



**Recommendations for the Use of Antiretroviral Drugs in  
Pregnant Women with HIV Infection 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 December 7, 2018; last reviewed December 7, 2018)

### Panel's Recommendations

- Multiple factors must be considered when choosing an antiretroviral (ARV) drug regimen for a pregnant woman. These factors include the adverse effects, drug interactions, pharmacokinetics (PKs), convenience of individual drugs and drug combinations in the regimen, experience with the use of these drugs in pregnancy, and the patient's resistance test results and comorbidities (AIII).
- In general, the same regimens that are recommended for the treatment of nonpregnant adults should be used in pregnant women when sufficient data suggest that appropriate drug exposure is achieved during pregnancy, unless there are known adverse effects for women, fetuses, or infants that outweigh the benefits if these regimens (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, boosting, or more frequent viral load monitoring (AII).

### Interim Panel Recommendations Regarding the Use of Dolutegravir in Pregnancy:<sup>a</sup>

- Dolutegravir **is not recommended** for use in pregnant women **during the first trimester**<sup>b,c</sup> and in **nonpregnant women who are trying to conceive**, due to concerns about a possible increased risk of neural tube defects (NTDs) (AIII).
- Dolutegravir is a preferred integrase strand transfer inhibitor for use in pregnant women after the first trimester;<sup>b</sup> this designation is based on available PK, safety, and efficacy data (AII).
- For pregnant women who are receiving dolutegravir and who present to care during the first trimester,<sup>b,c</sup> provide counseling about the risks and benefits of continuing dolutegravir or switching to another ARV regimen (AIII). The following considerations should be addressed:
  - NTDs may have already occurred;
  - Depending on the current gestational age, the additional risk of NTDs developing during the remaining time in first trimester may be small;
  - There is a background risk of NTDs regardless of antiretroviral treatment (ART) regimen or HIV status (this risk ranges from 0.05% to 0.1% for women without HIV, and women with HIV who are receiving ART that does not include dolutegravir); *and*
  - Changes in ART, even in the first trimester, are often associated with viral rebound that may increase the risk of perinatal HIV transmission.
- When dolutegravir use is continued after delivery, clinicians should recommend the use of postpartum contraception and discuss contraceptive options with patients (AIII).
- For additional information, see subsection below for Interim Guidance about the Use of Dolutegravir in Pregnancy and [Teratogenicity](#).

**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

<sup>a</sup> These are intended to be conservative, interim recommendations and will be revised, if indicated, as additional data become available in 2019.

<sup>b</sup> The first trimester is less than 14 weeks (up to 13 6/7 weeks) gestational age by last menstrual period. The term "12 weeks post-conception," used in the Adult and Adolescent ARV Guidelines, is consistent with the first trimester.

<sup>c</sup> Although dolutegravir is not Food and Drug Administration-approved for use in the first trimester, some Perinatal Panel members would consider using dolutegravir at 12 weeks gestational age by last menstrual period on an individual patient basis.

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. Additional [recommendations for women who have never received antiretroviral therapy \(ART-naïve women\)](#), [women who are currently receiving ART](#), and [women who were previously on ART or who have used ARV drugs for prophylaxis](#) are listed in the three sections that follow this overview. [Table 6](#) provides specific information about recommended ARV drugs when **initiating** ART in treatment-naïve pregnant women. The table also **includes**

considerations regarding ART regimen selection and modification in pregnant women who are treatment-experienced and women who are attempting to become pregnant. Table 10 and Appendix B provide information about individual drugs, including dosing and PK data in pregnancy.

In addition, a new table (Table 7) consolidates situation-specific recommendations about the use of ARV drugs in women with HIV during conception and pregnancy into a single table for ease of reference. Table 7 includes recommendations for the use of ARV drugs in the following situations:

- Initiating ART in pregnant women who have never received ARV drugs;
- Continuing ART in women who become pregnant while on a regimen that has been well tolerated and resulted in virologic suppression;
- Restarting ART in pregnant women who received ART or ARV drugs for prophylaxis in the past;
- Changing to a new ART regimen in pregnant women whose current ART is not well tolerated and/or is not resulting in virologic suppression; *and*
- Initiating or modifying ART in women who are trying to conceive.

