Recommendations for Use of Antiretroviral Drugs During Pregnancy: Overview
(Last updated February 10, 2021; last reviewed February 10, 2021)

Panel's Recommendations
• When choosing an antiretroviral (ARV) drug regimen for a pregnant woman, providers and patients should consider multiple factors, including adverse effects, drug interactions, pharmacokinetics (PKs), convenience of the individual drugs and drug combinations in the regimen, available pregnancy safety and outcome data, and the patient's resistance test results and comorbidities **(AIII)**.
• 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; clinicians should weigh the risks of adverse effects for women, fetuses, or infants against the benefits of these regimens and recognize that there are often incomplete data on the safety of ARV drugs in pregnancy **(AII)**. For more information, see Tables 4 and 5.
• 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 some ARV drugs and necessitate increased doses, more frequent dosing, boosting, more frequent viral load monitoring, or a change in ARV regimen; see Pregnant Women with HIV Who Are Currently Receiving Antiretroviral Therapy **(AII)**.
• The Panel emphasizes the importance of counseling and informed decision-making regarding all ARV regimens for people with HIV **(AIII)**. For additional information, see Preconception Counseling and Care for Women of Childbearing Age with HIV, Teratogenicity, Appendix C: Antiretroviral Counseling Guide for Health Care Providers, and Tables 4 and 5.
• After delivery, clinicians should discuss reproductive desires, the risks and benefits of conceiving on the current ARV regimen, and contraceptive options **(AIII)**. See Preconception Counseling and Postpartum Care for more information.
• Folic acid is known to prevent neural tube defects in the general population. All pregnant women and women who might conceive should take at least 400 mcg of folic acid daily **(AI)**.
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 that are relevant to the selection of specific antiretroviral (ARV) drugs for use in pregnancy. Additional recommendations for women with HIV who have never received antiretroviral therapy (antiretroviral therapy [ART]-naive women), women who are currently receiving ART, and women who were previously on ART or who have used ARV drugs for prophylaxis can be found in the other sections that follow this overview. Table 4 provides specific information about recommended ARV drugs when **initiating** ART in treatment-naive pregnant women. The table also includes considerations for ARV regimen selection and modification in pregnant women who are treatment-experienced and women who are attempting to become pregnant. For recommendations about the use of ARV drugs in people of childbearing potential who are not actively trying to conceive, see Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV.

Table 5 consolidates situation-specific recommendations for the use of ARV drugs in women with HIV during conception and pregnancy into a single table for ease of reference. Table 5 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 fully suppressive regimen that has been well

tolerated;
- Restarting ART in pregnant women who received ART or ARV drugs for prophylaxis in the past;
- Changing to a new ARV 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.

Table 10 and Appendix B provide information about individual drugs, including dosing and PK data in pregnancy.

Pregnant women often are excluded from initial HIV clinical trials. As a result, data regarding the PKs, drug safety, and efficacy of new ARVs often are limited to nonpregnant adults.[1,2] Drugs with known benefits to women should not be withheld during pregnancy unless they have known adverse effects to the woman, 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. Pregnancy and the potential for pregnancy **should not preclude** the use of optimal drug regimens. **The decision about which ARV drugs to use during pregnancy should be made by a woman after discussing the known and potential benefits and risks to her and her fetus**; see Appendix C: Antiretroviral Counseling Guide for Health Care Providers.[3]

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 U.S. Food and Drug Administration review that are 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, but not limited to, preterm birth, mutagenicity, and carcinogenicity;
- Available safety and outcome data on the use of the drug in pregnancy;
- PK changes in pregnancy; *and*
- Potential adverse effects for the woman, 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 on the 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.[4]

Categories of ARV drugs and drug combinations 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 efficacy and durability with acceptable toxicity and ease of use, and when pregnancy-specific PK data are available to guide dosing. In addition, the available data must suggest a favorable risk-benefit balance for the drug or drug combination compared to other ARV drug options; the assessment of risks and benefits should incorporate outcomes for women, fetuses, and infants. Some *Preferred* drugs or regimens may have minimal toxicity or teratogenicity risks that are offset by other advantages for women with HIV who are pregnant or trying to conceive.
- **Alternative:** Drugs or drug combinations are designated as *Alternative* options for therapy in pregnant women when clinical trial data in adults show efficacy and the data in pregnant individuals are generally favorable but limited. Most *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. Some *Alternative* drugs or regimens may have known toxicity or teratogenicity risks that are offset by other advantages for women with HIV who are pregnant or trying to conceive.
- **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 initial ART in ART-naive 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-naive 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 fully suppressive ART that has been well tolerated, though viral load monitoring should be performed more frequently in these instances. See Pregnant Women with HIV Who Are Currently Receiving Antiretroviral Therapy and Monitoring of the Woman and Fetus During Pregnancy.

