



Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States

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Recommendations for Use of Antiretroviral Drugs during Pregnancy (Last updated August 6, 2015; last reviewed August 6, 2015)

Panel's Recommendations

- In general, the same regimens as recommended for treatment of non-pregnant adults should be used in pregnant women unless there are known adverse effects for women, fetuses, or infants that outweigh benefits (**All**).
- Multiple factors must be considered when choosing a regimen for a pregnant woman including comorbidities, convenience, adverse effects, drug interactions, resistance testing results, pharmacokinetics, and experience with use in pregnancy (**All**).
- Pharmacokinetic changes in pregnancy may lead to lower plasma levels of drugs and necessitate increased dosages, more frequent dosing, or boosting, especially of protease inhibitors (**All**).

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

Antiretroviral (ARV) drug recommendations for HIV-infected, pregnant women have been based on the concept that drugs of known benefit to women should not be withheld during pregnancy unless there are known adverse effects to the mother, fetus, or infant **and** unless these adverse effects outweigh the benefits to the woman.¹ Pregnancy should not preclude the use of optimal drug regimens. The decision to use any ARV drug during pregnancy should be made by a woman after discussing with her health care provider the known and potential benefits and risks to her and her fetus.

The Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission (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 are particularly important for ensuring adherence and preserving future treatment options. Regimen selection should be individualized and the following factors should be considered:

- Potential teratogenic effects and other short- and long-term adverse effects on fetuses or newborns including preterm birth, mutagenicity, and carcinogenicity,
- Experience with use in pregnancy,
- Potential drug interactions with other medications,
- Results of genotypic resistance testing and prior antiretroviral exposure,
- Pharmacokinetic (PK) changes in pregnancy and degree of placental transfer,
- Potential adverse maternal drug effects that may be exacerbated during pregnancy,
- Comorbidities,
- Ability of patient to adhere to regimen, and
- Convenience.

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

- Data from randomized clinical trials and prospective cohort studies 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 pregnancy; and
- Data from animal teratogenicity studies.

Physiologic changes that occur during pregnancy can affect drug absorption, distribution, biotransformation, and elimination, thereby also affecting requirements for drug dosing and potentially altering the susceptibility of pregnant women to drug toxicity.^{2,3} During pregnancy, gastrointestinal transit time becomes prolonged; body water and fat increase throughout gestation and are accompanied by increases in cardiac output, ventilation, and liver and renal blood flow; plasma protein concentrations decrease; renal sodium reabsorption increases; and changes occur in cellular transporters and drug metabolizing enzymes in the liver and intestine. Placental transport of drugs, compartmentalization of drugs in the embryo/fetus and placenta, biotransformation of drugs by the fetus and placenta, and elimination of drugs by the fetus also can affect drug PK in the pregnant woman.

Currently available data on the PKs and dosing of ARV drugs in pregnancy are summarized in [Table 7](#). In general, the PKs of nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) are similar in pregnant and non-pregnant women (although data on etravirine are limited), whereas protease inhibitor (PI) PKs are more variable, particularly in later pregnancy. Current data suggest that with standard adult dosing, plasma concentrations of nelfinavir and lopinavir/ritonavir, atazanavir, and darunavir are reduced during the second and/or third trimesters (see [Table 7](#)). The need for a dose adjustment depends on the PI, an individual patient's treatment experience, and use (if any) of concomitant medications with potential for drug interactions.⁴⁻¹¹ Raltegravir levels in the third trimester were quite variable but not significantly different than postpartum or historical data in non-pregnant individuals.^{12,13} Data on enfuvirtide, maraviroc, dolutegravir, and elvitegravir in pregnancy are too limited to allow recommendations on dosing.

Although clinical data are more limited on ARV drugs in pregnant women than in non-pregnant individuals, sufficient data exist on which to base recommendations related to drug choice for many of the available ARV drugs. Drugs and drug regimens for pregnant antiretroviral-naïve women are classified as preferred, alternative, insufficient data to recommend use, and not recommended ([Table 6](#)).