ARV drug recommendations for pregnant women living with HIV have been based on the approach 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 adequate drug levels are not likely to be attained during pregnancy.<sup>1</sup> 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 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 the treatment of adult women with HIV, both those who are pregnant and those who are not. 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-term and long-term adverse effects on fetuses or newborns, including preterm birth, mutagenicity, and carcinogenicity;
- Experience with use of the drug in pregnancy;
- PK changes in pregnancy; *and*
- Potential adverse effects for the mother, especially those that may be exacerbated during pregnancy.

Individual-level factors include:

- Potential drug interactions with other medications;
- Results of genotypic resistance testing and the woman's prior exposure to ARV drugs;
- Comorbidities;
- Ability of the patient to adhere to a regimen; *and*
- Convenience.

The Panel uses information from several sources to develop recommendations on specific drugs or regimens for pregnant women. These sources include:

- 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-term 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 pregnancy;
- Data from animal teratogenicity studies; *and*
- Antiretroviral Pregnancy Registry data and other post-marketing surveillance data.<sup>2</sup>

Categories of ARV regimens for use in pregnancy include:

- **Preferred:** Drugs or drug combinations are designated as preferred for therapy 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 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 nonhuman 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 patients (also see [Appendix B: Supplement: Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy](#)).
- **Alternative:** Drugs or drug combinations are designated as alternative options for therapy in pregnant women when clinical trial data in adults show efficacy, **and experience in pregnancy and data on teratogenic effects are generally favorable but limited. Alternative** drugs or regimens are associated with more PK, dosing, tolerability, formulation, administration, or interaction concerns **than those in the preferred category, but they are acceptable for use in pregnancy.**
- **Insufficient Data to Recommend:** The drugs and drug combinations in this category are approved for use in adults, but pregnancy-specific PK or safety data are too limited to make a recommendation for use in pregnant women. **In some cases, it may be appropriate to continue using these drugs or drug combinations in women who become pregnant on ART that has been well tolerated.**
- **Not Recommended Except in Special Circumstances:** **Although some drugs are not recommended for ART initiation in ART-naïve women due to specific safety concerns or very limited safety and efficacy data in pregnancy, there may be circumstances in which ART-experienced women need to initiate or continue using specific drugs to reach or maintain viral suppression.**
- **Not Recommended:** Drugs and drug combinations listed in this category are not recommended for use in pregnancy due to inferior virologic efficacy or potentially serious maternal or fetal safety concerns. They may also be categorized as not recommended for initial therapy in ARV-naïve populations regardless of pregnancy status. **This category includes drugs or drug combinations for which PK data demonstrate low drug levels and risk of viral rebound during pregnancy. Levels of these drugs are often low in late pregnancy (during the second and third trimesters), when risk for perinatal transmission is high if maternal viremia occurs.** In some situations, it may be appropriate to continue using these drugs or drug combinations in women who become pregnant on ART that has been well tolerated and resulted in virologic suppression, though viral load monitoring should be performed more frequently in these instances. See [Pregnant Women Living with HIV Who Are Currently Receiving Antiretroviral Therapy](#) and the section below titled Increased Viral Load Monitoring for Women Receiving Cobicistat-boosted Regimens.

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. In pregnant women (as in nonpregnant adults, adolescents, and children) ART that includes at least three agents is recommended. For ARV-naive women, an ART regimen that includes two nucleoside reverse transcriptase inhibitors (NRTIs) and a ritonavir-boosted protease inhibitor (PI) or an integrase strand transfer inhibitor (INSTI) is preferred ([Table 6](#)). In general, **women who are already on a fully suppressive regimen when pregnancy occurs should continue their regimens**. Key exceptions include regimens that involve medications with a high risk for toxicity or inferior virologic efficacy that are not recommended for use in adults (e.g., didanosine, indinavir, nelfinavir, stavudine, and treatment-dose ritonavir) and drugs that should not be used in pregnant women (see [Table 6](#)). **For women who have achieved virologic suppression and who are receiving** regimens that may increase risk of virologic failure during pregnancy (e.g., darunavir/cobicistat and elvitegravir/cobicistat), **consider changing the ART regimen or continuing the same regimen and increasing the frequency of viral load monitoring**. Women who are not fully suppressed and who are 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 (see [Lack of Viral Suppression](#)). When treating women who have previously received ARV drugs but who are not currently taking ARV drugs, clinicians will need to take previous regimens and potential for genotypic resistance into consideration. Specific recommendations for each type of patient are described in [Table 7](#) and in the following sections: [Pregnant Women Living with HIV Who Have Never Received Antiretroviral Drugs \(Antiretroviral Naive\)](#), [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 Antiretroviral Drugs***

