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

Downloaded from http://aidsinfo.nih.gov/guidelines on 3/18/2013

Antepartum Care (Last updated August 7, 2012; last reviewed July 31, 2012)

General Principles Regarding Use of Antiretroviral Drugs during Pregnancy

Panel's Recommendations
• Initial evaluation of infected pregnant women should include assessment of HIV disease status and recommendations regarding initiation of antiretroviral (ARV) drugs or the need for any modification if currently receiving antiretroviral therapy (ART) **(AIII)**. The National Perinatal HIV Hotline (1-888-448-8765) provides free clinical consultation on all aspects of perinatal HIV care.
• Regardless of plasma HIV RNA copy number or CD4 T-lymphocyte count, all pregnant HIV-infected women should receive a combination ARV drug regimen antepartum to prevent perinatal transmission **(AI)**. A combination regimen is recommended both for women who require therapy for their own health **(AI)** and for prevention of perinatal transmission in those who do not yet require therapy **(AII)**.
• The known benefits and potential risks of ARV use during pregnancy should be discussed with all women **(AIII)**.
• ARV drug-resistance studies should be performed before starting or modifying ARV drug regimens in women whose HIV RNA levels are above the threshold for resistance testing (that is, >500 to 1,000 copies/mL) (see Antiretroviral Drug Resistance and Resistance Testing in Pregnancy) **(AIII)**. When HIV is diagnosed later in pregnancy, ART or combination ARV prophylaxis should be initiated promptly without waiting for results of resistance testing **(BIII)**.
• In counseling patients, the importance of adherence to their ARV regimens should be emphasized **(AII)**.
• Considerations regarding continuing the ARV regimen for maternal treatment after delivery are the same as in non-pregnant individuals. The pros and cons of continuing versus discontinuing ARV drugs postpartum should be discussed with women so they can make educated decisions about postpartum ARV use before delivery **(AIII)**. Those decisions should be made in consultation with the provider who will assume responsibility for the women's HIV care after delivery.
• Coordination of services among prenatal care providers, primary care and HIV specialty care providers, mental health and drug abuse treatment services, and public assistance programs is essential to ensure that infected women adhere to their ARV drug regimens **(AIII)**.
Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*
Rating of Evidence: *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*

In addition to the standard antenatal assessments for all pregnant women, the initial evaluation of those who are HIV infected should include assessment of HIV disease status and recommendations for HIV-related medical care. This initial assessment should include the following:

a. review of prior HIV-related illnesses and past CD4 T-lymphocyte (CD4-cell) counts and plasma HIV viral loads;
b. current CD4-cell count;
c. current plasma HIV RNA copy number;
d. assessment of the need for prophylaxis against opportunistic infections such as *Pneumocystis jirovecii* pneumonia and *Mycobacterium avium* complex (see *Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents*)[1];

e. screening for hepatitis C virus and tuberculosis in addition to standard screening for hepatitis B virus (HBV) infection;

f. evaluation of immunization status per guidelines from the American College of Obstetricians and Gynecologists, with particular attention to hepatitis A, HBV, influenza, pneumococcus, and Tdap immunizations;[2, 3]

g. baseline complete blood cell count and renal and liver function testing;

h. HLA-B*5701 testing if abacavir use is anticipated (see Table 5);

i history of prior and current antiretroviral (ARV) drug use, including prior ARV use for prevention of perinatal transmission or treatment of HIV and history of adherence problems;

j. results of prior and current HIV ARV drug-resistance studies;

k. history of side effects or toxicities from prior ARV regimens; and

l. assessment of supportive care needs.

ARV drugs for prevention of perinatal transmission of HIV are recommended for all pregnant women, regardless of CD4-cell counts and HIV RNA levels. In general, guidelines for the use of antiretroviral therapy (ART) for the benefit of maternal health during pregnancy are the same as for women who are not pregnant, with some modifications based on concerns about specific drugs and limited experience during pregnancy with newer drugs.

Decisions regarding initiation or modification of ARV drug regimens during pregnancy include considerations regarding the benefits and risks of ARV drugs that are common to all HIV-infected adults plus those unique to pregnancy. In general, the ARV drug combinations now available are more convenient and better tolerated than regimens used previously, resulting in greater efficacy and improved adherence. During pregnancy, maternal ARV toxicities must be considered, along with the potential impact of the ARV regimen on pregnancy outcome and on fetuses and infants. Decisions about ARV drug regimens are further complicated because only limited data exist on the long-term maternal consequences of use of agents during pregnancy solely for preventing transmission. Similarly, only limited data are available on the long-term consequences to infants of *in utero* exposure to ARVs.

The known benefits and known and unknown risks of ARV drug use during pregnancy should be considered and discussed with women (see Special Considerations Regarding the Use of Antiretroviral Drugs by HIV-Infected Pregnant Women and Their Infants). Results from preclinical and animal studies and available clinical information about use of the various agents during pregnancy also should be discussed (see Supplement: Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy). Potential risks of these drugs should be placed into perspective by reviewing the substantial benefits of ARV drugs for maternal health and in reducing the risk of transmission of HIV to infants. Counseling of pregnant women about ARV use should be noncoercive, and providers should help them make informed decisions regarding use of ARV drugs.

Discussions with women about initiation of ARV drug regimens should include information about:

a. maternal risk of disease progression and the benefits and risks of initiation of therapy for maternal health;

b. benefit of combination ARV regimens for preventing perinatal transmission of HIV;[4]

c. benefits of therapy for reducing sexual transmission to discordant partners when viral suppression is maintained;[5]

d. potential adverse effects of ARV drugs for mothers, fetuses, and infants, including potential interactions with other medications the women may already be receiving;

e. the limited long-term outcome data for both women who temporarily use ARV drugs during

pregnancy for prophylaxis of transmission and infants with *in utero* drug exposure; and

f. the need for strict adherence to the prescribed drug regimen to avoid resistance.