Selection of ARV drugs **should be individualized** according to a pregnant woman's specific ARV history, the results of drug-resistance assays, and the presence of comorbidities, as well as the individual woman's preferences for balancing known and unknown risks and benefits. In pregnant women (as in nonpregnant adults, adolescents, and children), ART that includes at least three agents is recommended. For ARV-naive women, an ARV regimen that includes two nucleoside reverse transcriptase inhibitors (NRTIs) and a ritonavir (RTV)-boosted protease inhibitor (PI) or an integrase strand transfer inhibitor (INSTI) is preferred (Table 4). 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 that are not recommended for use in adults because of high risk for toxicity (e.g., didanosine [ddI], indinavir [IDV], stavudine [d4T], and treatment-dose RTV) or inferior virologic efficacy (nelfinavir [NFV]), and drugs that should not be used in pregnant women because of PK or toxicity concerns (see Table 4).

For women who have achieved virologic suppression and are receiving regimens with an increased risk of

virologic failure during pregnancy (e.g., darunavir/cobicistat [DRV/c], atazanavir/cobicistat [ATV/c], and elvitegravir/cobicistat [EVG/c]), clinicians should consider whether to continue or change the ARV regimen. A regimen change carries a risk for viral rebound at the time of the switch.[5] If a decision is made with the patient to continue the same regimen, viral load should be monitored more frequently (i.e., every 1–2 months). 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 rapid and full virologic suppression through adherence interventions or medication changes (see Women Who Have Not Achieved Viral Suppression on Antiretroviral Therapy). 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 the potential for genotypic resistance into consideration. Specific recommendations for each type of patient are described in Table 5 and in the following sections: Pregnant Women with HIV Who Have Never Received Antiretroviral Drugs, Pregnant Women with HIV Who Are Currently Receiving Antiretroviral Therapy, and Pregnant Women with HIV Who Have Previously Received Antiretroviral Treatment or Prophylaxis but Are Not Currently Receiving Any Antiretroviral Medications.

Balancing risks and benefits of ART in the face of limited data

It is important to weigh the available data about risks and benefits of all *Preferred* and *Alternative* agents. These agents include dolutegravir (DTG), atazanavir/ritonavir (ATV/r), darunavir/ritonavir (DRV/r), and raltegravir (RAL) (*Preferred*), as well as efavirenz (EFV) and rilpivirine (Alternative). Of these, systematic birth-surveillance data are available only for EFV and DTG.[6,7] Although early data raised concerns about risk for neural tube defects (NTDs) with DTG, and similar concerns have not been raised for other agents, data are too limited to identify or calculate the specific risks that are associated with the use of these drugs at the time of conception or during early pregnancy (see Teratogenicity, Dolutegravir, Elvitegravir, Raltegravir, and Bictegravir). To determine whether a drug carries an increased risk of a rare event, such as an NTD, more than 2,000 periconception exposures need to be monitored to rule out a threefold increase in risk. **Clinicians are encouraged to submit to the** Antiretroviral Pregnancy Registry **data for all patients who conceive while receiving ARV drugs or who receive ARV drugs during pregnancy.**

The risk of other adverse pregnancy outcomes, many of which are more common than birth defects, also should be considered. For example, the use of PIs, particularly lopinavir/ritonavir, has been associated with an increased risk of preterm birth, which may lead to an increase in infant morbidity and mortality.[6-8] In addition, data are needed on important clinical pregnancy outcomes, such as hypertension and weight gain (see Antiretroviral Drug Regimens and Maternal and Neonatal Outcomes). In the Tsepamo study in Botswana, the risks of adverse pregnancy outcomes other than NTDs were similar for women who received DTG-based regimens and women who received EFV-based regimens.[9,10] Overall, data are extremely limited on the risks associated with using other *Preferred* and *Alternative* ARV drugs preconception or in very early pregnancy; this lack of data does not indicate either the presence or absence of risk when using medications other than DTG and EFV. It remains critically important to **counsel all patients on the potential risks and benefits of ARV drugs in order to promote informed, individual decision-making (**see Appendix C: Antiretroviral Counseling Guide for Health Care Providers).[11]

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, increasing the risk for virologic failure or drug toxicity.[12-14] During pregnancy, gastrointestinal transit time becomes prolonged, and body water and fat increase throughout gestation. These changes are accompanied by increases in cardiac output, ventilation, and liver and renal blood flow. Plasma protein concentrations also decrease, which can reduce the total plasma drug levels but not necessarily the free or unbound plasma drug levels. Furthermore, renal sodium reabsorption increases, and changes occur in cellular transporters and drug metabolizing enzymes

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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 can also 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 [ETR] are limited). PI and INSTI PKs are more variable, particularly during the second and third trimesters. 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

Preferred NRTI combinations for use in ARV-naive pregnant women are abacavir (ABC) used in combination with lamivudine (3TC) and tenofovir disoproxil fumarate (TDF) used in combination with emtricitabine (FTC) or 3TC.

Abacavir plus 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.[15] Testing for the HLA-B*5701 allele should be performed and documented as negative before starting ABC, 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 HBV/HIV coinfection, two NRTIs that are active against HBV should be chosen (e.g., TDF with FTC or 3TC) in place of ABC plus 3TC (see HBV/HIV Coinfection).

