



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: Overview (Last updated October 26, 2016; last reviewed October 26, 2016)

Panel's Recommendations

- Multiple factors must be considered when choosing an antiretroviral (ARV) drug regimen for a pregnant woman, including comorbidities, convenience, adverse effects, drug interactions, resistance testing results, pharmacokinetics (PK), and experience with use in pregnancy (AIII).
- In general, the same regimens as recommended for treatment of non-pregnant adults should be used in pregnant women if appropriate drug exposure is achieved in pregnancy, unless there are known adverse effects for women, fetuses, or infants that outweigh benefits (AII).
- In most cases, women who present for obstetric care on fully suppressive ARV regimens should continue their current regimens (AIII).
- PK changes in pregnancy may lead to lower plasma levels of drugs and necessitate increased dosages, more frequent dosing, or boosting, especially of protease inhibitors (AII).

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

This section provides an overview of the key clinical and pharmacokinetic (PK) issues relevant to the selection of specific antiretroviral (ARV) drugs for use in pregnancy. [Specific recommendations for women who have never received ARV drugs \(ARV-naive women\)](#), for [women who are currently receiving ARV drugs](#), and for [women with previous \(but not current\) ARV use](#) are listed in the three sections that follow this overview. [Table 6](#) provides specific information about recommended ARVs when **initiating** ART in treatment-naive pregnant women, and [Table 8](#) provides dosing and PK data.

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** these adverse effects outweigh the benefits to the woman (or unless adequate drug levels are not likely to be attained during pregnancy).¹ Pregnancy should not preclude the use of optimal drug regimens. The decision about which ARV drug to use 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 ARV exposure,
- PK changes in pregnancy,
- Potential adverse maternal drug effects, especially those 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 perinatal transmission of HIV;
- PK (drug exposure) data during the pregnancy;
- Data from animal teratogenicity studies; and
- Antiretroviral Pregnancy Registry (and other post-marketing surveillance) data.²

Categories of ARV regimens include:

- **Preferred:** Drugs or drug combinations are designated as preferred for initiating ART in ARV-naive pregnant women when clinical trial data in adults have demonstrated optimal efficacy and durability with acceptable toxicity and ease of use; pregnancy-specific PK data are available to guide dosing; and no established association with teratogenic effects (from animal and/or human studies) or clinically significant adverse outcomes for mothers, fetuses, or newborns have been reported. Drugs in the preferred category may have toxicity or teratogenicity 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 Perinatal Guidelines before administering any of these medications to your patients (also see [Appendix B: Supplement: Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy](#)).
- **Alternative:** Drugs or drug combinations are designated as alternatives for initial therapy in ARV-naive pregnant women when clinical trial data in adults show efficacy, but 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 initiating ART in ARV-naive pregnant women.
- **Not Recommended:** Drugs and drug combinations listed in this category are not recommended for initial 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-naive populations regardless of pregnancy status. While this section pertains primarily to initiating ARVs, Table 6 also includes information on medications that should be stopped due to toxicity in women who become pregnant.

In pregnant women, as in non-pregnant adults, ART 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 ART may become pregnant and present for obstetric care. In general, women who are already on a fully suppressive regimen should continue their regimens. Key exceptions include medications with high risk for toxicity in pregnancy (didanosine, stavudine, and treatment-dose ritonavir;

see [Table 6](#)). Other HIV-infected women may not be receiving ART 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. [Specific recommendations for each type of patient are described in the following three sections: HIV-Infected Women Who Have Never Received Antiretroviral Drugs \(ARV-naive\); HIV-Infected Pregnant Women Who Are Currently Receiving Antiretroviral Therapy; and HIV-Infected Pregnant Women Who Have Previously Received Antiretroviral Treatment or Prophylaxis but Are Not Currently Receiving Any Antiretroviral Medications.](#)

For ARV-naive women, an ART regimen including two nucleoside reverse transcriptase inhibitors (NRTIs) combined with a [ritonavir-boosted](#) protease inhibitor (PI) or an integrase inhibitor is preferred ([Table 6](#)).

Nucleoside Reverse Transcriptase Inhibitors and Pregnancy

There are two preferred NRTI combinations for use in ARV-naive pregnant women: abacavir in combination with lamivudine, and tenofovir disoproxil fumarate (TDF) in combination with emtricitabine (or with lamivudine).

Abacavir/lamivudine is the NRTI component in some Preferred regimens for non-pregnant adults. It offers the advantage of once-daily dosing and is well tolerated in pregnancy.³ 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.

TDF with emtricitabine or lamivudine is the NRTI component in some Preferred regimens for non-pregnant adults. Based on extensive experience with use in pregnancy, once-daily dosing, enhanced activity against hepatitis B, and less frequent toxicity compared to zidovudine/lamivudine, it is considered a Preferred combination in pregnancy. Although there have been concerns about bone and growth abnormalities in infants exposed to TDF *in utero*, the duration and clinical significance of study findings require further evaluation (see [Tenofovir Disoproxil Fumarate](#)).⁴

Zidovudine/lamivudine is now an Alternative NRTI regimen for ARV-naive women, despite efficacy studies in preventing perinatal transmission and extensive experience with safe use in pregnancy. This is because it requires twice-daily dosing and is associated with higher rates of mild-to-moderate adverse effects, including nausea, headache, and reversible maternal and neonatal anemia and neutropenia.

Women receiving **didanosine** or **stavudine** in pregnancy should be switched to Preferred or Alternative NRTI regimens.

Safety and PK data about the use of **tenofovir alafenamide** in pregnancy are insufficient to recommend initiation of this medication in pregnant women.