Studies of zidovudine in prevention of perinatal transmission suggest that an important mechanism of infant pre-exposure prophylaxis is transplacental drug passage. Thus, when selecting an ARV regimen for a pregnant woman, at least one nucleoside/nucleotide reverse transcriptase inhibitor (NRTI) agent with high placental transfer should be included as a component of the dual-NRTI backbone (see Table 5).[6-9]

In women with plasma HIV RNA levels above the threshold for resistance testing (that is, >500–1,000 copies/mL), ARV drug-resistance studies should be performed before starting ARV drugs for maternal health or prophylaxis. When HIV is diagnosed later in pregnancy, however, ARV drugs should be initiated promptly without waiting for results of resistance testing (see Antiretroviral Drug Resistance and Resistance Testing in Pregnancy).

Counseling should emphasize the importance of adherence to the ARV drug regimen. Support services, mental health services, and drug abuse treatment may be required, depending on women's individual circumstances. Coordination of services among prenatal care providers, primary care and HIV specialty care providers, mental health and drug abuse treatment services, and public assistance programs is essential to ensure that infected women adhere to their ARV drug regimens.

Providers should work with women to develop long-range plans regarding continuity of medical care and decisions about continuing ARV drugs postpartum. Considerations regarding postpartum continuation of ARV drugs for maternal therapeutic indications are the same as for non-pregnant individuals. The impact on short- and long-term maternal health is unknown for postpartum discontinuation of combination ARV drug regimens used solely to prevent perinatal transmission. This is particularly important because women may have multiple pregnancies resulting in episodic receipt of ARV drugs. No increase in disease progression has been seen so far, however, in studies of pregnant women with relatively high CD4-cell counts who stop combination ARV drug regimens after delivery.[10-12] The risks versus benefits of stopping ARV drug regimens postpartum in women with high CD4-cell counts are being evaluated in the ongoing PROMISE study (clinical trial number NCT00955968).

Current adult treatment guidelines strongly recommend ART for all individuals with CD4-cell counts <350 cells/mm^3 based on randomized, controlled clinical trial data demonstrating a clear benefit in reduction of mortality and morbidity. Pregnant women with CD4-cell counts <350 cells/mm^3 should begin ART as soon as possible during pregnancy and be counseled about the need to continue therapy after delivery and the importance of adherence to the regimen.

Based on observational cohort data and recent results from a randomized trial, the adult treatment guidelines also recommend initiating lifelong ART in individuals with CD4-cell counts between 350 and 500 cells/mm^3. Observational studies suggest a relative decrease in mortality (although the overall number of events was small) and possibly a decrease in complications such as cardiovascular events with initiation of ART in this setting compared with waiting until CD4-cell counts drop below 350 cells/mm^3.[13, 14] The HPTN 052 study was a large, multinational randomized trial evaluating whether treatment of HIV-infected individuals reduces transmission to their uninfected sexual partners.[5] An additional objective was to examine if ART reduced clinical events in the HIV-infected participants. This trial enrolled 1,763 HIV-infected participants with CD4-cell counts between 350 and 550 cells/mm^3 and their HIV-uninfected partners. The infected participants were randomized to immediate initiation of ART or delay of initiation until they had 2 consecutive CD4-cell counts <250 cells/mm^3. At median follow-up of 1.7 years, there were 40 events/deaths in participants assigned to immediate ART versus 65 in participants assigned to delayed initiation (hazard ratio [HR]: 0.59; 95% confidence interval [CI]: 0.40–0.88). The observed difference was driven mainly by the incidence of extrapulmonary tuberculosis (3 vs. 17 events). There was no significant difference in mortality rates

observed in the immediate versus deferred therapy arms (10 vs. 13 deaths, respectively; HR: 0.77; 95% CI: 0.34–1.76). The trial was stopped early because of a significantly reduced rate of transmission to sexual partners in the group who started therapy immediately compared with those who delayed. Of 28 transmissions that were virologically linked to the infected partner, only 1 occurred in the immediate-therapy arm (HR, 0.04; 95% CI, 0.01–0.27; P <0.001).[5]

Pregnant women with CD4-cell counts between 350 and 500 cells/mm^3 should be started on a combination ARV regimen during pregnancy to prevent perinatal transmission of HIV and counseled about the current treatment recommendations, the potential risks versus benefits of stopping versus continuing the regimen after delivery (including reduction in transmission to discordant partners with continuing therapy when viral suppression is maintained), and the need for sustained strict adherence if the regimen is continued postpartum.

For individuals with CD4-cell counts >500 cells/mm^3, the adult guidelines recommend initiating lifelong therapy as a moderate recommendation, given that data are incomplete on the clinical benefit of starting treatment at higher CD4-cell counts (>500 cells/mm^3). So far, no increased risk of disease progression has been shown in studies of pregnant women with relatively high CD4-cell counts who stop ARV drugs after delivery.[10-12] The potential benefits of early therapy must be weighed against possible drug toxicity, cost, and the risk of development of viral resistance with suboptimal adherence, which may be more likely postpartum.[15] Pregnant women with CD4-cell counts >500 cells/mm^3 should be started on a combination ARV regimen during pregnancy to prevent perinatal transmission. They should be assessed for their willingness and ability to commit to ongoing continuous therapy and counseled about the current treatment guidelines, the benefits and risks of therapy, the inconclusive nature of data on the clinical benefit of starting lifelong treatment at CD4-cell counts >500 cells/mm^3, and the importance of adherence if the regimen is continued postpartum.