TDF plus 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 (ZDV) plus 3TC. Although there have been concerns about bone and growth abnormalities in infants who were exposed to TDF *in utero*, the duration and clinical significance of study findings require further evaluation (see Tenofovir Disoproxil Fumarate).[16] The authors of one meta-analysis have suggested that ZDV plus 3TC should be used in place of TDF plus FTC;[17] however, this suggestion was based on data from a single study, the Promoting Maternal and Infant Survival Everywhere (PROMISE) trial.[18] The generalizability of the PROMISE findings is limited by study design and statistical considerations (for details, see Tenofovir Disoproxil Fumarate and Lopinavir/Ritonavir). After considering all available evidence, the Panel concluded that the assessment of expected benefits and risks favored the use of TDF plus FTC over ZDV plus 3TC. The Panel maintains the *Preferred* classification for TDF plus FTC and the *Alternative* classification for ZDV plus 3TC.

Tenofovir alafenamide (TAF) is recommended as an *Alternative* NRTI for initiation in pregnant women. Limited data exist on the safety of TAF exposure at conception and during the first trimester. Available PK data for TAF indicate that exposure is adequate in pregnancy and a change in dosing is not indicated.[19,20] A randomized controlled trial (IMPAACT 2010) of 643 pregnant women initiating ART at >14 weeks gestational age found a lower risk of adverse birth outcomes with TAF/FTC/DTG than TDF/FTC/DTG (24% vs. 33%) but greater maternal weight gain (0.38 kg vs. 0.32 kg per week); the two regimens were equally efficacious with respect to viral suppression.[21]

Zidovudine plus lamivudine is an *Alternative* NRTI combination for ARV-naive pregnant women. Despite proven efficacy in preventing perinatal HIV transmission and extensive experience with 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).

Pregnant women who are receiving **didanosine** or **stavudine** should be switched to *Preferred* or *Alternative*

medications.

Integrase Strand Transfer Inhibitors

Dolutegravir is a *Preferred* INSTI for pregnant women, because there are sufficient data about the efficacy and safety of DTG when it is initiated during pregnancy. The Panel has reviewed all the data available as of September 2020 regarding DTG use preconception or during the first trimester of pregnancy. Based on these data, DTG **is considered a *Preferred* drug for use throughout pregnancy** and **for women who are trying to conceive** (see [Adult and Adolescent Antiretroviral Guidelines](#)).

Efficacy and tolerability. DTG is associated with higher rates of virologic suppression, faster rates of viral load decline, greater tolerability, and a higher genetic barrier to drug resistance than other Preferred and Alternative agents.[9,10,22] A randomized clinical trial that compared DTG plus two NRTIs to EFV plus two NRTIs in ART-naive women who initiated therapy at a median gestational age of 31 weeks found that DTG-based ART produced more rapid viral suppression, with a greater proportion of women reaching an undetectable viral load (<50 copies/mL) at the time of delivery.[23]

Safety. The large Tsepamo birth-surveillance study in Botswana has shown that the risk of NTDs is lower than previously reported in preliminary data from the study.[6] In this study, DTG exposure around the time of conception was associated with a small but statistically significant increase in the prevalence of infant NTDs in Botswana; see [Teratogenicity](#). Although this prevalence with periconception DTG (0.19%) was higher than the prevalence for NTDs in infants born to women who were receiving efavirenz (0.07%) and women without HIV (0.07%), the risk was not significantly increased compared with women with HIV receiving any non-dolutegravir antiretroviral regimen at conception (0.11%, risk difference [0.09% difference]; 95% CI, 0.03% to 0.30%); see [Teratogenicity](#).

If a causal association exists between the use of DTG and the occurrence of NTDs, mechanistic etiologies remain unknown, including whether folic acid deficiency is a mediating factor (thus, whether risk would be reduced by folic acid supplementation) and whether a similar risk may exist for other INSTIs. No link has been established between DTG use and impaired folate metabolism, nor does evidence exist that folate prevents DTG-associated NTDs. Folic acid is known to prevent NTDs in the general population.[24,25] **All pregnant women and women who might conceive should take at least 400 mcg of folic acid daily.**

Pharmacokinetics. Although PK studies have found that DTG levels during the third trimester are lower than a pre-specified target level[26] and lower than levels assessed postpartum,[27] data regarding placental transfer and comparisons to levels in nonpregnant adults indicate that dose adjustments are not needed during pregnancy (see [Dolutegravir](#)). Furthermore, unbound plasma levels of DTG in pregnant women met the proposed 90% inhibitory concentration for unbound DTG.[14]