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 virologic failure or drug toxicity.<sup>3-5</sup> 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 PKs in the pregnant woman. In general, the PKs of NRTIs and non-nucleoside reverse transcriptase inhibitors (NNRTIs) are similar in pregnant and nonpregnant women (although PK data for etravirine are limited). PI and INSTI PKs are more variable, particularly during 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 10](#).

### ***Nucleoside Reverse Transcriptase Inhibitors***

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

**Abacavir/lamivudine** is the NRTI component in some preferred regimens for nonpregnant adults. It offers the advantage of once-daily dosing and is well tolerated in pregnancy.<sup>6</sup> 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. **Clinicians should determine whether a patient has hepatitis B virus (HBV)/HIV coinfection**; for women with HIV/HBV coinfection, two NRTIs that are active against HBV should be chosen (e.g., TDF with emtricitabine or lamivudine) in place of abacavir/lamivudine (see [HIV/HBV Coinfection](#)).



**TDF with emtricitabine or lamivudine** is the NRTI component in some preferred regimens for nonpregnant adults. This combination has several advantages, including extensive experience with use in pregnancy, once-daily dosing, enhanced activity against HBV, and less-toxicity than zidovudine/lamivudine. 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](#)).<sup>7</sup> Although some authors have suggested that zidovudine/lamivudine be used in place of TDF/emtricitabine,<sup>8</sup> this suggestion is based on data from a single study, the Promoting Maternal and Infant Survival Everywhere (PROMISE) trial.<sup>9</sup> The generalizability of the PROMISE findings is limited by important study design and statistical considerations (for details, see the [Tenofovir Disoproxil Fumarate](#) and [Lopinavir/Ritonavir](#) sections). After considering all available evidence, the Panel concluded that the assessment of expected benefits and risks favored the use of TDF/emtricitabine over zidovudine/lamivudine. The Panel maintains the preferred classification for TDF/emtricitabine and the alternative classification for zidovudine/lamivudine.

**Zidovudine/lamivudine** is an alternative NRTI regimen for ARV-naïve pregnant women. Despite proven efficacy in preventing perinatal transmission and extensive experience with safe use in pregnancy, this NRTI combination is classified as alternative rather than preferred 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](#)).

Women who are receiving **didanosine or stavudine** in pregnancy should be switched to preferred or alternative medications.

Safety and PK data for the use of **tenofovir alafenamide (TAF)** during pregnancy are insufficient to recommend initiation of this medication in pregnant women. **However, it may be appropriate to continue using TAF in some pregnant women who are virally suppressed. Available PK data for TAF indicate that exposure is adequate in pregnancy, and a change in dosing is not indicated.**<sup>10</sup>

#### *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 depletion and dysfunction.<sup>11-13</sup> 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 the risks associated with these drugs are very likely to be outweighed by the importance of maternal and infant ARV drug use to prevent perinatal HIV transmission.<sup>14,15</sup> For pregnant women, uncommon but important clinical disorders that are linked to mitochondrial toxicity include neuropathy, myopathy, cardiomyopathy, pancreatitis, hepatic steatosis, and lactic acidosis; hepatic steatosis and lactic acidosis may be more common in women than in men.<sup>16,17</sup> 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 who are 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.<sup>18</sup> Thus, clinicians should not prescribe combination didanosine/stavudine for pregnant (or even nonpregnant) adults, and women who become pregnant while receiving these medications should switch to safer options (see above and the [Adult and Adolescent Antiretroviral Guidelines](#)).