In general, when drugs are discontinued postnatally, all drugs should be stopped simultaneously. However, as discussed later (see Stopping Antiretroviral Therapy during Pregnancy), in women receiving non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens, continuing the dual-NRTI backbone for a period of time after stopping the NNRTI is recommended to reduce the development of NNRTI resistance. An alternative strategy is to replace the NNRTI with a protease inhibitor (PI) while continuing the NRTI and then discontinue all the drugs at the same time.[16] The optimal interval between stopping an NNRTI and stopping the other ARV drugs is unknown, but a minimum of 7 days is recommended. Drug concentrations may be detectable for more than 3 weeks after efavirenz is stopped in patients receiving an efavirenz-based NNRTI regimen. Therefore, for patients receiving the drug, some experts recommend continuing the other ARV agents or substituting a PI plus two other agents for up to 30 days.

Medical care of HIV-infected pregnant women requires coordination and communication between HIV specialists and obstetrical providers. General counseling should include current knowledge about risk factors for perinatal transmission. Risk of perinatal transmission of HIV has been associated with potentially modifiable factors, including cigarette smoking, illicit drug use, genital tract infections, and unprotected sexual intercourse with multiple partners during pregnancy.[17-21] Besides improving maternal health, cessation of cigarette smoking and drug use, treatment of genital tract infections, and use of condoms with sexual intercourse during pregnancy may reduce risk of perinatal transmission. In addition, the Centers for Disease Control and Prevention recommends that HIV-infected women in the United States (including those receiving ART) refrain from breastfeeding to avoid postnatal transmission of HIV to their infants through breast milk[22] and avoid premastication of food for their infants, a potential risk factor for transmission.[23]

The National Perinatal HIV Hotline (1-888-448-8765)

The National Perinatal HIV Hotline is a federally funded service providing free clinical consultation to providers caring for HIV-infected women and their infants.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Recommendations for Use of Antiretroviral Drugs during Pregnancy

The Panel recommends that choice of ARV drug regimens for HIV-infected pregnant women be based on the same principles used to choose regimens for non-pregnant individuals, unless there are compelling pregnancy-specific maternal or fetal safety issues associated with specific drugs. The Panel reviews clinical trial data published in peer-reviewed journals and data prepared by manufacturers for Food and Drug Administration review related to treatment of HIV-infected adult women, both pregnant and non-pregnant. The durability, tolerability, and simplicity of a medication regimen is particularly important for preserving future options for women who decide to stop medications after delivery and those who meet standard criteria for initiation of ART per adult guidelines and will continue their regimens after pregnancy. Regimen selection should be individualized and the following factors should be considered:

- comorbidities,
- patient adherence potential,
- convenience,
- potential adverse maternal drug effects,
- potential drug interactions with other medications,
- results of genotypic resistance testing,
- pharmacokinetic (PK) changes in pregnancy,
- potential teratogenic effects and other adverse effects on fetuses or newborns, and
- experience with use in pregnancy.

Information used by the Panel for recommendations on specific drugs or regimens for pregnant women include:

- Data from randomized, prospective clinical trials that demonstrate durable viral suppression as well as immunologic and clinical improvement;
- Incidence rates and descriptions of short- and long-term drug toxicity of ARV regimens, with special attention to maternal toxicity and potential teratogenicity and fetal safety;
- Specific knowledge about drug tolerability and simplified dosing regimens;
- Known efficacy of ARV drug regimens in reducing mother-to-child transmission of HIV;
- PK data during the prenatal period. (The physiologic changes of pregnancy have the potential to alter drug PK. ARV dosing during pregnancy should be based on PK data from studies in pregnant women. Physiologic changes are not fixed throughout pregnancy but, rather, reflect a continuum of change as pregnancy progresses, with return to baseline at various rates in the postpartum period.); and
- Data from animal teratogenicity studies.

Categories of ARV regimens include:

- ***Preferred:*** Drugs or drug combinations are designated as preferred for use in 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 evidence of teratogenic effects or established association with teratogenic or clinically significant adverse outcomes for mothers, fetuses, or newborn are present.
- ***Alternative:*** Drugs or drug combinations are designated as alternatives for initial therapy in pregnant women when clinical trial data in adults show efficacy but any one or more of the following conditions apply: Experience in pregnancy is limited; data are lacking on teratogenic effects on the

fetus; or the drug or regimen is associated with dosing, formulation, administration, or interaction issues.

- ***Use in Special Circumstances:*** Drug or drug combinations in this category can be considered for use when intolerance or resistance prohibits use of other drugs with fewer toxicity concerns or in women who have comorbidities or require concomitant medications that may limit drug choice, such as active tuberculosis requiring rifampin therapy.
- ***Not Recommended:*** Drugs and drug combinations listed in this category are not recommended for therapy in pregnant women because of inferior virologic response, potentially serious maternal or fetal safety concerns, or pharmacologic antagonism.
- ***Insufficient Data to Recommend:*** The drugs and drug combinations in this category are approved for use in adults but lack pregnancy-specific PK or safety data or such data are too limited to make a recommendation for use in pregnancy.

In pregnancy, a combination ARV regimen with at least three agents is recommended for either treatment or prophylaxis. Recommendations for choice of ARV drug regimen during pregnancy must be individualized according to a pregnant woman's specific ARV history and the presence of comorbidities. Some women may become pregnant and present for obstetrical care while receiving ART for their own health. In these cases, the choice of active drugs with known safety data in pregnancy may be more limited. In general, women who are already on a fully suppressive regimen should continue their regimens (see HIV-Infected Pregnant Women Who Are Currently Receiving Antiretroviral Therapy).

Other HIV-infected women may not be receiving ART at the time they present for obstetrical care. Some women have never received ARV drugs, and others may have taken ARV drugs for treatment that was stopped, for prophylaxis to prevent perinatal transmission of HIV in prior pregnancies, or for pre- or post-exposure prophylaxis. The following sections provide detailed discussions of recommendations based on maternal ARV history and whether there are maternal indications for therapy.

For ARV-naive women, a combination regimen including two NRTIs and either an NNRTI or a PI (generally with low-dose ritonavir) would be preferred.