Maternal health outcomes. As experience with DTG in pregnancy and the postpartum period accumulates, maternal weight gain during and after pregnancy is an important consideration. Substantial weight gain on DTG-based regimens, especially among women and among people also receiving TAF, has been observed in nonpregnant populations.[28,29] In pregnancy, DTG-associated weight gain has also been observed, but this may reflect better maternal health (e.g., lower rates of insufficient weight gain or weight loss during pregnancy). Studies have seen greater weight gain during pregnancy with TAF/FTC/DTG (0.08 kg/week)[21] and TDF/FTC/DTG (0.03–0.05 kg/week)[21,30] compared with TDF/FTC/EFV. However, weekly weight gain during pregnancy in women on DTG- or EFV-based ART remained less than in women without HIV[30] and less than recommended for the general population.[21] In the DOLPHIN-2 study[31] and others,[32] postpartum weight gain was greater in women receiving DTG than in those receiving EFV-based but was similar to postpartum women without HIV infection.[32]

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Raltegravir (RAL) is a *Preferred* INSTI for use in ARV-naive pregnant women, based on PK, safety, and other data on the use of RAL during pregnancy.[33-37] Clinical trial data demonstrate a more rapid viral decay and greater proportion of viral suppression at delivery with the use of RAL compared with EFV or lopinavir/ritonavir (LPV/r).[38,39]

Although a once-daily formulation of RAL is approved for use in nonpregnant adults, PK data are insufficient to support its use in pregnancy; twice-daily dosing remains the recommended dosing schedule.[40]

Elvitegravir/cobicistat (EVG/c) is an INSTI for which data about use in pregnancy are currently limited.[41-43] Data from the P1026 study and the PANNA study suggest that coadministration of EVG and cobicistat (COBI) led to significantly lower levels of both drugs in the third trimester than in the postpartum period (levels in the third trimester were below the levels that are expected to lead to virologic suppression).[44] Viral breakthroughs did occur in the P1026 study, with only 74% of women maintaining viral suppression at delivery.[45,46] Based on these data, EVG/c **is not recommended** for initial use in pregnancy. In a retrospective cohort of 134 women at nine tertiary care centers in the United States who received EVG at any time during pregnancy, viral suppression at delivery was 81% (88% among those who initiated EVG before pregnancy), and overall perinatal HIV transmission was 0.8%.[43,47] In women already receiving EVG/c who become pregnant and are virally suppressed, continuation of the regimen with frequent viral load monitoring during the second and third trimester (e.g., every 1–2 months) can be considered, or the regimen can be switched to another *Preferred* regimen during pregnancy. If pregnancy is planned, EVG/c can be changed and viral suppression on a new regimen confirmed prior to conception.

Bictegravir (BIC) is an INSTI that is recommended for initial use in nonpregnant adults. No data on BIC PKs have been published, and data on clinical outcomes in pregnancy are extremely limited; in an abstract presented by the manufacturer of BIC, no NTDs were reported among 18 women with prospectively reported periconception exposures.[48]

Protease Inhibitors

Atazanavir/ritonavir and **darunavir/ritonavir** are *Preferred* PIs 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 (for ATV/r), and the requirement for twice-daily dosing (for DRV/r). Although the use of once-daily dosing for DRV/r is approved for nonpregnant adults, PK data are insufficient to support its use in pregnancy.[49]

Atazanavir is associated with increased indirect bilirubin levels, which theoretically may increase the risk of hyperbilirubinemia in neonates; however, pathologic elevations have not been seen in studies to date.[50] In the analyses from the Pediatric HIV/AIDS Cohort Study (PHACS) and Surveillance Monitoring for ART Toxicity (SMARTT) study, *in utero* exposure to atazanavir was associated with small but statistically significant reductions in language and social-emotional scores compared with exposure to other drugs.[51] ATV exposure was also associated with the risk of late language emergence at 12 months but was no longer significant at 24 months.[52,53] The clinical significance of these findings associated with *in utero* ATV exposure is not known. **Lopinavir/ritonavir (LPV/r) is not recommended for initiation in pregnancy, except in special circumstances.** There are extensive clinical experience and PK data for the use of LPV/r in pregnancy, but it requires twice-daily dosing in pregnancy and frequently causes nausea and diarrhea; it has also been associated with an increased risk of preterm delivery and small-for-gestational-age infants (see Antiretroviral Drug Regimens and Maternal and Neonatal Outcomes). People who conceive on a suppressive, well-tolerated regimen, including LPV/r, should continue this regimen.

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Darunavir/cobicistat (DRV/c) and **atazanavir/cobicistat (ATV/c) are not recommended** for use in pregnancy.[46,54,55] PK studies suggest that low levels of both DRV and COBI 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. Levels of ATV were similarly lower in the second and third trimesters;[46] it is anticipated that the virologic and transmission outcomes with ATV/c will be similar to those observed with DRV/c and EVG/c. In addition, once-daily dosing of DRV **is not recommended** for initial therapy in pregnancy. For women who become pregnant while receiving DRV/c or ATV/c and are virally suppressed, the regimen can be continued with frequent viral load monitoring during the second and third trimester (e.g., every 1–2 months), or the regimen can be switched to another *Preferred* regimen during pregnancy. For both DRV and ATV, COBI can be replaced by ritonavir as the pharmacologic booster, but careful attention must be paid to dosing of ATV (higher if used with TDF or antacids) and DRV (twice-daily dosing).

