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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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 (AII).
- 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 (All).
- 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 (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

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. Table 6 provides specific information about recommended ARV drugs when initiating antiretroviral therapy (ART) in treatment-naive pregnant women, and Table 9 provides dosing and PK data. Additional 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.

ARV drug recommendations for pregnant women living with HIV 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). 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 Pregnant Women with HIV Infection 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 adult women living with HIV, 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 based on several factors that apply to all pregnant women, as well as factors that will vary for individual patients. Pregnancy-related factors include:

- 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,
- PK changes in pregnancy,
- Potential adverse maternal drug effects, especially those that may be exacerbated during pregnancy,

Individual-level factors include:

- Potential drug interactions with other medications,
- Results of genotypic resistance testing and prior ARV exposure,
• 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 in pregnancy, as well as immunologic and clinical improvement;
• Incidence rates and descriptions of short- and long-term drug toxicity of ARV regimens
• Evidence from clinical studies of risk of maternal toxicity, teratogenicity, adverse pregnancy outcomes, and adverse infant outcomes;
• 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 (APR) (and other post-marketing surveillance) data.

Categories of ARV regimens refer to initial therapy for ARV-naive pregnant women, and include:
• Preferred: Drugs or drug combinations are designated as preferred for initial therapy 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 PK, dosing, tolerability, formulation, administration, or interaction concerns.
• Insufficient Data to Recommend: The drugs and drug combinations in this category are approved for use in ART-naive 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 insufficient drug levels and/or inferior virologic response in pregnancy, potentially serious maternal or fetal safety concerns, or are not recommended for ARV-naive populations regardless of pregnancy status. While this section pertains primarily to initiating ARV drugs, 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, adolescents, and children, 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. 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). 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), and may include medications that may increase risk of viral failure in pregnancy (elvitegravir/cobicistat); see Table 6. Women who are not fully suppressed and currently taking ART should be carefully evaluated for adherence and genotypic resistance, with every effort made to achieve full virologic suppression through adherence interventions or medication changes. Women who have received ARV drugs in the past but are not currently taking ARV drugs will need additional consideration of previous regimens and potential for genotypic resistance. Specific recommendations for each type of patient are described in the following three sections: Women Living with HIV Who Have Never Received Antiretroviral Drugs (ARV-Naive); Pregnant Women Living with HIV Who Are Currently Receiving Antiretroviral Therapy; and Pregnant Women Living with HIV Who Have Previously Received Antiretroviral Treatment or Prophylaxis but Are Not Currently Receiving Any Antiretroviral Medications.

**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. 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. In general, the PKs of NRTIs and non-nucleoside reverse transcriptase inhibitors (NNRTIs) are similar in pregnant and non-pregnant women (although data on etravirine are limited), whereas PI and integrase inhibitor PKs are more variable, particularly in the second and third trimesters of pregnancy. Currently available data on the PKs and dosing of ARV drugs in pregnancy are listed for each drug below, and summarized in Table 9.

**Nucleoside Reverse Transcriptase Inhibitors**

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. 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. Testing for hepatitis B virus (HBV) should be performed; for women living with HIV/HBV coinfection, two NRTIs active against HBV should be chosen (e.g., TDF with emtricitabine or lamivudine), in place of abacavir/lamivudine.

**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 HBV, 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). Although some authors have suggested that zidovudine/lamivudine be used in place of TDF/emtricitabine, this suggestion is based on data from a single study, the PROMISE trial. However, the generalizability of the PROMISE findings is limited by important study design and statistical considerations that limit (for details see the Tenofovir Disoproxil Fumarate and Lopinavir/Ritonavir sections). In consideration of all available evidence, the Panel concluded that the
assessment of expected benefits and harms favored TDF/emtricitabine over zidovudine/lamivudine, leading
the Panel to maintain TDF/emtricitabine designation as a Preferred recommendation and zidovudine/
lamivudine as an Alternative recommendation.

**Zidovudine/lamivudine** is 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 (see Zidovudine Section).

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. 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 infants exposed to ARV drugs, their clinical
significance remains uncertain, and they are very likely to be outweighed by the importance of maternal
and infant ARV drug use to prevent perinatal HIV transmission. For pregnant women, uncommon but
important clinical disorders linked to mitochondrial toxicity include neuropathy, myopathy, cardiomyopathy,
pancreatitis, hepatic steatosis, and lactic acidosis. 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 women with HIV 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. 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).

**Integrase Inhibitors**

**Raltegravir** is a Preferred integrase inhibitor for use in ARV-naive pregnant women, based on PK, safety,
and other data on the use of raltegravir during pregnancy. Clinical trial data from non-pregnant adults
suggest a more rapid viral decay with the use of raltegravir compared to efavirenz. 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. The rate of viral decay with raltegravir compared to efavirenz or lopinavir/ritonavir in late-presenting
pregnant women is currently under investigation. 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. Although a once-daily formulation
of raltegravir is approved for non-pregnant adults, there are insufficient PK data to support its use in
pregnancy; recommended dosing remains twice-daily.