The preferred NRTI combination for ARV-naive pregnant women is zidovudine/lamivudine, based on efficacy studies in preventing perinatal transmission (see Lessons from Clinical Trials of Antiretroviral Interventions to Reduce Perinatal HIV Transmission) and extensive experience with safe use in pregnancy. Alternate regimens can be used in women who are intolerant of zidovudine because of toxicity such as severe anemia or who have known resistance to the drug.

Tenofovir is a preferred NRTI for non-pregnant women. Data from the Antiretroviral Pregnancy Registry on 1,219 pregnancies with first-trimester exposure to the drug have shown no increase in overall birth defects compared with the general population.[25] Animal studies, however, have shown decreased fetal growth and reduction in fetal bone porosity, and some studies in infected children on chronic tenofovir-based therapy have shown bone demineralization in some children. Therefore, tenofovir would be considered an alternative NRTI during pregnancy for ARV-naive women. For pregnant women with chronic HBV infection, however, tenofovir in combination with emtricitabine or lamivudine would be the preferred NRTI backbone in a combination ARV regimen. The combination of stavudine/didanosine should not be used in pregnant women because fatal cases of lactic acidosis and hepatic failure have been reported in women who received this combination throughout pregnancy.

In addition to the two NRTIs, either an NNRTI or a PI would be preferred for combination regimens in ARV-naive pregnant women. Efavirenz, the preferred NNRTI for non-pregnant adults, is not recommended for initiation in ARV-naive women in the first trimester because of concerns related to teratogenicity (see

Teratogenicity). Non-pregnant women of childbearing potential should undergo pregnancy testing before initiation of EFV and counseling about the potential risk to the fetus and desirability of avoiding pregnancy while on EFV-containing regimens. Alternate ARV regimens that do not include EFV should be strongly considered in women who 1) are planning to become pregnant or 2) are sexually active and not using effective contraception, assuming these alternative regimens are acceptable to the provider and are not thought to compromise the health of the woman. Because the risk of neural tube defects is restricted to the first 5–6 weeks of pregnancy and pregnancy is rarely recognized before 4–6 weeks of pregnancy, and unnecessary ARV drug changes during pregnancy may be associated with loss of viral control and increased risk of perinatal transmission, EFV may be continued in pregnant women receiving an EFV-based regimen who present for antenatal care in the first trimester, provided there is virologic suppression on the regimen (see HIV-Infected Pregnant Women Who are Currently Receiving Antiretroviral Treatment). Initiation of efavirenz can be considered after the first trimester, based on clinical indication, but current data are limited in defining the safety of this use. Nevirapine would be the preferred NNRTI for ARV-naive pregnant women with CD4-cell counts <250 cells/mm^3, and it can be continued in ARV-experienced women already receiving a nevirapine-based regimen, regardless of CD4-cell count. In general, nevirapine should not be initiated in treatment-naive women with CD4-cell counts >250 cells/mm^3 because of an increased risk of symptomatic and potentially fatal rash and hepatic toxicity (see Special Considerations Regarding the Use of Antiretroviral Drugs by HIV-Infected Pregnant Women and their Infants). Elevated transaminase levels at baseline also may increase the risk of nevirapine toxicity.[73] Safety and PK data on etravirine and rilpivirine in pregnancy are insufficient to recommend use of these NNRTI drugs in ARV-naive women.

Lopinavir/ritonavir and atazanavir with low-dose ritonavir boosting are the preferred PI drugs for use in ARV-naive pregnant women, based on efficacy studies in adults and experience with use in pregnancy (see Table 5 for dosing considerations). Alternative PIs include ritonavir-boosted saquinavir or darunavir, although experience is more limited with these regimens in pregnancy.[59, 74, 75] Nelfinavir can be considered in special circumstances when used solely for prophylaxis of perinatal transmission in ARV-naive women for whom therapy would not otherwise be indicated and who cannot tolerate alternative agents. PK data and extensive clinical experience do exist for nelfinavir in pregnancy, but the rate of viral response to nelfinavir-based regimens was lower than lopinavir/ritonavir or efavirenz-based regimens in clinical trials of initial therapy in non-pregnant adults. Indinavir also can be considered in special circumstances for women in whom preferred or alternative drugs cannot be used. Indinavir may be associated with renal stones and has a higher pill burden than many other PI drugs. Data on use in pregnancy are too limited to recommend routine use of fosamprenavir and tipranavir in pregnant women, although they can be considered for women who are intolerant of other agents.

Safety and PK data in pregnancy are insufficient to recommend use of the entry inhibitors enfuvirtide and maraviroc in ARV-naive women during pregnancy. Use of these agents can be considered for women who have failed therapy with several other classes of ARV drugs after consultation with HIV and obstetric specialists.

Data on the integrase inhibitor raltegravir during pregnancy are limited but increasing; ART regimens including raltegravir can be considered for use in pregnancy in special circumstances when preferred and alternative agents cannot be used.[71, 72, 74, 76, 77]

Although data are insufficient to support or refute the teratogenic risk of ARV drugs when administered during the first trimester, information to date does not support major teratogenic effects for the majority of such agents. (For further data, see www.APRegistry.com.) However, certain drugs are of more concern than others—for example, efavirenz should be avoided during the first trimester when possible (see Supplement: Safety and Toxicity of Individual Antiretroviral Drugs in Pregnancy).

Table 5 provides recommendations for use of specific ARV drugs in pregnancy and data on PK and toxicity in pregnancy. Table 6 summarizes management recommendations for the mothers and infants in a variety of clinical scenarios.

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

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

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

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

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

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

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

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

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

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

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

References

1. Kaplan JE, Benson C, Holmes KH, et al. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR Recomm Rep*. Apr 10 2009;58(RR-4):1-207; quiz CE201-204. Available at http://www.ncbi.nlm.nih.gov/pubmed/19357635.
2. Centers for Disease Control and Prevention C. Guidelines for vaccinating pregnant women, Available at: http://www.cdc.gov/vaccines/pubs/downloads/b_preg_guide.pdf. 2007; Atlanta, GA.