Current data suggest that with standard adult dosing, plasma concentrations of LPV, ATV, and DRV are reduced during the second and/or third trimesters. Dose adjustment is recommended for LPV/r and may be considered for ATV/r, but dose adjustment is not recommended for DRV/r (see Table 10).[56] 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.[56-64] Clinicians may consider therapeutic drug monitoring in specific situations.

Some older PIs—IDV, NFV, RTV (as the 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 because of concerns that include lower efficacy, toxicities, PK changes in pregnancy, and limited data and experience with use in pregnant women. See Table 4, as well as What Not to Use and Table 10 in the Adult and Adolescent Antiretroviral Guidelines, for details on individual ARV drugs, ARV drug combinations, and ARV regimens that are not recommended or should not be used in adults.

Non-Nucleoside Reverse Transcriptase Inhibitors

There are no *Preferred* NNRTIs for use in ARV-naive pregnant women.

For all women, screening for both antenatal and postpartum depression is recommended. Because the use of some NNRTIs may increase the risk of depression and suicidality, this screening is particularly critical for women on EFV- and RPV-containing regimens.[65-67]

Efavirenz is an *Alternative* NNRTI for both pregnant and nonpregnant ARV-naive adults. EFV may be suitable for women who desire a once-daily, fixed-dose combination regimen and who tolerate EFV without adverse effects. Although data on the use of EFV in pregnancy are reassuring with regard to NTDs and EFV is increasingly used during pregnancy worldwide, adverse effects associated with EFV include dizziness, fatigue, rare and occasionally severe hepatotoxicity, vivid dreams and/or nightmares, and increased risk of suicidality.[9,66,68-72]

Although the EFV package insert cautions women not to become pregnant while taking EFV, recent large meta-analyses and the data from Botswana described above have been reassuring that the risk of NTDs in infants with first-trimester EFV exposure is not greater than the risk in the general population.[7,9,68,69,73] As a result, the Perinatal Guidelines do not restrict the use of EFV in pregnancy or in women who are planning to become pregnant; this is consistent with the British HIV Association Guidelines and the World Health Organization guidelines, both of which note that EFV can be used throughout pregnancy[74] (see Teratogenicity and Pregnant Women with HIV Who Are Currently Receiving Antiretroviral Therapy). A recent observational study reported

a twofold increased risk of microcephaly among infants born to 141 women receiving EFV compared to women receiving other ARV drugs in the United States; although other factors—such as alcohol use, unintended pregnancy, gestational age at ART initiation, changes in ARV practice patterns over time, and small numbers of women taking more recently recommended ARV drugs as comparators (e.g., DTG [n = 52], RAL [n = 167], and DRV [n = 254])—may have contributed to this association. Importantly, the Panel recommends that women who become pregnant on suppressive, EFV-containing regimens **should continue** using these regimens as is recommended for most regimens[75] (see Table 4 and Table 5).

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/mm³. Sufficient data from use in pregnancy exist to recommend RPV as an *Alternative* agent for ARV-naive pregnant women who meet these same CD4 count and viral load criteria.[5,43,76] Although PK data indicate that RPV plasma concentration is reduced during the second and third trimesters, the reduction is less than the reductions seen with EVG/c or DRV/c, and most women will have adequate exposure;[5] however, viral breakthroughs may be possible. Higher-than-standard doses of RPV have not been studied, so data are insufficient to recommend a dosing change in pregnancy. RPV must be taken with a meal, which may make it difficult to tolerate in pregnancy. With standard dosing of RPV, viral loads should be monitored frequently (e.g., every 1–2 months; see Monitoring of the Woman and Fetus During Pregnancy).

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 of insufficient safety and PK data on the use of ETR during pregnancy. Available PK data in women who received ETR as part of clinical care suggest that a standard adult dose is appropriate during pregnancy; unlike other ARV drugs, ETR exposure is increased during pregnancy.[27,77] 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 who become pregnant on well-tolerated, fully suppressive regimens that include these drugs.

Doravirine has not yet been studied in pregnancy; data are insufficient to recommend its use in pregnancy.

Entry, Attachment, and Fusion Inhibitors

Enfuvirtide and **maraviroc** (MVC) **are not recommended** for initial ART in pregnancy, because they are not recommended for initial ART in nonpregnant adults, and because the safety and PK data for these drugs in pregnancy are limited. Available PK data in women who received MVC as part of clinical care suggest that a standard adult dose is appropriate during pregnancy, despite a decrease in MVC exposure during pregnancy (see Maraviroc).[78] Use of these agents can be considered for women who have experienced virologic failure with several other classes of ARV drugs and for women who become pregnant on well-tolerated, suppressive regimens that include these drugs; however, data are insufficient to inform safety or dosing guidance for their use in pregnancy, these drugs should be used only after consulting HIV and obstetric specialists.