#### ***Integrase Strand Transfer Inhibitors***

**Interim Guidance about the Use of Dolutegravir in Pregnancy: Dolutegravir is now a preferred INSTI for pregnant women after the first trimester because it is a recommended option for initial ART regimens**

in adults, and there are sufficient data about the efficacy and safety of dolutegravir when it is initiated during pregnancy. Dolutegravir **is not recommended for use during the first trimester** (less than 14 weeks [up to 13 6/7 weeks] gestational age by last menstrual period) or in women who are trying to conceive, due to concerns about a possible increased risk of neural tube defects (NTDs). Published data on the PKs and safety of dolutegravir when this drug is initiated during pregnancy are available from one large birth surveillance study and one two-hospital retrospective cohort analysis, with other clinical data remaining primarily in abstract form.<sup>19-22</sup> The Panel has developed conservative interim recommendations regarding the use of dolutegravir during **pregnancy** and at **conception** in coordination with the Panel on Antiretroviral Guidelines for Adults and Adolescents with HIV; these recommendations will be revised, if necessary, as new data become available.

**Use of Dolutegravir before Conception or in Early Pregnancy:** In May of 2018, an unplanned interim evaluation of the Botswana birth surveillance data revealed four NTDs among infants born to 426 women (0.94%) who conceived while taking dolutegravir-based ART. These data were updated during a planned analysis that was performed in July of 2018. No new NTDs observed in infants born to women who were taking dolutegravir before conception leading to an updated prevalence of dolutegravir exposure at conception (4 infants born to 596 women [0.67%]) and a revised risk of NTDs (95% CI, 0.26% to 1.7%). This risk is higher than the risk of NTDs observed among infants born to women who received efavirenz-based ART before conception (0.05%) or any preconception ART that did not include dolutegravir (0.12%), and it is higher than the risk in infants born to women without HIV (0.09%). The neural tube closes by 4 weeks post-conception, usually approximately 6 weeks after the last menstrual period. Using these data, and allowing for uncertain pregnancy dating, the Panel conservatively recommends that dolutegravir-based ART **should not be initiated** during the first trimester, and it **should not be initiated** in nonpregnant women who are attempting conception (see [Teratogenicity](#)). However, when women conceive while taking dolutegravir and present in the first trimester, clinicians must consider whether to continue using dolutegravir or whether to switch to another ARV in collaboration with their patients.

**Continuing Dolutegravir in Women who Conceived While Taking Dolutegravir and who Present to Care During the First Trimester:** The neural tube closes by approximately 4 weeks post-conception, or approximately 6 weeks after the last menstrual period in women with regular menses. The early data from Botswana suggest that two of the four observed defects may be defects that can occur during the first trimester but after the neural tube has closed (post-neurulation events). For this reason, the Panel has conservatively recommended that dolutegravir not be initiated during the first trimester of pregnancy (less than 14 weeks [up to 13 6/7 weeks] gestational age by last menstrual period) as an interim recommendation, pending the availability of additional data.

However, women often detect pregnancy earlier and present to care between 6 and 14 weeks of gestational age. In these situations, providers should review the following considerations with their patients:

- NTDs may have already occurred by this time;
- Depending on the current gestational age, the additional risk of an NTD occurring in the time remaining during the first trimester may be small;
- There is a background risk of NTDs regardless of the ART regimen used (this risk ranges from 0.05% to 0.1% for women without HIV and women with HIV who are receiving ART that does not include dolutegravir); *and*
- Changes in ART, even in the first trimester, are often associated with viral rebound, which may increase the risk of perinatal HIV transmission.

A careful consideration of these risks and benefits will allow patients and providers to reach individualized decisions about whether to continue using dolutegravir or whether to switch to a different ART regimen during the first trimester.

If a causal association exists between the use of dolutegravir and the occurrence of NTDs, it remains

unknown what the mechanism of effect may be, whether folic acid is a mediating factor (and thus whether risk would be reduced by folic acid supplementation), and whether a similar risk may exist for other INSTIs. When patients plan to continue using dolutegravir after delivery, clinicians should recommend the use of postpartum contraception and discuss contraceptive options with patients.