3. Centers for Disease Control and Prevention. Updated recommendations for use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine (Tdap) in pregnant women and persons who have or anticipate having close contact with an infant aged <12 months --- Advisory Committee on Immunization Practices (ACIP), 2011. *MMWR Morb Mortal Wkly Rep*. Oct 21 2011;60(41):1424-1426. Available at http://www.ncbi.nlm.nih.gov/pubmed/22012116.

4. Cooper ER, Charurat M, Mofenson L, et al. Combination antiretroviral strategies for the treatment of pregnant HIV-1-infected women and prevention of perinatal HIV-1 transmission. *J Acquir Immune Defic Syndr*. Apr 15 2002;29(5):484-494. Available at http://www.ncbi.nlm.nih.gov/pubmed/11981365.

5. Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med*. Aug 11 2011;365(6):493-505. Available at http://www.ncbi.nlm.nih.gov/pubmed/21767103.

6. Hirt D, Urien S, Rey E, et al. Population pharmacokinetics of emtricitabine in human immunodeficiency virus type 1-infected pregnant women and their neonates. *Antimicrob Agents Chemother*. Mar 2009;53(3):1067-1073. Available at http://www.ncbi.nlm.nih.gov/pubmed/19104016.

7. Hirt D, Urien S, Ekouevi DK, et al. Population pharmacokinetics of tenofovir in HIV-1-infected pregnant women and their neonates (ANRS 12109). *Clin Pharmacol Ther*. Feb 2009;85(2):182-189. Available at http://www.ncbi.nlm.nih.gov/pubmed/18987623.

8. Moodley D, Pillay K, Naidoo K, et al. Pharmacokinetics of zidovudine and lamivudine in neonates following coadministration of oral doses every 12 hours. *J Clin Pharmacol*. Jul 2001;41(7):732-741. Available at http://www.ncbi.nlm.nih.gov/pubmed/11452705.

9. Wade NA, Unadkat JD, Huang S, et al. Pharmacokinetics and safety of stavudine in HIV-infected pregnant women and their infants: Pediatric AIDS Clinical Trials Group protocol 332. *J Infect Dis*. Dec 15 2004;190(12):2167-2174. Available at http://www.ncbi.nlm.nih.gov/pubmed/15551216.

10. Watts DH, Lu M, Thompson B, et al. Treatment interruption after pregnancy: effects on disease progression and laboratory findings. *Infect Dis Obstet Gynecol*. 2009;2009:456717. Available at http://www.ncbi.nlm.nih.gov/pubmed/19893751.

11. Palacios R, Senise J, Vaz M, Diaz R, Castelo A. Short-term antiretroviral therapy to prevent mother-to-child transmission is safe and results in a sustained increase in CD4 T-cell counts in HIV-1-infected mothers. *HIV Med*. Mar 2009;10(3):157-162. Available at http://www.ncbi.nlm.nih.gov/pubmed/19245537.

12. Tai JH, Udoji MA, Barkanic G, et al. Pregnancy and HIV disease progression during the era of highly active antiretroviral therapy. *J Infect Dis*. Oct 1 2007;196(7):1044-1052. Available at http://www.ncbi.nlm.nih.gov/pubmed/17763327.

13. When To Start Consortium, Sterne JA, May M, et al. Timing of initiation of antiretroviral therapy in AIDS-free HIV-1-infected patients: a collaborative analysis of 18 HIV cohort studies. *Lancet*. Apr 18 2009;373(9672):1352-1363. Available at http://www.ncbi.nlm.nih.gov/pubmed/19361855.

14. Kitahata MM, Gange SJ, Abraham AG, et al. Effect of early versus deferred antiretroviral therapy for HIV on survival. *N Engl J Med*. Apr 30 2009;360(18):1815-1826. Available at http://www.ncbi.nlm.nih.gov/pubmed/19339714.

15. Mellins CA, Chu C, Malee K, et al. Adherence to antiretroviral treatment among pregnant and postpartum HIV-infected women. *AIDS Care*. Sep 2008;20(8):958-968. Available at http://www.ncbi.nlm.nih.gov/pubmed/18608073.

16. Fox Z, Phillips A, Cohen C, et al. Viral resuppression and detection of drug resistance following interruption of a suppressive non-nucleoside reverse transcriptase inhibitor-based regimen. *AIDS*. Nov 12 2008;22(17):2279-2289. Available at http://www.ncbi.nlm.nih.gov/pubmed/18981767.

17. Burns DN, Landesman S, Muenz LR, et al. Cigarette smoking, premature rupture of membranes and vertical transmission of HIV-1 among women with low CD4+ levels. *J Acquir Immune Defic Syndr Hum Retrovirol*. 1994;7(7):718-726. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7911527&dopt=Abstract.

18. Turner BJ, Hauck WW, Fanning TR, Markson LE. Cigarette smoking and maternal-child HIV transmission. *J Acquir Immune Defic Syndr Hum Retrovirol*. Apr 1 1997;14(4):327-337. Available at http://www.ncbi.nlm.nih.gov/pubmed/9111474.

19. Rodriguez EM, Mofenson LM, Chang BH, et al. Association of maternal drug use during pregnancy with maternal HIV culture positivity and perinatal HIV transmission. *AIDS*. 1996;10(3):273-282. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8882667&dopt=Abstract.

20. Bulterys M, Landesman S, Burns DN, et al. Sexual behavior and injection drug use during pregnancy and vertical transmission of HIV-1. *J Acquir Immune Defic Syndr Human Retrovirol*. 1997;15(1):76-82. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9215658&dopt=Abstract.