Ibalizumab is a humanized monoclonal antibody to the CD4 receptor. **Fostemsavir** is an attachment inhibitor. Both drugs are indicated for patients with multi-drug resistant HIV for whom no therapeutic alternatives may be available. However, no data exist on the use of these drugs 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 ARV drugs (ATV, DRV, or EVG) **are not**

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recommended for use in pregnancy. As noted above, EVG, DRV, ATV, and COBI levels have been found to be significantly lower during the third trimester than during the postpartum period.[46,54,55] However, for women who become pregnant while receiving COBI-boosted regimens and are virally suppressed, the regimen can be continued with frequent viral load monitoring during the second and third trimester (e.g., every 1–2 months), or the regimen can be switched to another Preferred regimen during pregnancy. See Pregnant Women with HIV Who Are Currently Receiving Antiretroviral Therapy and Monitoring of the Woman and Fetus During Pregnancy for issues to address with patients when making decisions about whether to switch to another ARV regimen or continue the current regimen with frequent viral load monitoring.

References

1. The PHASES Working Group. Ending the evidence gap for pregnant women around HIV & co-infections: a call to action. Chapel Hill, NC: 2020. Available at: http://www.hivpregnancyethics.org/.

2. Abrams EJ, Mofenson LM, Pozniak A, et al. Enhanced and timely investigation of ARVs for use in pregnant women. *J Acquir Immune Defic Syndr*. 2020 (Online ahead of print). Available at: https://www.ncbi.nlm.nih.gov/pubmed/33298793.

3. Lytvyn L, Siemieniuk RA, Dilmitis S, et al. Values and preferences of women living with HIV who are pregnant, postpartum or considering pregnancy on choice of antiretroviral therapy during pregnancy. *BMJ Open*. 2017;7(9):e019023. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28893759.

4. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral Pregnancy Registry international interim report for 1 January 1989–31 January 2020. Wilmington, NC: Registry Coordinating Center. 2020. Available at: http://www.apregistry.com/.

5. Frange P, Tubiana R, Sibiude J, et al. Rilpivirine in HIV-1-positive women initiating pregnancy: to switch or not to switch? *J Antimicrob Chemother*. 2020;75(5):1324-1331. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32157283.

6. Zash R, Holmes L, Diseko M, et al. Update on neural tube defects with antiretroviral exposure in the Tsepamo study, Botswana. Presented at: International AIDS Conference. 2020.

7. Zash R, Holmes L, Diseko M, et al. Neural-tube defects and antiretroviral treatment regimens in Botswana. *N Engl J Med*. 2019;381(9):827-840. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31329379.

8. Tshivuila-Matala COO, Honeyman S, Nesbitt C, Kirtley S, Kennedy SH, Hemelaar J. Adverse perinatal outcomes associated with antiretroviral therapy regimens: systematic review and network meta-analysis. *AIDS*. 2020;34(11):1643-1656. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32701581.

9. Zash R, Jacobson DL, Diseko M, et al. Comparative safety of dolutegravir-based or efavirenz-based antiretroviral treatment started during pregnancy in Botswana: an observational study. *Lancet Glob Health*. 2018;6(7):e804-e810. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29880310.

10. Venter WDF, Moorhouse M, Sokhela S, et al. Dolutegravir plus two different prodrugs of tenofovir to treat HIV. *N Engl J Med*. 2019;381(9):803-815. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31339677.

11. Redfield RR, Modi S, Moore CA, Delaney A, Honein MA, Tomlinson HL. Health care autonomy of women living with HIV. N *Engl J Med*. 2019;381(9):798-800. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31339674.

12. Mirochnick M, Capparelli E. Pharmacokinetics of antiretrovirals in pregnant women. *Clin Pharmacokinet*. 2004;43(15):1071-1087. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15568888.

13. Roustit M, Jlaiel M, Leclercq P, Stanke-Labesque F. Pharmacokinetics and therapeutic drug monitoring of antiretrovirals in pregnant women. *Br J Clin Pharmacol*. 2008;66(2):179-195. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18537960.

14. Bollen P, Freriksen J, Konopnicki D, et al. The effect of pregnancy on the pharmacokinetics of total and unbound dolutegravir and its main metabolite in women living with human immunodeficiency virus. *Clin Infect Dis*. 2020;ciaa006. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32103260.

15. Shapiro RL, Hughes MD, Ogwu A, et al. Antiretroviral regimens in pregnancy and breast-feeding in Botswana. *N Engl J Med*. 2010;362(24):2282-2294. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20554983.

16. Siberry GK, Jacobson DL, Kalkwarf HJ, et al. Lower newborn bone mineral content associated with maternal use of tenofovir disoproxil fumarate during pregnancy. *Clin Infect Dis*. 2015;61(6):996-1003. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26060285.

17. Siemieniuk RA, Foroutan F, Mirza R, et al. Antiretroviral therapy for pregnant women living with HIV or hepatitis B: a systematic review and meta-analysis. *BMJ Open*. 2017;7(9):e019022. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28893758.

18. Fowler MG, Qin M, Fiscus SA, et al. Benefits and risks of antiretroviral therapy for perinatal HIV prevention. *N Engl J Med*. 2016;375(18):1726-1737. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27806243.