Categories of ARV regimens include:

- **Preferred:** Drugs or drug combinations are designated as preferred for use in ARV-naïve pregnant women when clinical trial data in adults have demonstrated optimal efficacy and durability with acceptable toxicity and ease of use; pregnancy-specific PK data are available to guide dosing; and no established association with teratogenic effects or clinically significant adverse outcomes for mothers, fetuses, or newborns have been reported. Drugs in the preferred category may have toxicity concerns based on non-human data that have not been verified or established in humans. Therefore, it is important to read the full discussion of each drug in the Guidelines before administering any of these medications to your patients (also see [Appendix B: Supplement: Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy](#)). For example, efavirenz is now listed in the preferred category, but only with initiation after 8 weeks' gestation because of unresolved questions regarding teratogenicity.
- **Alternative:** Drugs or drug combinations are designated as alternatives for initial therapy in ARV-naïve 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, **tolerability**, formulation, administration, or interaction issues.
- **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 ARV-naïve pregnant women.
- **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 or are not recommended for ARV-naïve populations regardless of pregnancy status.

In pregnant women, as in non-pregnant adults, a combination ARV treatment (cART) regimen with at least three agents is recommended. Recommendations for choice of ARV drug regimen during pregnancy must be individualized according to a pregnant woman's specific ARV history, the results of drug-resistance assays, and the presence of comorbidities. Women receiving cART may become pregnant and present for obstetrical care. 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 cART at the time they present for obstetrical care. Some women have never received ARV drugs in the past and some may have been treated in previous pregnancies. The following sections provide detailed discussions of recommendations based on maternal ARV history and current and previous resistance testing.

For ARV-naïve women, a cART regimen including two NRTIs combined with a PI with low-dose ritonavir or an NNRTI or an integrase inhibitor is preferable ([Table 6](#)).

NRTIs and Pregnancy

Nucleoside reverse transcriptase inhibitor (NRTI) drugs are well-tolerated medications in general. However, NRTIs are known to induce some level of mitochondrial dysfunction because the drugs have varying affinity for mitochondrial gamma DNA polymerase. This affinity can interfere with mitochondrial replication, resulting in mitochondrial DNA (mtDNA) depletion and dysfunction.¹⁴⁻¹⁶ These toxicities may be of particular concern for pregnant women and infants with *in utero* exposure to NRTI drugs, both because the intrauterine environment may affect later disease development in the child (fetal epigenetic programming),^{17,18} and because mitochondria are exclusively inherited from the maternal ovum.¹⁹ The degrees to which these theoretical concerns, and even documented mitochondrial abnormalities, are clinically relevant is not yet known with certainty, but are very likely to be outweighed by the importance of maternal and infant ARV use to prevent perinatal HIV transmission.^{20,21}

Uncommon clinical disorders linked to mitochondrial toxicity include neuropathy, myopathy, cardiomyopathy, pancreatitis, hepatic steatosis, and lactic acidosis. Among these disorders, symptomatic lactic acidosis and hepatic steatosis may have a female preponderance.^{22,23} These syndromes have similarities to two rare but life-threatening syndromes that occur during pregnancy, most often during the third trimester: the hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome, and acute hepatic steatosis (with or without lactic acidosis). The frequency of HELLP syndrome or lactic acidosis and hepatic steatosis in pregnant HIV-infected women receiving NRTI drugs is unknown, but a small number of cases have been reported, including several in which didanosine and stavudine were used in combination during pregnancy. Nonfatal cases of lactic acidosis also have been reported in pregnant women receiving combination didanosine/stavudine.²⁴ Thus, clinicians should not prescribe combination didanosine/stavudine for pregnant (or even non-pregnant) adults (see [Adult and Adolescent ARV Guidelines](#)).

Some studies have reported that NRTI use in pregnant women is associated with depletion of mtDNA in the placenta, albeit without evidence of ultrastructural damage to placental cells; altered maternal and fetal mitochondrial protein synthesis; and reduced levels of fetal mtDNA.^{25,26} However, no adverse clinical outcomes were linked to these findings.

For ARV-naïve pregnant women, abacavir in combination with lamivudine is considered a preferred dual NRTI combination. This combination offers the advantage of once daily dosing and is well tolerated in pregnancy.²⁷ Testing for the HLA-B*5701 allele should be performed and documented as negative before starting abacavir, and women should be educated about symptoms of hypersensitivity reactions.

Tenofovir disoproxil fumarate (tenofovir) with emtricitabine or lamivudine is the NRTI component in some preferred regimens for non-pregnant adults and, based on increased experience with use in pregnancy, once-daily dosing, enhanced activity against hepatitis B, and less frequent toxicity compared to zidovudine/lamivudine, is considered a preferred combination in pregnancy. Although there have been concerns about

bone and growth abnormalities in infants exposed to tenofovir *in utero*, the duration and clinical significance of study findings require further evaluation (see [Tenofovir Disoproxil Fumarate](#)).