21. Matheson PB, Thomas PA, Abrams EJ, et al. Heterosexual behavior during pregnancy and perinatal transmission of HIV-1. New York City Perinatal HIV Transmission Collaborative Study Group. *AIDS*. Sep 1996;10(11):1249-1256. Available at http://www.ncbi.nlm.nih.gov/pubmed/8883587.

22. Branson BM, Handsfield HH, Lampe MA, et al. Revised recommendations for HIV testing of adults, adolescents, and pregnant women in health-care settings. *MMWR Recomm Rep*. Sep 22 2006;55(RR-14):1-17; quiz CE11-14. Available at http://www.ncbi.nlm.nih.gov/pubmed/16988643.

23. Gaur AH, Freimanis-Hance L, Dominguez K, et al. Knowledge and practice of prechewing/prewarming food by HIV-infected women. *Pediatrics*. May 2011;127(5):e1206-1211. Available at http://www.ncbi.nlm.nih.gov/pubmed/21482608.

24. Moodley J, Moodley D, Pillay K, et al. Pharmacokinetics and antiretroviral activity of lamivudine alone or when coadministered with zidovudine in human immunodeficiency virus type 1-infected pregnant women and their offspring. *J Infect Dis*. Nov 1998;178(5):1327-1333. Available at http://www.ncbi.nlm.nih.gov/pubmed/9780252.

25. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral pregnancy registry international interim report for 1 Jan 1989 - 31 January 2012. Wilmington, NC: Registry Coordinating Center; 2012. Available at http://www.APRegistry.com.

26. O'Sullivan MJ, Boyer PJ, Scott GB, et al. The pharmacokinetics and safety of zidovudine in the third trimester of pregnancy for women infected with human immunodeficiency virus and their infants: phase I acquired immunodeficiency syndrome clinical trials group study (protocol 082). Zidovudine Collaborative Working Group. *Am J Obstet Gynecol*. 1993;168(5):1510-1516. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=8098905.

27. Best BM, Mirochnick M, Capparelli EV, et al. Impact of pregnancy on abacavir pharmacokinetics. *AIDS*. Feb 28 2006;20(4):553-560. Available at http://www.ncbi.nlm.nih.gov/pubmed/16470119.

28. Mallal S, Phillips E, Carosi G, et al. HLA-B*5701 screening for hypersensitivity to abacavir. *N Engl J Med*. Feb 7 2008;358(6):568-579. Available at http://www.ncbi.nlm.nih.gov/pubmed/18256392.

29. Saag M, Balu R, Phillips E, et al. High sensitivity of human leukocyte antigen-b*5701 as a marker for immunologically confirmed abacavir hypersensitivity in white and black patients. *Clin Infect Dis*. Apr 1 2008;46(7):1111-1118. Available at http://www.ncbi.nlm.nih.gov/pubmed/18444831.

30. Best BM, Stek AM, Mirochnick M, et al. Lopinavir tablet pharmacokinetics with an increased dose during pregnancy. *J Acquir Immune Defic Syndr*. Aug 2010;54(4):381-388. Available at http://www.ncbi.nlm.nih.gov/pubmed/20632458.

31. Burchett SK, Best B, Mirochnick M, et al. Tenofovir pharmacokinetics during pregnancy, at delivery and postpartum. Paper presented at: 14th Conference on Retroviruses and Opportunistic Infections (CROI); February 25-28, 2007; Los Angeles, CA. Abstract 738b.

32. Mirochnick M, Best BM, Stek AM, et al. Atazanavir pharmacokinetics with and without tenofovir during pregnancy. *J Acquir Immune Defic Syndr*. Apr 15 2011;56(5):412-419. Available at http://www.ncbi.nlm.nih.gov/pubmed/21283017.

33. Mirochnick M, Kunwenda N, Joao E, et al. Tenofovir disoproxil fumarate (TDF) pharmacokinetics (PK) with increased doses in HIV-1 infected pregnant women and their newborns (HPTN 057). Paper presented at: 11th International

Workshop on Clinical Pharmacology of HIV Therapy; April 7-9, 2010; Sorrento, Italy. Abstract 3.

34. Flynn PM, Mirochnick M, Shapiro DE, et al. Pharmacokinetics and safety of single-dose tenofovir disoproxil fumarate and emtricitabine in HIV-1-infected pregnant women and their infants. *Antimicrob Agents Chemother*. Dec 2011;55(12):5914-5922. Available at http://www.ncbi.nlm.nih.gov/pubmed/21896911.

35. Mirochnick M, Kafulafula G, et al. The pharmacokinetics (PK) of tenofovir disoproxil fumarate (TDF) after administration to HIV-1 infected pregnant women and their newborns. Paper presented at: 16th Conference on Retroviruses and Opportunistic Infections (CROI); February 8-11, 2009; Montreal, Canada. Abstract 940.

36. Tarantal AF, Castillo A, Ekert JE, Bischofberger N, Martin RB. Fetal and maternal outcome after administration of tenofovir to gravid rhesus monkeys (Macaca mulatta). *J Acquir Immune Defic Syndr*. Mar 1 2002;29(3):207-220. Available at http://www.ncbi.nlm.nih.gov/pubmed/11873070.

37. Gafni RI, Hazra R, Reynolds JC, et al. Tenofovir disoproxil fumarate and an optimized background regimen of antiretroviral agents as salvage therapy: impact on bone mineral density in HIV-infected children. *Pediatrics*. Sep 2006;118(3):e711-718. Available at http://www.ncbi.nlm.nih.gov/pubmed/16923923.

38. Schooley RT, Ruane P, Myers RA, et al. Tenofovir DF in antiretroviral-experienced patients: results from a 48-week, randomized, double-blind study. *AIDS*. Jun 14 2002;16(9):1257-1263. Available at http://www.ncbi.nlm.nih.gov/pubmed/12045491.

