without regard to meals *Body Weight <60 kg:* • 30 mg twice daily without regard to meals PK in Pregnancy: • PK not significantly altered in pregnancy. Dosing in Pregnancy: • No change in dose indicated.	High placental transfer.[b] No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects). d4T should not be used with ddI or ZDV. Lactic acidosis, sometimes fatal, has been reported in pregnant women receiving ddI and d4T together.	June 7, 2016

Table 8. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy[a] (page 4 of 19)

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations	Use in Pregnancy	Last Reviewed
Tenofovir Alafenamide (TAF) (TAF/FTC/EVG/COBI) *Genvoya* (TAF/FTC/RPV) *Odefsey* (TAF/FTC) *Descovy*	Genvoya: • TAF 10 mg plus FTC 200 mg plus EVG 150 mg plus COBI 150 mg tablet Odefsey: • TAF 25 mg plus FTC 200 mg plus RPV 25 mg tablet Descovy: • TAF 25 mg plus FTC 200 mg tablet	Standard Adult Dose *Genvoya, Odefsey:* • 1 tablet once daily with food *Descovy:* • 1 tablet once daily with or without food • Same dose (TAF 25 mg) can be used with or without pharmacoenhancers PK in Pregnancy: • No PK studies in human pregnancy Dosing in Pregnancy: • Insufficient data to make dosing recommendation	No data on placental transfer of TAF are available. Insufficient data to assess for teratogenicity in humans. No evidence of teratogenicity in rats. Renal function should be monitored because of potential for renal toxicity.	October 26, 2016
Tenofovir Disoproxil Fumarate (TDF) *Viread* (TDF/FTC) *Truvada* (TDF/FTC/EFV) *Atripla* (TDF/FTC/RPV) *Complera* (TDF/FTC/EVG/COBI) *Stribild*	TDF (Viread) *Tablet:* • 300 mg *Powder:* • 40 mg/1 g oral powder Truvada: • TDF 300 mg plus FTC 200 mg tablet Atripla: • TDF 300 mg plus FTC 200 mg plus EFV[c] 600 mg tablet Complera: • TDF 300 mg plus FTC 200 mg plus RPV 25 mg tablet Stribild: • TDF 300 mg plus FTC 200 mg plus EVG 150 mg plus COBI 150 mg tablet	Standard Adult Dose *TDF (Viread)* *Tablet:* • 300 mg once daily without regard to food *Powder:* • 8 mg/kg (up to maximum 300 mg), take with food *Truvada:* • 1 tablet once daily without regard to food *Atripla:* • 1 tablet once daily at or before bedtime. Take on an empty stomach to reduce side effects. *Complera:* • 1 tablet once daily with food *Stribild:* • 1 tablet once daily with food PK in Pregnancy: • AUC lower in third trimester than postpartum but trough levels adequate Dosing in Pregnancy: • No change in dose indicated.	High placental transfer to fetus.[b] No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects). 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. Human studies demonstrate no effect on intrauterine growth, but data are conflicting about potential effects on growth outcomes later in infancy. If HBV-coinfected, it is possible that an HBV flare may occur if TDF is stopped; see HIV/Hepatitis B Virus Coinfection. Renal function should be monitored because of potential for renal toxicity.	June 7, 2016

Table 8. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy[a] (page 5 of 19)

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations	Use in Pregnancy	Last Reviewed
Zidovudine (ZDV, AZT) *Retrovir* (ZDV/3TC) *Combivir* (ZDV/3TC/ABC) *Trizivir*	ZDV (Retrovir) *Capsule:* • 100 mg *Tablet:* • 300 mg *Oral Solution:* • 10 mg/mL *Intravenous Solution:* • 10 mg/mL Combivir: • ZDV 300 mg plus 3TC 150 mg tablet Trizivir: • ZDV 300 mg plus 3TC 150 mg plus ABC 300 mg tablet	Standard Adult Dose(s) *ZDV (Retrovir):* • 300 mg BID or 200 mg TID, without regard to food *Active Labor:* • 2 mg/kg IV loading dose, followed by 1 mg/kg/hour continuous infusion from beginning of active labor until delivery *Combivir:* • One tablet twice daily, without regard to food *Trizivir:* • One tablet twice daily, without regard to food PK in Pregnancy: • PK not significantly altered in pregnancy. Dosing in Pregnancy: • No change in dose indicated.	High placental transfer to fetus.[b] No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects).	October 26, 2016