**Pregnancy Outcomes Among Patients Who Initiated Dolutegravir in Pregnancy:** An earlier published study from Botswana about outcomes among women who started dolutegravir-based or efavirenz-based ART during pregnancy reported that no birth defects occurred among infants born to 280 women who started dolutegravir during the first trimester (all women initiated at >4 weeks and most initiated at >6 weeks gestational age) and no birth defects occurred among infants born to 729 women who started dolutegravir in the second or third trimesters.<sup>19</sup> These data were updated during a planned analysis in July 2018. One NTD was observed among infants born to 3,104 women who started dolutegravir at any time during pregnancy (0.03%); in this case, dolutegravir was initiated at 8 weeks gestational age.<sup>23</sup>

A multicenter retrospective cohort study of infants born to 66 women (42% of whom began dolutegravir-based ART preconception, 24% of whom initiated dolutegravir-based ART during pregnancy, and 33% of whom switched to dolutegravir-based ART during pregnancy) found two anomalies and no NTDs.<sup>20</sup>

Published data that was reported to the Antiretroviral Pregnancy Registry through January 2018 include reports of anomalies in five of 161 infants (3.1%) who experienced first-trimester exposures to dolutegravir and in two of 94 infants (2.1%) who experienced second-trimester or third-trimester exposures; none of these anomalies were NTDs. Additional data that was presented at the International AIDS Society meeting in 2017 include reports of anomalies in three of 42 infants (7.1%) with first-trimester exposures and an anomaly in one of 38 infants (2.6%) with second-trimester or third-trimester exposures in a pooled analysis from the EPPICC, NEAT-ID, and PANNA cohorts.<sup>21,24</sup> Data from the Botswana cohort also suggest that dolutegravir-based ART and efavirenz-based ART have similar risks of adverse pregnancy outcomes (defined as preterm/very preterm delivery, small/very small for gestational age, stillbirth, neonatal death, or combinations of these outcomes).<sup>19</sup>

#### *Pharmacokinetic Data About INSTIs*

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 nonpregnant adults, and no viral failures occurred.<sup>25</sup>

**Raltegravir** is a preferred INSTI for use in ARV-naive pregnant women, based on PK, safety, and other data on the use of raltegravir during pregnancy.<sup>26-31</sup> Clinical trial data from nonpregnant adults suggest a more rapid viral decay with the use of raltegravir than with efavirenz.<sup>32</sup> Case series have reported rapid viral decay when raltegravir is initiated late in pregnancy to achieve viral suppression.<sup>26,28,33-40</sup> **A pilot study of late-presenting pregnant women in Brazil, found that a greater proportion of women receiving raltegravir reached viral suppression at 2, 4, and 6 weeks compared to women who were receiving lopinavir/ritonavir.**<sup>41</sup> The rate of viral decay in women receiving raltegravir compared to those receiving efavirenz is currently being investigated in a separate study.<sup>41,42</sup> A case study reported a marked elevation of liver transaminases after raltegravir was initiated in late pregnancy. This elevation resolved rapidly after stopping the drug, suggesting that monitoring of transaminases may be indicated when raltegravir is initiated in late pregnancy.<sup>43</sup> Although a once-daily formulation of raltegravir is approved for use in nonpregnant adults, there are insufficient PK data to support its use in pregnancy; twice-daily dosing remains the recommended dosing schedule.

There are currently limited data on the use of **elvitegravir/cobicistat** in pregnancy.<sup>37,44</sup> Data from the P1026 study suggest that coadministration of elvitegravir and cobicistat led to significantly lower drug levels of both medications in the third trimester than in the postpartum period (below the levels that are expected to lead to virologic suppression). Viral breakthroughs did occur, with only 74% of women maintaining viral suppression at delivery.<sup>25</sup> Based on these data, elvitegravir/cobicistat **is not recommended** for use in pregnancy. For women who become pregnant 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. Some providers may monitor **every 1 to 2** months in the second and third trimesters (see Increased Viral Load Monitoring for Women Receiving Cobicistat-boosted Regimens section below and also [Pregnant Women Living with HIV Who Are Currently Receiving Antiretroviral Treatment](#)).

**Bictegravir** is an INSTI that is recommended for initial use in nonpregnant adults. There are no published data on bictegravir PKs or clinical outcomes in pregnancy.