19. Momper J, Best B, Wang J, et al. Tenofovir alafenamide pharmacokinetics with and without cobicistat in pregnancy. Presented at: 22nd International AIDS Conference. 2018. Amsterdam, Netherlands.

20. Brooks K, Pinilla M, Shapiro D, et al. Pharmacokinetics of tenofovir alafenamide 25 mg with PK boosters during pregnancy and postpartum. Presented at: Workshop on Clinical Pharmacology of HIV, Hepatitis, and Other Antiviral Drugs; 2019. Noordwijk, Netherlands.

21. Chinula L, Brummel SS, Ziemba L, Stranix-Chibanda L, Coletti A, Krotje Cea. Safety and efficacy of DTG vs. EFV and TDF vs. TAF in pregnancy: IMPAACT 2010 trial. Presented at: Conference on Retroviruses and Opportunistic Infections. 2020. Boston, MA.

22. Zash R, Rough K, Jacobson DL, et al. Effect of gestational age at tenofovir-emtricitabine-efavirenz initiation on adverse birth outcomes in Botswana. *J Pediatric Infect Dis Soc*. 2018;7(3):e148-e151. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29688554.

23. Kintu K, Malaba TR, Nakibuka J, et al. Dolutegravir versus efavirenz in women starting HIV therapy in late pregnancy (DolPHIN-2): an open-label, randomised controlled trial. *Lancet HIV*. 2020;7(5):e332-e339. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32386721.

24. Zamek-Gliszczynski MJ, Zhang X, Mudunuru J, et al. Clinical extrapolation of the effects of dolutegravir and other HIV integrase inhibitors on folate transport pathways. *Drug Metab Dispos*. 2019;47(8):890-898. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31167838.

25. Cabrera RM, Souder JP, Steele JW, et al. The antagonism of folate receptor by dolutegravir: developmental toxicity reduction by supplemental folic acid. *AIDS*. 2019;33(13):1967-1976. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31259764.

26. Waitt C, Orrell C, Walimbwa S, et al. Safety and pharmacokinetics of dolutegravir in pregnant mothers with HIV infection and their neonates: a randomised trial (DolPHIN-1 study). *PLoS Med*. 2019;16(9):e1002895. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31539371.

27. Mulligan N, Best BM, Wang J, et al. Dolutegravir pharmacokinetics in pregnant and postpartum women living with HIV. AIDS. 2018;32(6):729-737. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29369162.

28. Venter F, Sokhela S, Fairlie L, Serenata C. The ADVANCE trial: Phase 3, randomised comparison of TAF/FTC+DTG, TDF/FTC+DTG or TDF/FTC/EFV for first-line treatment of HIV-1 infection. Presented at: International AIDS Conference Virtual. 2020.

29. Kouanfack C, Sanchez T, Wandji M, et al. Dolutegravir versus low-dose efavirenz-based regimen for the initial treatment of HIV-1 infection in Cameroon: week 96 results of the ANRS 12313 NAMSAL trial. Presented at: International AIDS Conference Virtual. 2020.

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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30. Caniglia EC, Shapiro R, Diseko M, et al. Weight gain during pregnancy among women initiating dolutegravir in Botswana. *EClinicalMedicine*. 2020;29-30:100615. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33437946.

31. Malaba TR, Chen T, Kintu K, et al. Postpartum weight changes in women initiating DTG vs EFV in pregnancy: dolphin-2. Presented at: Conference on Retroviruses and Opportunistic Infections. 2020. Boston, MA. Available at: https://www.croiconference.org/abstract/postpartum-weight-changes-in-women-initiating-dtg-vs-efv-in-pregnancy-dolphin-2/.

32. Jao J, Sun S, Legbedze J, et al. Dolutegravir use is associated with higher postpartum weight compared to efavirenz. Presented at: Conference on Retroviruses and Opportunistic Infections. 2020. Boston, MA. Available at: https://www.croiconference.org/abstract/dolutegravir-use-is-associated-with-higher-postpartum-weight-compared-to-efavirenz/.

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

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

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

36. Blonk M, Colbers A, Hidalgo-Tenorio C, et al. Raltegravir in HIV-1 infected pregnant women: pharmacokinetics, safety and efficacy. *Clin Infect Dis*. 2015;61(5):809-816. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25944344.

37. Watts DH, Stek A, Best BM, et al. Raltegravir pharmacokinetics during pregnancy. *J Acquir Immune Defic Syndr*. 2014;67(4):375-381. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25162818.

38. Joao EC, Morrison RL, Shapiro DE, et al. Raltegravir versus efavirenz in antiretroviral-naive pregnant women living with HIV (NICHD P1081): an open-label, randomised, controlled, phase 4 trial. *Lancet HIV*. 2020;7(5):e322-e331. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32386720.

39. Brites C, Nobrega I, Luz E, Travassos AG, Lorenzo C, Netto EM. Raltegravir versus lopinavir/ritonavir for treatment of HIV-infected late-presenting pregnant women. *HIV Clin Trials*. 2018;19(3):94-100. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29629852.