Table 8. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy[a] (page 6 of 19)

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations	Use in Pregnancy	Last Reviewed
NNRTI 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.				
Efavirenz (EFV) *Sustiva* (EFV/TDF/FTC) *Atripla*	EFV (Sustiva) *Capsules:* • 50 mg • 200 mg *Tablet:* • 600 mg Atripla: • EFV 600 mg plus TDF 300 mg plus FTC 200 mg tablet	Standard Adult Dose *EFV (Sustiva):* • 600 mg once daily at or before bedtime, on empty stomach to reduce side effects *Atripla:* • 1 tablet once daily at or before bedtime, on empty stomach to reduce side effects PK in Pregnancy: • AUC decreased during third trimester, compared with postpartum, but nearly all third-trimester participants exceeded target exposure. Dosing in Pregnancy: • No change in dose indicated.	Moderate placental transfer to fetus.[b] Potential fetal safety concern: cynomolgus monkeys receiving EFV during the first trimester at a dose resulting in plasma levels comparable to systemic human therapeutic exposure had 3 of 20 infants with significant CNS or other malformations. In humans, there is no increase in overall birth defects with first-trimester EFV exposure. However, in humans with first-trimester exposure, there have been 6 retrospective case reports and 1 prospective case report of CNS defects and 1 prospective case report of anophthalmia with facial clefts. The relative risk with first-trimester exposure is unclear. Non-pregnant women of childbearing potential should undergo pregnancy testing before EFV initiation and counseling about 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 are planning to become pregnant or who are sexually active and not using effective contraception. 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, 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 (see HIV-Infected Pregnant Women Who are Currently Receiving Antiretroviral Treatment).	October 26, 2016

Table 8. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy[a] (page 7 of 19)

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations	Use in Pregnancy	Last Reviewed
Etravirine (ETR) *Intelence*	Tablets: • 25 mg • 100 mg • 200 mg For patients unable to swallow tablets whole, the tablets may be dispersed in a glass of water.	Standard Adult Dose(s): • 200 mg twice daily with food PK in Pregnancy: • PK data in pregnancy (n = 26) suggest 1.2–1.6 fold increased etravirine exposure during pregnancy. Dosing in Pregnancy: • No change in dose indicated.	Variable placental transfer, usually in the moderate to high categories, ranging from 0.19–4.25 (data from 18 mother-infant pairs).[b] Insufficient data to assess for teratogenicity in humans. No evidence of teratogenicity in rats or rabbits.	April 29, 2016
Nevirapine (NVP) *Viramune Viramune XR (Extended Release)* **Note:** Generic available for all formulations	NVP (Viramune) *Tablets:* • 200 mg *Oral Suspension:* • 50 mg/5 mL Viramune XR Tablets: • 100 mg • 400 mg	Standard Adult Dose: • 200 mg once daily Viramune immediate release for 14 days (lead-in period); thereafter, 200 mg twice daily or 400 mg (Viramune XR tablet) once daily, without regard to food. • 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. PK in Pregnancy: • PK not significantly altered in pregnancy. Dosing in Pregnancy: • No change in dose indicated.	High placental transfer to fetus.[b] No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects and 2-fold increase in risk of birth defects in more common classes, cardiovascular and genitourinary). Increased risk of symptomatic, often rash-associated, and potentially fatal liver toxicity among women with CD4 counts ≥250/mm^3 when first initiating therapy; pregnancy does not appear to increase risk. NVP should be initiated in pregnant women with CD4 cell counts ≥250 cells/mm^3 only if benefit clearly outweighs risk because of potential increased risk of life-threatening hepatotoxicity in women with high CD4 cell counts. Elevated transaminase levels at baseline 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.	June 7, 2016