39. Wang Y, Livingston E, Patil S, et al. Pharmacokinetics of didanosine in antepartum and postpartum human immunodeficiency virus—infected pregnant women and their neonates: an AIDS clinical trials group study. *J Infect Dis*. 1999;180(5):1536-1541. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=10515813.

40. Bristol-Myers Squibb Company. Healthcare provider important drug warning letter. January 5, 2001. Available at http://www.bms.com.

41. Sarner L, Fakoya A. Acute onset lactic acidosis and pancreatitis in the third trimester of pregnancy in HIV-1 positive women taking antiretroviral medication. *Sex Transm Infect*. Feb 2002;78(1):58-59. Available at http://www.ncbi.nlm.nih.gov/pubmed/11872862.

42. Capparelli EV, Aweeka F, Hitti J, et al. Chronic administration of nevirapine during pregnancy: impact of pregnancy on pharmacokinetics. *HIV Med*. Apr 2008;9(4):214-220. Available at http://www.ncbi.nlm.nih.gov/pubmed/18366444.

43. Aweeka F, Lizak P, Frenkel L, et al. Steady state nevirapine pharmacokinetics during 2nd and 3rd trimester pregnancy and postpartum: PACTG 1022. Paper presented at: 11th Conference on Retroviruses and Opportunistic Infections (CROI); February 8-11, 2004; San Francisco, CA. Abstract 932.

44. Mirochnick M, Siminski S, Fenton T, Lugo M, Sullivan JL. Nevirapine pharmacokinetics in pregnant women and in their infants after in utero exposure. *Pediatr Infect Dis J*. Aug 2001;20(8):803-805. Available at http://www.ncbi.nlm.nih.gov/pubmed/11734746.

45. Baylor MS, Johann-Liang R. Hepatotoxicity associated with nevirapine use. *J Acquir Immune Defic Syndr*. 2004;35(5):538-539. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15021321.

46. Dieterich DT, Robinson PA, Love J, Stern JO. Drug-induced liver injury associated with the use of nonnucleoside reverse-transcriptase inhibitors. *Clin Infect Dis*. 2004;38 (Suppl 2):S80-89. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14986279.

47. Cressey TR, Stek A, Capparelli E, et al. Efavirenz pharmacokinetics during the third trimester of pregnancy and postpartum. *J Acquir Immune Defic Syndr*. 2012 Mar 1;59(3):245-52. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22083071.

48. De Santis M, Carducci B, De Santis L, Cavaliere AF, Straface G. Periconceptional exposure to efavirenz and neural tube defects. *Arch Intern Med*. Feb 11 2002;162(3):355. Available at http://www.ncbi.nlm.nih.gov/pubmed/11822930.

49. Fundaro C, Genovese O, Rendeli C, Tamburrini E, Salvaggio E. Myelomeningocele in a child with intrauterine exposure to efavirenz. *AIDS*. Jan 25 2002;16(2):299-300. Available at http://www.ncbi.nlm.nih.gov/pubmed/11807320.

50. Izurieta P, Kakuda TN, Feys C, Witek J. Safety and pharmacokinetics of etravirine in pregnant HIV-1-infected women. *HIV Med*. Apr 2011;12(4):257-258. Available at http://www.ncbi.nlm.nih.gov/pubmed/21371239.

51. Ripamonti D, Cattaneo D, Maggiolo F, et al. Atazanavir plus low-dose ritonavir in pregnancy: pharmacokinetics and placental transfer. *AIDS*. Nov 30 2007;21(18):2409-2415. Available at http://www.ncbi.nlm.nih.gov/pubmed/18025877.

52. Conradie F, Zorrilla C, Josipovic D, et al. Safety and exposure of once-daily ritonavir-boosted atazanavir in HIV-infected pregnant women. *HIV Med*. 2011 Oct;12(9):570-9. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21569187.

53. Mirochnick M, Stek A, Capparelli EV, et al. Pharmacokinetics of increased dose atazanavir with and without tenofovir during pregnancy. Paper presented at: 12th International Workshop on Clinical Pharmacology of HIV Therapy; April 13-16, 2011; Miami, FL.

54. Natha M, Hay P, Taylor G, et al. Atazanavir use in pregnancy: a report of 33 cases. Paper presented at: 14th Conference on Retoviruses and Opportunistic Infections (CROI); February 25-28, 2007; Los Angeles, CA. Abstract 750.

55. Cressey TR, Jourdain G, Rawangban B, et al. Pharmacokinetics and virologic response of zidovudine/lopinavir/ritonavir initiated during the third trimester of pregnancy. *AIDS*. Sep 10 2010;24(14):2193-2200. Available at http://www.ncbi.nlm.nih.gov/pubmed/20625263.

56. Stek AM, Mirochnick M, Capparelli E, et al. Reduced lopinavir exposure during pregnancy. *AIDS*. Oct 3 2006;20(15):1931-1939. Available at http://www.ncbi.nlm.nih.gov/pubmed/16988514.

57. Lambert JS, Else LJ, Jackson V, et al. Therapeutic drug monitoring of lopinavir/ritonavir in pregnancy. *HIV Med*. Mar 2011;12(3):166-173. Available at http://www.ncbi.nlm.nih.gov/pubmed/20726906.

58. Scott GB, Rodman JH, Scott WA, et al. for the PACTG 354 Protocol Team. Pharmacokinetic and virologic response to ritonavir (RTV) in combination with zidovudine (XDV) and lamivudine (3TC) in HIV-1 infected pregnant women and their infants. Paper presented at: 9th Conference on Retroviruses and Opportunistic Infections (CROI); February 24-28, 2002; Seattle, WA. Abstract 794-W. Available at http://www.retroconference.org/2002/.

59. Capparelli EV, Best BM, Stek A, et al. Pharmacokinetics of darunavir once or twice daily during pregnancy and postpartum. Paper presented at: 3rd International Workshop on HIV Pediatrics; July 15-16, 2011; Rome, Italy.