**Dolutegravir** is an Alternative integrase inhibitor for use in ARV-naive pregnant women. This is based on
both PK and safety data, however, these data have been presented in only abstract form and have not yet been

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published at the time of writing. Data from the P1026 study suggest that while dolutegravir levels in the third trimester are lower than in the postpartum period, this is due to higher-than-expected postpartum levels; third-trimester levels were comparable to those observed in non-pregnant adults, and no viral failures occurred.\textsuperscript{37} Published data reported to the APR through January 2017 include anomalies in 2 of 77 (2.6\%) first-trimester and 2 of 56 (3.5\%) second-/third-trimester exposures. Additional data presented at the International AIDS Society meeting (not yet published) include 0 anomalies among 116 first-trimester and 729 second-/third-trimester exposures in Botswana, and anomalies in 3 of 42 (7.1\%) first-trimester and 1 of 38 (2.6\%) second-/third-trimester exposures in a pooled analysis from the EPICC, NEAT-ID, and PANNA cohorts.\textsuperscript{38,39} Including all exposures and outcomes from these 3 reports, the calculated risk would be 2.1\% with first-trimester and 0.4\% with second-/third-trimester exposure. Data from the Botswana cohort also suggest similar risks of adverse pregnancy outcomes (preterm/very preterm delivery, small/very small for gestational age, stillbirth, neonatal death, or combinations of these outcomes) compared to efavirenz-based ART.\textsuperscript{38}

There are currently limited data on the use of \textit{elvitegravir/cobicistat} in pregnancy.\textsuperscript{29,40} Data from the P1026 study suggest that elvitegravir and cobicistat levels in the third trimester were significantly lower than in the postpartum period (below the levels expected to lead to virologic suppression); viral breakthroughs did occur, with only 74\% of women maintaining viral suppression at delivery.\textsuperscript{37} Based on these data, elvitegravir/cobicistat \textbf{is not recommended} for initial use in pregnancy until more data are available. For women who present on elvitegravir/cobicistat, providers should consider switching to more effective, recommended regimens. If an elvitegravir/cobicistat regimen is continued, viral load should be monitored frequently, and therapeutic drug monitoring (TDM) (if available) may be useful.

\textbf{Protease Inhibitors}

\textit{Atazanavir/ritonavir} and \textit{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. Factors impacting the decision between these two medications may include limitations in administering concomitant antacid, H2 blocker, or proton pump inhibitors (atazanavir) and the requirement for twice-daily dosing (darunavir; although a once-daily formulation is approved for non-pregnant adults, there are insufficient PK data to support its use in pregnancy). The Alternative PI is \textit{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. Atazanavir is 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.\textsuperscript{41} In analyses from the PHACS SMARTT study, \textit{in utero} exposure to atazanavir compared to other drugs was associated with statistically significant but small reductions in language and social-emotional scores,\textsuperscript{42} and was associated with risk of late language emergence at 12 months that was no longer significant at 24 months.\textsuperscript{43,44} The clinical significance of these findings associated with \textit{in utero} atazanavir exposure is not known. \textit{Nelfinavir}, \textit{saquinavir}, and \textit{indinavir} are not recommended for initial therapy in pregnancy due to concerns about lower efficacy and higher toxicity than preferred or alternative PIs (\textbf{Table 6}). Data on use in pregnancy are too limited to recommend routine use of \textit{fosamprenavir} or \textit{tipranavir/ritonavir} in pregnant women; these medications are also not recommended for use in ART-naive non-pregnant adults. As described below, the use of cobicistat as a pharmacologic booster for darunavir is also not recommended.

Current data suggest that with standard adult dosing, plasma concentrations of lopinavir, atazanavir, and darunavir are reduced during the second and/or third trimesters. Dose adjustment is recommended for lopinavir/ritonavir and may be considered for atazanavir (see \textbf{Table 9}). Specific dosing recommendations depend on the PI, an individual patient’s treatment experience, and use (if any) of concomitant medications with potential for drug interactions.\textsuperscript{45-53} Clinicians may consider TDM in specific situations.

\textbf{Non-Nucleoside Reverse Transcriptase Inhibitors}

There are no preferred NNRTIs for use in ARV-naive pregnant women.
Efavirenz is 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.\textsuperscript{54,55} 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.\textsuperscript{54-56} Both British and World Health Organization guidelines note that efavirenz can be used throughout pregnancy (see Teratogenicity and Pregnant Women Living with HIV Who Are Currently Receiving Antiretroviral Treatment). Importantly, women who become pregnant on suppressive efavirenz-containing regimens should continue their current regimens, as is recommended for most regimens (Table 6).

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/mm$^3$. 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.\textsuperscript{57} 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 because it is not recommended for ARV-naive non-pregnant patients, and because there are insufficient safety and PK data on etravirine in pregnancy.

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.\textsuperscript{58}

Entry and Fusion Inhibitors

Enfuvirtide and maraviroc are not recommended for initial ART in pregnancy because they are not recommended as initial ART in non-pregnant adults and because of the lack of safety and PK data in pregnancy. Use of these agents can be considered for women who have failed therapy with several other classes of ARV drugs; however, because there are insufficient data to inform safety or dosing guidance for their use in pregnancy, their use should only be undertaken after consultation with HIV and obstetric specialists.

Pharmacologic Boosters

There are currently limited data on the use of cobicistat in pregnancy, therefore, this drug cannot be recommended for ARV-naive pregnant women at this time. As noted above, both elvitegravir and cobicistat levels in the P1026 study were significantly lower in the third trimester than in the postpartum period. Low-dose ritonavir as a pharmacologic booster for other PIs, as described above, is currently the preferred pharmacologic booster for initial ART regimens in pregnancy.

References


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