Table 8. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy[a] (page 8 of 19)

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations	Use in Pregnancy	Last Reviewed
Rilpivirine (RPV) *Edurant* (RPV/TDF/FTC) *Complera*	RPV (Edurant) *Tablets:* • 25 mg Complera: • RPV 25 mg plus TDF 300 mg plus FTC 200 mg tablet	Standard Adult Dose *RPV (Edurant):* • 25 mg once daily with food *Complera:* • 1 tablet once daily with food PK in Pregnancy: • RPV PK highly variable during pregnancy. RPV AUC and trough concentration reduced 20% to 30% in pregnancy compared with postpartum, but most pregnant women exceeded target exposure. Dosing in Pregnancy: • Routine dosing adjustment in all women is not recommended for RPV during pregnancy. Individual patients should be closely monitored.	Moderate to high placental transfer to fetus.[b] No evidence of teratogenicity in rats or rabbits. Insufficient data to assess for teratogenicity in humans.	June 7, 2016

Table 8. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy[a] (page 9 of 19)

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations	Use in Pregnancy	Last Reviewed
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 Combination Antiretroviral Drug Regimens and Pregnancy Outcomes).				
Atazanavir (ATV) *Reyataz* **Note:** Must be combined with low-dose RTV boosting in pregnancy **Atazanavir/ Cobicistat** (ATV/COBI) *Evotaz*	ATZ (Reyataz) *Capsules*: • 150 mg • 200 mg • 300 mg *Oral Powder:* • 50 mg packet Evotaz: • ATV 300 mg plus COBI 150 mg tablet	Standard Adult Dose ATZ (Reyataz) *ARV-Naive Patients* *Without RTV Boosting:* • ATV 400 mg once daily with food; ATV without RTV boosting **is not recommended** when used with TDF, H_2-receptor antagonists, or PPIs, or during pregnancy. *With RTV Boosting:* • ATV 300 mg plus RTV 100 mg once daily with food • When combined with EFV in ARV-naive patients: ATV 400 mg plus RTV 100 mg once daily with food *ARV-Experienced Patients:* • ATV 300 mg plus RTV 100 mg once daily with food • Do not use with PPIs or EFV. • If combined with an H_2-receptor antagonist: ATV 300 mg plus RTV 100 mg once daily with food • If combined with an H_2-receptor antagonist and TDF: ATV 400 mg plus RTV 100 mg once daily with food Powder Formulation: • Oral powder is taken once daily with food at the same recommended adult dosage as the capsules along with ritonavir. Evotaz: • One tablet once daily with food. PK in Pregnancy *Atazanavir (Reyataz):* • ATV concentrations reduced during pregnancy; further reduced when given concomitantly with TDF or H_2-receptor antagonist. *Evotaz:* • No PK studies in human pregnancy.	Low placental transfer to fetus.[b] No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects). Must be given as low-dose RTV-boosted regimen in pregnancy. Effect of *in utero* ATV exposure on infant indirect bilirubin levels is unclear. Non-pathologic elevations of neonatal hyperbilirubinemia have been observed in some but not all clinical trials to date. Oral powder (but **not** capsules) contains phenylalanine, which can be harmful to patients with phenylketonuria.	June 7, 2016

Table 8. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy[a] (page 10 of 19)