60. van der Lugt J, Colbers A, Molto J, et al. The pharmacokinetics, safety and efficacy of boosted saquinavir tablets in HIV type-1-infected pregnant women. *Antivir Ther*. 2009;14(3):443-50. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19474478.

61. Unadkat JD, Wara DW, Hughes MD, et al. Pharmacokinetics and safety of indinavir in human immunodeficiency virus-infected pregnant women. *Antimicrob Agents Chemother*. Feb 2007;51(2):783-786. Available at http://www.ncbi.nlm.nih.gov/pubmed/17158945.

62. Hayashi S, Beckerman K, Homma M, Kosel BW, Aweeka FT. Pharmacokinetics of indinavir in HIV-positive pregnant women. *AIDS*. May 26 2000;14(8):1061-1062. Available at http://www.ncbi.nlm.nih.gov/pubmed/10853990.

63. Ghosn J, De Montgolfier I, Cornelie C, et al. Antiretroviral therapy with a twice-daily regimen containing 400 milligrams of indinavir and 100 milligrams of ritonavir in human immunodeficiency virus type 1-infected women during pregnancy. *Antimicrob Agents Chemother*. Apr 2008;52(4):1542-1544. Available at http://www.ncbi.nlm.nih.gov/pubmed/18250187.

64. Bryson YJ, Mirochnick M, Stek A, et al. Pharmacokinetics and safety of nelfinavir when used in combination with zidovudine and lamivudine in HIV-infected pregnant women: Pediatric AIDS Clinical Trials Group (PACTG) Protocol 353. *HIV Clin Trials*. Mar-Apr 2008;9(2):115-125. Available at http://www.ncbi.nlm.nih.gov/pubmed/18474496.

65. Villani P, Floridia M, Pirillo MF, et al. Pharmacokinetics of nelfinavir in HIV-1-infected pregnant and nonpregnant women. *Br J Clin Pharmacol*. Sep 2006;62(3):309-315. Available at http://www.ncbi.nlm.nih.gov/pubmed/16934047.

66. Read JS, Best BM, Stek AM, et al. Pharmacokinetics of new 625 mg nelfinavir formulation during pregnancy and postpartum. *HIV Med*. Nov 2008;9(10):875-882. Available at http://www.ncbi.nlm.nih.gov/pubmed/18795962.

67. Capparelli EV, Stek A, Best B, et al. Boosted fosamprenavir pharmacokinetics during Pregnancy. Paper presented at: 17th Conference on Retroviruses and Opportunistic Infections (CROI); February 16-19, 2010; San Francisco, CA. Abstract 908.

68. Weizsaecker K, Kurowski M, Hoffmeister B, Schurmann D, Feiterna-Sperling C. Pharmacokinetic profile in late pregnancy and cord blood concentration of tipranavir and enfuvirtide. *Int J STD AIDS*. May 2011;22(5):294-295. Available at http://www.ncbi.nlm.nih.gov/pubmed/21571982.

69. Brennan-Benson P, Pakianathan M, Rice P, et al. Enfurvitide prevents vertical transmission of multidrug-resistant HIV-1 in pregnancy but does not cross the placenta. *AIDS*. Jan 9 2006;20(2):297-299. Available at http://www.ncbi.nlm.nih.gov/pubmed/16511429.

70. Meyohas MC, Lacombe K, Carbonne B, Morand-Joubert L, Girard PM. Enfuvirtide prescription at the end of pregnancy to a multi-treated HIV-infected woman with virological breakthrough. *AIDS*. Sep 24 2004;18(14):1966-1968. Available at http://www.ncbi.nlm.nih.gov/pubmed/15353987.

71. Best BM, Capparelli EV, Stek A, et al. Raltegravir pharmacokinetics during pregnancy. Paper presented at: 50th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); September 12-15, 2010; Boston, MA.

72. McKeown DA, Rosenvinge M, Donaghy S, et al. High neonatal concentrations of raltegravir following transplacental transfer in HIV-1 positive pregnant women. *AIDS*. Sep 24 2010;24(15):2416-2418. Available at http://www.ncbi.nlm.nih.gov/pubmed/20827058.

73. Peters PJ, Stringer J, McConnell MS, et al. Nevirapine-associated hepatotoxicity was not predicted by CD4 count ≥250 cells/muL among women in Zambia, Thailand and Kenya. *HIV Med*. Nov 2010;11(10):650-660. Available at http://www.ncbi.nlm.nih.gov/pubmed/20659176.

74. Jaworsky D, Thompson C, Yudin MH, et al. Use of newer antiretroviral agents, darunavir and etravirine with or without raltegravir, in pregnancy: a report of two cases. *Antivir Ther*. 2010;15(4):677-680. Available at http://www.ncbi.nlm.nih.gov/pubmed/20587860.

75. Ivanovic J, Bellagamba R, Nicastri E, et al. Use of darunavir/ritonavir once daily in treatment-naive pregnant woman: pharmacokinetics, compartmental exposure, efficacy and safety. *AIDS*. Apr 24 2010;24(7):1083-1084. Available at http://www.ncbi.nlm.nih.gov/pubmed/20386380.

76. Taylor N, Touzeau V, Geit M, et al. Raltegravir in pregnancy: a case series presentation. *Int J STD AIDS*. Jun 2011;22(6):358-360. Available at http://www.ncbi.nlm.nih.gov/pubmed/21680678.

77. Pinnetti C, Baroncelli S, Villani P, et al. Rapid HIV-RNA decline following addition of raltegravir and tenofovir to ongoing highly active antiretroviral therapy in a woman presenting with high-level HIV viraemia at week 38 of pregnancy. *J Antimicrob Chemother*. Sep 2010;65(9):2050-2052. Available at http://www.ncbi.nlm.nih.gov/pubmed/20630894.