Mitochondrial Toxicity with Nucleoside Reverse Transcriptase Inhibitors

NRTIs 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.⁵⁻⁷ [Mitochondrial dysfunction is less common with currently recommended NRTI agents than with older medications \(didanosine, stavudine\).](#) Although several syndromes linked to mitochondrial toxicity have been reported in ARV-exposed infants, their clinical significance remains uncertain, and they are very likely to be outweighed by the importance of maternal and infant ARV use to prevent perinatal HIV transmission.^{8,9} [For pregnant women, uncommon but important clinical disorders linked to mitochondrial toxicity include neuropathy, myopathy, cardiomyopathy, pancreatitis, hepatic steatosis, and lactic acidosis; the latter two may be more common in women than in men.](#)^{10,11} These syndromes have similarities to two 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.¹² Thus, clinicians should not prescribe combination didanosine/stavudine for pregnant (or even non-pregnant) adults, and women becoming pregnant while receiving these medications should switch to safer options (see above) (see [Adult and Adolescent Guidelines](#)).

Non-Nucleoside Reverse Transcriptase Inhibitors and Pregnancy

There are no preferred non-nucleoside reverse transcriptase inhibitors (NNRTIs) for use in ARV-naive pregnant women.

Efavirenz is now an Alternative NNRTI for both pregnant and non-pregnant ARV-naive adults. Although increasing data on use of efavirenz in pregnancy are reassuring with regard to neural tube defects, and it is increasingly used in pregnancy worldwide, it is associated with dizziness, fatigue, vivid dreams and/or nightmares, and increased suicidality risk.^{13,14} Efavirenz remains an Alternative agent for use in pregnancy, and may be suitable for women who desire a once-daily fixed-dose combination regimen and who tolerate efavirenz without adverse effect.

In prior guidelines, efavirenz use was not recommended before 8 weeks' gestational age, because of concerns regarding potential teratogenicity. Although this caution remains in the package insert information, recent large meta-analyses have been reassuring that risks of neural tube defects after first-trimester efavirenz exposure are not greater than those in the general population.¹³⁻¹⁵ Both British and World Health Organization guidelines note that efavirenz can be used throughout pregnancy (see [Teratogenicity](#) and [HIV-Infected Pregnant Women Who Are Currently Receiving Antiretroviral Treatment](#)). Importantly, women who become pregnant on suppressive efavirenz-containing regimens should continue their current regimens.

As for all women, screening for both antenatal and postpartum depression is recommended; because efavirenz may increase risk of depression and suicidality, this is particularly critical for women on efavirenz-containing regimens.¹⁶

Rilpivirine may be used as part of an Alternative regimen for non-pregnant adults with pretreatment HIV RNA <100,000 copies/mL and CD4 T lymphocyte (CD4) cell count >200 cells/mm³. There are sufficient data from use in pregnancy to recommend it as an Alternative agent for ARV-naive pregnant women **who meet these same CD4 and viral load criteria**. **Nevirapine** is not recommended for initial ART in 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. **Etravirine** is not recommended for ARV-naive non-pregnant patients, and safety and PK data on etravirine in pregnancy are insufficient to recommend use of this NNRTI drug in ARV-naive pregnant women.

Protease Inhibitors 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 8](#) for dosing considerations). The Alternative PI is **lopinavir/ritonavir**, for which there are extensive clinical experience and PK data in pregnancy, but which requires twice-daily dosing in pregnancy and frequently causes nausea and diarrhea. PK data and extensive clinical experience 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 for initial ART in pregnancy. **Saquinavir** is not recommended for initial ART 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 initial ART 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.¹⁷ 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 this finding was no longer significant at 24 months.^{18,19} Data on use in pregnancy are too limited to recommend routine use of **fosamprenavir** and **tipranavir/ritonavir** in pregnant women.

Entry and Fusion Inhibitors and Pregnancy

Safety and PK data in pregnancy are insufficient to recommend use of the entry inhibitors **enfuvirtide** and **maraviroc** for initial ART 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

Raltegravir is the Preferred integrase inhibitor for use in ARV-naive pregnant women. PK, safety, and other data on the use of raltegravir during pregnancy are available and increasing; ART regimens including raltegravir can be considered as Preferred regimens in ARV-naive pregnant women as they are for ARV-naive non-pregnant adults.²⁰⁻²⁵ Clinical trial data from non-pregnant adults suggest a more rapid viral decay with the use of raltegravir compared to efavirenz.²⁶ 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.^{20,22,27-32} The rate of viral decay with raltegravir compared to efavirenz in late-presenting pregnant women is currently under investigation.³³ 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.³⁴

There are currently **limited data** on the use of **dolutegravir** or **elvitegravir/cobicistat** in pregnancy; thus these drugs cannot be recommended for initial ART in ARV-naive pregnant women at this time.^{31,35}

Pharmacologic Boosters

There are currently **limited data** on the use of **cobicistat** in pregnancy; thus this drug cannot be recommended for ARV-naive pregnant women at this time. **Low-dose ritonavir** as a pharmacologic booster for other PIs is described above.

Pharmacokinetic Considerations for Antiretrovirals

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.^{36,37} 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 8](#). In general, the PKs of NRTIs and NNRTIs are similar in pregnant and non-pregnant women (although data on etravirine are limited), whereas 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 8](#)). 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.³⁸⁻⁴⁵ Raltegravir levels in the third trimester were quite variable but not significantly different than postpartum or historical data in non-pregnant individuals.^{24,25} Data on enfuvirtide

and maraviroc in pregnancy are too limited to allow recommendations on dosing. Limited data exist about dolutegravir and elvitegravir/cobicistat PK during pregnancy, but available data suggest that levels of both integrase inhibitors are lower in pregnancy compared to the postpartum period.^{46,47}

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 initiating ART in pregnant antiretroviral-naïve women are shown in [Table 6](#).

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