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations	Use in Pregnancy	Last Reviewed
		Dosing in Pregnancy *Atazanavir (Reyataz):* • Use of unboosted ATV **is not recommended** during pregnancy. • Use of ATV not recommended for treatment-experienced pregnant women taking TDF **and** an H_2-receptor antagonist. • Use of an increased dose (400 mg ATV plus 100 mg RTV once daily with food) during the second and third trimesters results in plasma concentrations equivalent to those in non-pregnant adults on standard dosing. 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. *Evotaz:* • Insufficient data to make dosing recommendation.		June 7, 2016
Darunavir (DRV) *Prezista* **Note:** Must be combined with low-dose ritonavir (RTV) or cobicistat (COBI) boosting **Darunavir/ Cobicistat** (DRV/COBI) *Prezcobix*	DRV (Prezista): • 75 mg • 150 mg • 600 mg • 800 mg Oral Suspension: • 100 mg/mL Prezcobix (Co-Formulated): • DRV 800 mg plus COBI 150 mg	Standard Adult Dose *ARV-Naive Patients:* • DRV 800 mg plus RTV 100 mg once daily with food • DRV 800 mg plus COBI 150 mg once daily with food *ARV-Experienced Patients:* *If No DRV Resistance Mutations:* • DRV 800 mg plus RTV 100 mg once daily with food • DRV 800 mg plus COBI 150 mg once daily with food *If Any DRV Resistance Mutations:* • DRV 600 mg plus RTV 100 mg twice daily with food PK in Pregnancy: • Decreased exposure in pregnancy with use of DRV/RTV. Dosing in Pregnancy: • Once-daily dosing with DRV/RTV **is not recommended** during pregnancy. Twice-daily DRV/RTV dosing (DRV 600 mg plus RTV 100 mg with food) recommended for all pregnant women. Increased twice-daily DRV dose (DRV 800 mg plus RTV 100 mg with food) during pregnancy does not result in an increase in darunavir exposure and is not recommended. • No pregnancy PK/safety data for DRV/COBI co-formulation, so not recommended for use in pregnancy.	Low placental transfer to fetus.[b] No evidence of teratogenicity in mice, rats, or rabbits. No evidence of human teratogenicity. Must be given as low-dose, RTV-boosted regimen.	October 26, 2016

Table 8. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy[a] (page 11 of 19)

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations	Use in Pregnancy	Last Reviewed
Fosamprenavir (FPV) *Lexiva (a prodrug of amprenavir)* **Note:** Must be combined with low-dose RTV boosting in pregnancy	Tablets: • 700 mg Oral Suspension: • 50 mg/mL	Standard Adult Dose *ARV-Naive Patients:* • FPV 1400 mg twice daily without food, *or* • FPV 1400 mg plus RTV 100 or 200 mg once daily without food, *or* • FPV 700 mg plus RTV 100 mg twice daily without food *PI-Experienced Patients (Once-Daily Dosing Not Recommended):* • FPV 700 mg plus RTV 100 mg twice daily without food *Co-Administered with EFV:* • FPV 700 mg plus RTV 100 mg twice daily without food; *or* • FPV 1400 mg plus RTV 300 mg once daily without food PK in Pregnancy: • 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. Dosing in Pregnancy: • Use of unboosted FPV or once-daily FPV with RTV boosting **is not recommended** during pregnancy. No change is indicated in standard boosted twice-daily dose (FPV 700 mg plus RTV 100 mg twice daily without food).	Low placental transfer to fetus.[b] Insufficient data to assess for teratogenicity in humans. Increased fetal loss in rabbits but no increase in defects in rats and rabbits. Must be given as low-dose RTV-boosted regimen in pregnancy.	June 7, 2016
Indinavir (IDV) *Crixivan* **Note:** Must be combined with low-dose RTV boosting in pregnancy	Capsules: • 200 mg • 400 mg	Standard Adult Dose *Without RTV Boosting:* • IDV 800 mg every 8 hours, taken 1 hour before or 2 hours after meals; may take with skim milk or low-fat meal. *With RTV Boosting:* • IDV 800 mg plus RTV 100 mg twice daily without regard to meals PK in Pregnancy: • IDV exposure markedly reduced when administered without RTV boosting during pregnancy. IDV exposure low with IDV 400 mg/RTV 100 mg dosing during pregnancy; no PK data available on alternative boosted dosing regimens in pregnancy. Dosing in Pregnancy: • Use of unboosted IDV **is not recommended** during pregnancy.	Minimal placental transfer to fetus.[b] No evidence of human teratogenicity in cases reported to the APR (can rule out 2-fold increase in overall birth defects). Must be given as low-dose, RTV-boosted regimen in pregnancy. Theoretical concern regarding increased indirect bilirubin levels, which may exacerbate physiologic hyperbilirubinemia in neonates. Minimal placental passage mitigates this concern.	June 7, 2016