Based on efficacy studies in preventing perinatal transmission and extensive experience with safe use in pregnancy, zidovudine/lamivudine also remains a preferred dual NRTI combination for ARV-naive pregnant women.

NNRTIs and Pregnancy

Efavirenz is an alternative NNRTI for non-pregnant adults. Although increasing data on use of efavirenz in pregnancy are reassuring, because of concerns regarding potential teratogenicity, efavirenz^{28,29} is not recommended for initiation in ARV-naive women in the first 8 weeks of pregnancy (see [Teratogenicity and HIV-Infected Pregnant Women Who are Currently Receiving Antiretroviral Treatment](#)).

Efavirenz remains a preferred agent for initial therapy in ARV-naive pregnant women because of extensive experience with use in pregnancy and because of its availability in a once-daily single-pill regimen which can facilitate better adherence. Efavirenz based ARV regimens should be initiated after the first eight weeks of pregnancy with accurate dating parameters. Rilpivirine is part of an alternative regimen for non-pregnant adults with pre-treatment HIV RNA <100,000 copies/mL and CD4 T lymphocyte cell count >200 cells/mm³ and there is sufficient data from use in pregnancy to recommend it similarly as an alternative agent for ARV-naive pregnant women. Nevirapine is not recommended for ARV-naive pregnant women or for non-pregnant adults because of greater potential for adverse events, complex lead-in dosing, and low barrier to resistance. Safety and PK data on etravirine in pregnancy are insufficient to recommend use of these NNRTI drugs in ARV-naive women.

PIs and Pregnancy

Atazanavir/ritonavir and darunavir/ritonavir 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 7](#) for dosing considerations). The alternative PI is lopinavir/ritonavir for which there is extensive clinical experience and PK data in pregnancy, but which requires twice daily dosing in pregnancy and can cause issues with nausea. PK data and extensive clinical experience do exist for nelfinavir in pregnancy, but the rate of virologic response to nelfinavir-based regimens was lower than lopinavir/ritonavir or efavirenz-based regimens in clinical trials of initial therapy in non-pregnant adults. Because of its lower antiviral activity, nelfinavir use is not recommended. Saquinavir is not recommended in ARV-naive pregnant women because it requires a baseline electrocardiogram due to potential PR and QT prolongation, has a high pill burden, and is not recommended for use in initial therapy for non-pregnant adults. Indinavir may be associated with nephrolithiasis and has a higher pill burden than many other PI drugs; therefore, it is also not recommended for use in ARV-naive pregnant women. Both atazanavir and indinavir are associated with increased indirect bilirubin levels, which theoretically may increase the risk of hyperbilirubinemia in neonates although pathologic elevations have not been seen in studies to date.³⁰ In an analysis from PHACS, *in utero* exposure to atazanavir compared to other drugs was associated with risk of late language emergence at 12 months, but that was no longer significant at 24 months.^{31,32} Data on use in pregnancy are too limited to recommend routine use of fosamprenavir and tipranavir/ritonavir in pregnant women, although they can be considered for women who are intolerant of other agents or who require tipranavir/ritonavir because of resistance.

Entry and Fusion Inhibitors and Pregnancy

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.

Integrase Inhibitors and Pregnancy

PK, safety and other data on the use of the integrase inhibitor raltegravir during pregnancy are available and increasing; cART regimens including raltegravir can be considered as preferred regimens in ARV-naive pregnant women as they are for ARV-naive non-pregnancy adults.^{13,33-37} Clinical trial data from non-pregnant adults suggest a more rapid viral decay with the use of raltegravir compared to efavirenz.³⁸ Case series have reported rapid viral decay with the use of raltegravir initiated late in pregnancy to achieve viral suppression and reduce the risk of perinatal HIV transmission, but no comparative data are available in pregnancy.^{33,36,39-42} The rate of viral decay with raltegravir compared to efavirenz in late-presenting pregnant women is currently under investigation.⁴³ A case report of marked elevation of liver transaminases after initiation of raltegravir in late pregnancy, which resolved rapidly after stopping the drug, suggests that monitoring of transaminases may be indicated with use of this strategy.⁴⁴ **There are currently no data on the use of dolutegravir or elvitegravir in pregnancy;** thus these drugs cannot be recommended for ARV-naive pregnant women at this time.

Pharmacologic Boosters

There are currently no data on the use of cobicistat in pregnancy; thus this drug cannot be recommended for ARV-naive pregnant women at this time.

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