### **Protease Inhibitors**

**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. Factors that impact the decision of which medication to use may include limitations in administering concomitant antacid, H2 blocker, or proton pump inhibitors (**atazanavir**) and the requirement for twice-daily dosing (**darunavir**). Although the use of once-daily dosing of darunavir/ritonavir is approved for nonpregnant adults, there are insufficient PK data to support its use in pregnancy. The alternative PI is **lopinavir/ritonavir**. There is extensive clinical experience and PK data for the use of this combination in pregnancy, but it 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.<sup>45</sup> In analyses from the Pediatric HIV/AIDS Cohort Study (PHACS) Surveillance Monitoring for ART Toxicity (SMARTT) study, *in utero* exposure to atazanavir was associated with statistically significant but small reductions in language and social-emotional scores compared to other drugs.<sup>46</sup> Atazanavir exposure was also associated with risk of late language emergence at 12 months that was no longer significant at 24 months.<sup>47,48</sup> The clinical significance of these findings associated with *in utero* atazanavir exposure is not known.

**Darunavir/cobicistat** and **atazanavir/cobicistat** **are not recommended** for use in pregnancy. PK studies suggest that low levels of both darunavir and cobicistat occur in late pregnancy, and high rates of virologic failure have been observed in late pregnancy among women who were virally suppressed in early pregnancy. Although PK data on atazanavir/cobicistat are not yet available, it is anticipated that the PK changes seen with atazanavir/cobicistat will be similar to those observed with darunavir/cobicistat and elvitegravir/cobicistat. In addition, once-daily dosing of darunavir **is not recommended** in pregnancy. For women who become pregnant on darunavir/cobicistat or atazanavir/cobicistat, providers should consider switching to more effective, recommended regimens. If a darunavir/cobicistat or atazanavir/cobicistat regimen is continued for a woman who is virally suppressed, viral load should be monitored frequently (some providers may monitor monthly during the second and third trimesters; see Increased Viral Load Monitoring for Women Receiving Cobicistat-boosted Regimens below).

Some older PIs—indinavir, nelfinavir, ritonavir (as a sole PI), and unboosted saquinavir or tipranavir—**are not recommended** for use in adults, and others—boosted or unboosted fosamprenavir, saquinavir/ritonavir and tipranavir/ritonavir—**are not recommended** for initial therapy in adults. These drugs **are not recommended** and should not be used in pregnant women due to concerns that include lower efficacy, toxicities, PK changes in pregnancy, and limited data and experience with use in pregnant women. See [Table 6](#), as well as [What Not to Use](#) and [Table 10](#) in the [Adult and Adolescent ARV Guidelines](#), for details on individual ARV drugs, ARV drug combinations, and ART regimens that are not recommended or should not be used in adults.

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/ritonavir, but dose adjustment is not recommended for darunavir/ritonavir (see [Table 10](#)).<sup>49</sup> 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.<sup>49-57</sup> Clinicians may consider therapeutic drug monitoring in specific situations.

## ***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 nonpregnant ARV-naive adults. Although data on the use of efavirenz in pregnancy are reassuring with regard to NTDs, and efavirenz is increasingly used during pregnancy worldwide, this drug is associated with dizziness, fatigue, vivid dreams and/or nightmares, and increased suicidality risk.<sup>19,22,58,59</sup> 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 effects.

In prior guidelines, use of efavirenz 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 **and the data from Botswana described above** have been reassuring that the risks of NTDs associated with first-trimester efavirenz exposure are not greater than those in the general population.<sup>19,22,58-60</sup> 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 Therapy](#)). Importantly, women who become pregnant on suppressive efavirenz-containing regimens should continue using these regimens, as is recommended for most regimens (see [Table 6](#) and [Table 7](#)).