Table 8. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy[a] (page 12 of 19)

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations	Use in Pregnancy	Last Reviewed
Lopinavir/ Ritonavir (LPV/r) *Kaletra*	Tablets (Co-Formulated): • LPV 200 mg plus RTV 50 mg • LPV 100 mg plus RTV 25 mg Oral Solution: • LPV 400 mg plus RTV 100 mg/5 mL	Standard Adult Dose: • LPV 400 mg plus RTV 100 mg twice daily, *or* • LPV 800 mg plus RTV 200 mg once daily *Tablets:* • Take without regard to food. *Oral Solution:* • Take with food. With EFV or NVP (PI-Naive or PI-Experienced Patients): • LPV 500 mg plus RTV 125 mg tablets twice daily without regard to meals (use a combination of two LPV 200 mg plus RTV 50 mg tablets and one LPV 100 mg plus RTV 25 mg tablet), *or* • LPV 520 mg plus RTV 130 mg oral solution (6.5 mL) twice daily with food PK in Pregnancy: • With twice-daily dosing, LPV exposure is reduced in pregnant women receiving standard adult doses; increasing the dose by 50% results in exposure equivalent to that seen in non-pregnant adults receiving standard doses. • No PK data are available for once-daily dosing in pregnancy. Dosing in Pregnancy: • Once daily dosing **is not recommended** during pregnancy. • Some experts recommend that an increased dose (i.e., LPV 600 mg plus RTV 150 mg twice daily without regard to meals) should be used in the second and third trimesters, especially in PI- experienced pregnant women and women who start treatment during pregnancy with a baseline viral load >50 copies/mL. • If standard dosing is used, monitor virologic response and LPV drug levels, if available.	Low placental transfer to fetus.[b] No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects). Oral solution contains 42% alcohol and 15% propylene glycol and is not recommended for use in pregnancy. Once-daily LPV/r dosing is not recommended during pregnancy	October 26, 2016

Table 8. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy[a] (page 13 of 19)

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations	Use in Pregnancy	Last Reviewed
Nelfinavir (NFV) *Viracept*	Tablets: • 250 mg • 625 mg (tablets can be dissolved in small amount of water) Powder for Oral Suspension: • 50 mg/g	Standard Adult Dose: • 1250 mg twice daily or 750 mg three times daily with food PK in Pregnancy: • Lower NFV exposure in third trimester than postpartum in women receiving NFV 1250 mg twice daily; however, generally adequate drug levels are achieved during pregnancy, although levels are variable in late pregnancy. Dosing in Pregnancy: • Three-times-daily dosing with 750 mg with food not recommended during pregnancy. No change in standard dose (1250 mg twice daily with food) indicated.	Minimal to low placental transfer to fetus.[b] No evidence of human teratogenicity; can rule out 1.5-fold increase in overall birth defects and 2-fold increase in risk of birth defects in more common classes, cardiovascular, and genitourinary. Contains aspartame; should not be used in individuals with phenylketonuria.	June 7, 2016
Saquinavir (SQV) *Invirase* **Note:** Must be combined with low-dose RTV for PK boosting	Tablet: • 500 mg Capsule: • 200 mg	Standard Adult Dose: • SQV 1000 mg plus RTV 100 mg twice a day with food or within 2 hours after a meal PK in Pregnancy: • Based on limited data, SQV exposure may be reduced in pregnancy but not sufficient to warrant a dose change. Dosing in Pregnancy: • No change in dose indicated.	Low placental transfer to fetus.[b] Insufficient data to assess for teratogenicity in humans. No evidence of teratogenicity in rats or rabbits. Must be boosted with low-dose RTV. Baseline ECG recommended before starting because PR and/or QT interval prolongations have been observed. Contraindicated in patients with preexisting cardiac conduction system disease.	June 7, 2016

Table 8. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy[a] (page 14 of 19)

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations	Use in Pregnancy	Last Reviewed
Tipranavir (TPV) *Aptivus* **Note:** Must be combined with RTV for PK boosting	Capsules: • 250 mg Oral Solution: • 100 mg/mL	Standard Adult Dose: • TPV 500 mg plus RTV 200 mg twice daily *With RTV Tablets:* • Take with food. *With RTV Capsules or Solution:* • Take without regard to food; however, administering with food may help make the dose more tolerable. PK in Pregnancy: • Limited PK data in human pregnancy. Dosing in Pregnancy: • Insufficient data to make dosing recommendation.	Moderate placental transfer to fetus reported in one patient.[b] Insufficient data to assess for teratogenicity in humans. No evidence of teratogenicity in rats or rabbits. Must be given as low-dose RTV-boosted regimen.	June 7, 2016
Entry Inhibitors				
Enfuvirtide (T-20) *Fuzeon*	Injectable: • Supplied as lyophilized powder. Each vial contains 108 mg of T-20; reconstitute with 1.1 mL of sterile water for injection for SQ delivery of approximately 90 mg/1 mL.	T-20 is indicated for advanced HIV disease and must be used in combination with other ARV drugs to which the patient's virus is susceptible by resistance testing. Standard Adult Dose: • 90 mg (1 mL) twice daily without regard to meals PK in Pregnancy: • No PK data in human pregnancy. Dosing in Pregnancy: • Insufficient data to make dosing recommendation.	Minimal to low placental transfer to fetus.[b] No data on human teratogenicity.	October 26, 2016

Table 8. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy[a] (page 15 of 19)

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations	Use in Pregnancy	Last Reviewed
Maraviroc (MVC) *Selzentry*	Tablets: • 150 mg • 300 mg	Standard Adult Dose: • 300 mg twice daily with or without food • MVC must be used in combination with other ARVs in HIV-1-infected adults with only CCR5-tropic virus. Dose Adjustments: • Increase to 600 mg BID when used with potent CYP3A inducers: EFV, ETR, and rifampin. • Decrease to 150 mg BID when used with CYP3A inhibitors: all PIs except TPV/r and itraconazole. PK in Pregnancy: • A PK study in human pregnancy demonstrated a 20% to 30% overall decrease in AUC, but C_{trough} exceeded the recommended minimal concentration of 50 ng/mL. Dosing in Pregnancy: • Standard adult dosing adjusted for concomitant ARV use appears appropriate.	No evidence of teratogenicity in rats or rabbits; insufficient data to assess for teratogenicity in humans. MVC placental passage category should be moderate.[b]	October 26, 2016

Table 8. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy[a] (page 16 of 19)

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations	Use in Pregnancy	Last Reviewed
Integrase Inhibitors				
Dolutegravir (DTG) *Tivicay* (DTG/ABC/3TC) *Triumeq*	Tablets: • 50 mg Triumeq: • DTG 50 mg plus ABC 600 mg plus 3TC 300 mg tablet	Standard Adult Dose *ARV-Naive or ARV-Experienced (but Integrase Inhibitor-Naive Patients)* *DTG (Tivicay):* • 1 tablet once daily, without regard to food. *DTG/ABC/3TC (Triumeq):* • 1 tablet once daily, without regard to food. *ARV-Naive or ARV-Experienced (but Integrase Inhibitor-Naive) if Given with EFV, FPV/r, TPV/r, or Rifampin; or Integrase Inhibitor-Experienced* *DTG (Tivicay):* • 1 tablet twice daily, without regard to food. PK in Pregnancy: • Limited PK data in human pregnancy. Dosing in Pregnancy: • Insufficient data to make dosing recommendation.	Unknown placental transfer to fetus. Insufficient data to assess for teratogenicity in humans. No evidence of teratogenicity in mice, rats, or rabbits.	June 7, 2016