**Rilpivirine** may be used as part of an alternative regimen for nonpregnant adults with pretreatment HIV RNA <100,000 copies/mL and CD4 T lymphocyte (CD4) cell counts >200 cells/mm<sup>3</sup>. There are sufficient data from use in pregnancy to recommend rilpivirine as an **alternative** agent for ARV-naive pregnant women who meet these same CD4 count and viral load criteria.<sup>61</sup> Although PK data indicate that rilpivirine plasma concentration is reduced during the second and third trimesters, the reduction is less than the reductions seen **with elvitegravir/cobicistat or darunavir/cobicistat, and most women will have adequate exposure; although viral breakthroughs were observed. Higher-than-standard doses have not been studied, so there are insufficient data to recommend a dosing change in pregnancy. With standard dosing, viral loads should be monitored frequently (e.g., every 1 to 2 months).**

**Nevirapine** is not recommended for initial ART in ARV-naive pregnant women or for nonpregnant adults because of a greater potential for adverse effects, complex lead-in dosing, and a low barrier to resistance. **Etravirine** is not recommended for ARV-naive pregnant patients because it is not recommended for ARV-naive nonpregnant patients, and because there are insufficient safety and PK data on etravirine in pregnancy. **However, it may be appropriate to initiate either of these ARV drugs in special circumstances, or it may be appropriate to continue using them in ART-experienced women with viral suppression.**

**Doravirine** has not yet been studied in pregnancy, so there are insufficient data to recommend its use in pregnancy.

For all women, screening for both antenatal and postpartum depression is recommended; because the use of efavirenz may increase the risk of depression and suicidality, this screening is particularly critical for women on efavirenz-containing regimens.<sup>62</sup>

## ***Entry and Fusion Inhibitors***

**Enfuvirtide** and **maraviroc** are not recommended for initial ART in pregnancy because they are not recommended as initial ART in nonpregnant adults and because of limited safety and PK data for these drugs in pregnancy. **Available PK data in women who received maraviroc as part of clinical care suggest that a standard adult dose is appropriate during pregnancy, despite a decrease in maraviroc exposure during pregnancy (see [Maraviroc](#)).**<sup>63</sup> Use of these agents can be considered for women who have experienced failure with several other classes of ARV drugs **and for women who become pregnant on well-tolerated, suppressive regimens that include these drugs;** however, because there are insufficient data to inform safety or dosing guidance for their use in pregnancy, these drugs should only be used after consultation with HIV and

obstetric specialists.

**Ibalizumab** is a humanized monoclonal antibody to the CD4 receptor. There are no data on the use of ibalizumab in pregnancy.

### Pharmacologic Boosters

Low-dose **ritonavir** as a pharmacologic booster for other PIs, as described above, is currently the preferred pharmacologic booster for use in pregnancy. **Cobicistat-boosted ARVs (atazanavir, darunavir, or elvitegravir) are not recommended** for use in pregnancy. As noted above, both elvitegravir and cobicistat levels in the P1026 study were significantly lower in the third trimester than in the postpartum period, and both darunavir and cobicistat levels were lower in the second and third trimesters than in the postpartum period in a separate study.<sup>64</sup> Although data are not yet available for the use of atazanavir/cobicistat in pregnancy, it is anticipated that the PK changes will be similar to those observed for darunavir/cobicistat and elvitegravir/cobicistat. However, the Panel recognizes that there may be situations where it is appropriate to continue treatment in women who become pregnant while receiving one of these regimens and who remain virally suppressed (see Pregnant Women Living with HIV Who Are Currently Receiving Antiretroviral Therapy and the Increased Viral Load Monitoring for Women Receiving Cobicistat-boosted Regimens section below for issues to address with patients when making decisions about whether to switch to another ART regimen or continue the current regimen with frequent viral load monitoring).

#### *Increased Viral Load Monitoring for Women Receiving Cobicistat-Boosted Regimens (Elvitegravir, Atazanavir, or Darunavir)*

Although increasing the frequency of viral load monitoring may help detect viral rebound, this may be difficult to implement if visit attendance or access to viral load monitoring is limited. In addition, viremia detected in late pregnancy may be challenging to manage, requiring medication changes shortly before delivery. If a woman becomes pregnant while taking a fully suppressive cobicistat-boosted regimen, clinicians should talk with her about the risks associated with viral rebound requiring a change in ARV regimens in late pregnancy. Studies have shown that changing ARV regimens is associated with an increased risk of detectable viral loads at the time of delivery, which increases the risk of perinatal HIV transmission and necessitates a cesarean section delivery.<sup>65</sup>

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