Table 8. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy[a] (page 17 of 19)

<table>
<tr><th>Generic Name (Abbreviation)
Trade Name</th><th>Formulation</th><th>Dosing Recommendations</th><th>Use in Pregnancy</th><th>Last Reviewed</th></tr>
<tr>
<td>Elvitegravir (EVG)
Vitekta

Elvitegravir/ Cobicistat/ Emtricitabine/ Tenofovir Disoproxil Fumarate (EVG/COBI/ FTC/ TDF)
Stribild

Elvitegravir/ Cobicistat/ Emtricitabine/ Tenofovir Alafenamide (EVG/COBI/FTC/ TAF)
Genvoya</td>
<td>EVG Tablet (Vitekta):
• 85 mg
• 150 mg

Tablet (Stribild):
• EVG 150 mg plus COBI 150 mg plus FTC 200 mg plus TDF 300 mg

Tablet (Genvoya):
• EVG 150 mg plus COBI 150 mg plus FTC 200 mg plus TAF 10 mg</td>
<td>Standard Adult Dose (Vitekta):
• EVG (as Vitekta) must be used in combination with an HIV PI co-administered with RTV and another ARV drug.

Recommended Elvitegravir Dosage Taken Once Daily with Food (All Drugs Administered Orally)
<table>
<tr><th>Dosage of Elvitegravir</th><th>Dosage of Concomitant PI</th><th>Dosage of Concomitant RTV</th></tr>
<tr><td rowspan="2">85 mg once daily</td><td>ATV 300 mg once daily</td><td>100 mg once daily</td></tr>
<tr><td>LPV 400 mg twice daily</td><td>100 mg twice daily</td></tr>
<tr><td rowspan="3">150 mg once daily</td><td>DRV 600 mg twice daily</td><td>100 mg twice daily</td></tr>
<tr><td>FPV 700 mg twice daily</td><td>100 mg twice daily</td></tr>
<tr><td>TPV 500 mg twice daily</td><td>200 mg twice daily</td></tr>
</table>
Standard Adult Dose (Stribild and Genvoya):
• One tablet once daily with food.

PK in Pregnancy:
• PK studies in human pregnancy limited to case report of 1 woman.

Dosing in Pregnancy:
• Insufficient data to make dosing recommendation.</td>
<td>Insufficient data are available on placental transfer of EVG/COBI.

Insufficient data to assess for teratogenicity in humans. No evidence of teratogenicity in rats or rabbits.</td>
<td>October 26, 2016</td>
</tr>
<tr>
<td>Raltegravir (RAL)
Isentress</td>
<td>Film-Coated Tablets:
• 400 mg

Chewable Tablets:
• 25 mg
• 100 mg</td>
<td>Standard Adult Dose:
• 400-mg film-coated tablets twice daily without regard to food.
• Chewable and oral suspension doses are not interchangeable to either film-coated tablets or to each other.

With Rifampin:
• 800-mg film-coated tablets twice daily without regard to food.

PK in Pregnancy:
• Decreased levels in third trimester not of sufficient magnitude to warrant change in dosing.

Dosing in Pregnancy:
• No change in dose indicated.</td>
<td>High placental transfer to fetus.[b]

Insufficient data to assess for teratogenicity in humans. Increased skeletal variants in rats, no increase in defects in rabbits.

Case report of markedly elevated liver transaminases with use in late pregnancy. Severe, potentially life-threatening and fatal skin and hypersensitivity reactions have been reported in non-pregnant adults.

Chewable tablets contain phenylalanine.</td>
<td>October 26, 2016</td>
</tr>
</table>

Table 8. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy[a] (page 18 of 19)

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations	Use in Pregnancy	Last Reviewed
Pharmacoenhancers				
Cobicistat (COBI) *Tybost* **Elvitegravir/Cobicistat/ Tenofovir Disoproxil Fumarate/Emtricitabine** (EVG/COBI/ TDF/FTC) *Stribild* **Elvitegravir/Cobicistat/Tenofovir Alafenamide/Emtricitabine** (EVG/COBI/TAF/FTC) *Genvoya* **Atazanavir/Cobicistat** (ATV/COBI) *Evotaz* **Darunavir/Cobicistat** (DRV/COBI) *Prezcobix*	Tablet (Tybost): • 150mg Tablet (Stribild): • EVG 150 mg plus COBI 150 mg plus TDF 300 mg plus FTC 200 mg Tablet (Genvoya): • EVG 150 mg plus COBI 150 mg plus TAF 10 mg plus FTC 200 mg Tablet (Evotaz): • ATV 300 mg plus COBI 150 mg Tablet (Prezcobix): • DRV 800 mg plus COBI 150 mg	Standard Adult Dose *Tybost:* • As an alternative PK booster with atazanavir or darunavir: One tablet (150 mg) once daily with food. *Stribild, Genvoya, Evotaz, Prezcobix:* • One tablet once daily with food. PK in Pregnancy: • No PK studies in human pregnancy. Dosing in Pregnancy: • Insufficient data to make dosing recommendation.	No data on placental transfer of COBI are available. Insufficient data to assess for teratogenicity in humans. No evidence of teratogenicity in rats or rabbits	October 26, 2016
Ritonavir (RTV) *Norvir*	Capsules: • 100 mg Tablets: • 100 mg Oral Solution: • 80 mg/mL	Standard Adult Dose as PK Booster for Other PIs: • 100–400 mg per day in 1–2 divided doses (refer to other PIs for specific dosing recommendations.) *Tablet:* • Take with food. *Capsule or Oral Solution:* • To improve tolerability, recommended to take with food if possible. PK in Pregnancy: • Lower levels during pregnancy compared with postpartum. Dosing in Pregnancy: No dosage adjustment necessary when used as booster.	Low placental transfer to fetus.[b] No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects). Should only be used as low-dose booster for other PIs. Oral solution contains 43% alcohol and therefore may not be optimal for use in pregnancy.	June 7, 2016

Table 8. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy[a] (page 19 of 19)

[a] Individual antiretroviral drug dosages may need to be adjusted in renal or hepatic insufficiency (for details, 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: <0.3

[c] See Teratogenicity for discussion of EFV and risks in pregnancy.

[d] WHO recommends maximum dose of 30 mg twice daily regardless of weight.

Key to Abbreviations: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; ATV = atazanavir; AUC = area under the curve; AZT = zidovudine; BID = twice daily; CD4 = CD4 T lymphocyte; CI = confidence interval; CNS = central nervous system; COBI = cobicistat; d4T = stavudine; ddI = didanosine; DTG = dolutegravir; DRV = darunavir; EC = enteric coated; ECG = electrocardiogram; EFV = efavirenz; ETR = etravirine; EVG = elvitegravir; FDA = Food and Drug Administration; FPV/r = fosamprenavir/ritonavir; FTC = emtricitabine; HBV = hepatitis B virus; IDV = indinavir; IV = intravenous; LPV = lopinavir; LPV/r = lopinavir/ritonavir; MVC = maraviroc; NFV = nelfinavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; PK = pharmacokinetic; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SQ = subcutaneous; SQV = saquinavir; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TID = three times a day; TPV = tipranavir; TPV/r = tipranavir/ritonavir; T20 = enfuvirtide; WHO = World Health Organization; ZDV = zidovudine

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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