40. van der Galien R, Ter Heine R, Greupink R, et al. Pharmacokinetics of HIV-integrase inhibitors during pregnancy: mechanisms, clinical implications, and knowledge gaps. *Clin Pharmacokinet*. 2018;58(3):309-323. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29915921.

41. Pain JB, Le MP, Caseris M, et al. Pharmacokinetics of dolutegravir in a premature neonate after HIV treatment intensification during pregnancy. *Antimicrob Agents Chemother*. 2015;59(6):3660-3662. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25845873.

42. Rahangdale L, Cates J, Potter J, et al. Integrase inhibitors in late pregnancy and rapid HIV viral load reduction. *Am J Obstet Gynecol*. 2016;214(3):385 e381-387. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26928154.

Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States

C-13

43. Patel K, Huo Y, Jao J, et al. Viral suppression by delivery and birth outcomes among pregnant women living with HIV using dolutegravir in the United States: a comparative effectiveness and safety analysis. Presented at: International AIDS Conference Virtual. 2020. Available at: http://programme.aids2020.org/Abstract/Abstract/1174.

44. Bukkems V, Necsoi C, Tenorio CH, et al. Clinically significant lower elvitegravir exposure during third trimester of pregnant patients living with HIV: data from the PANNA study. *Clin Infect Dis.* 2020;ciaa488. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32330231.

45. Momper J, Best BM, Wang J, et al. Elvitegravir/cobicistat pharmacokinetics in pregnant and postpartum women with HIV. *AIDS.* 2018;32(17):2507-2516. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30134297.

46. Boyd SD, Sampson MR, Viswanathan P, Struble KA, Arya V, Sherwat AI. Cobicistat-containing antiretroviral regimens are not recommended during pregnancy: viewpoint. *AIDS.* 2019;33(6):1089-1093. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30946163.

47. Badell ML, Sheth AN, Momplaisir F, et al. A multicenter analysis of elvitegravir use during pregnancy on HIV viral suppression and perinatal outcomes. *Open Forum Infect Dis.* 2019;6(4):ofz129. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31037241.

48. Farrow T, Deaton C, Nguyen N, Serejo M, Muramoto D, etc. Cumulative safety review of elvitegravir and bictegravir use during pregnancy and risk of neural tube defects. Abstract P030. Presented at: HIV Drug Therapy. 2018. Glasgow, United Kingdom. Available at: http://hivglasgow.org/wp-content/uploads/2018/11/P030-4.pdf.

49. Schalkwijk S, Ter Heine R, Colbers A, et al. Evaluating darunavir/ritonavir dosing regimens for HIV-positive pregnant women using semi-mechanistic pharmacokinetic modelling. *J Antimicrob Chemother.* 2019;74(5):1348-1356. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30715324.

50. Floridia M, Ravizza M, Masuelli G, et al. Atazanavir and lopinavir profile in pregnant women with HIV: tolerability, activity and pregnancy outcomes in an observational national study. *J Antimicrob Chemother.* 2014;69(5):1377-1384. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24370933.

51. Caniglia EC, Patel K, Huo Y, et al. Atazanavir exposure in utero and neurodevelopment in infants: a comparative safety study. *AIDS.* 2016;30(8):1267-1278. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26867136.

52. Rice ML, Zeldow B, Siberry GK, et al. Evaluation of risk for late language emergence after in utero antiretroviral drug exposure in HIV-exposed uninfected infants. *Pediatr Infect Dis J.* 2013;32(10):e406-413. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24067563.

53. Sirois PA, Huo Y, Williams PL, et al. Safety of perinatal exposure to antiretroviral medications: developmental outcomes in infants. *Pediatr Infect Dis J.* 2013;32(6):648-655. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23340561.

54. Crauwels HM, Osiyemi O, Zorrilla C, Bicer C, Brown K. Reduced exposure to darunavir and cobicistat in HIV-1-infected pregnant women receiving a darunavir/cobicistat-based regimen. *HIV Med.* 2019;20(5):337-343. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30873741.

55. Momper J, Stek A, Wang J, et al. Pharmacokinetics of atazanavir boosted with cobicistat during pregnancy and postpartum. Presented at: Workshop on Clinical Pharmacology of HIV, Hepatitis, and other Antiviral Drugs. 2019. Noordwijk, The Netherlands.

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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56. Le MP, Mandelbrot L, Descamps D, et al. Pharmacokinetics, safety and efficacy of ritonavir-boosted atazanavir (300/100 mg once daily) in HIV-1-infected pregnant women. *Antivir Ther*. 2015;20(5):507-513. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25599649.

57. Food and Drug Administration. Reyataz (atazanavir) [package insert]. 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021567s042,206352s007lbl.pdf.

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

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

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

61. Mirochnick M, Best BM, Stek AM, et al. Lopinavir exposure with an increased dose during pregnancy. *J Acquir Immune Defic Syndr*. 2008;49(5):485-491. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18989231.

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

63. Bouillon-Pichault M, Jullien V, Azria E, et al. Population analysis of the pregnancy-related modifications in lopinavir pharmacokinetics and their possible consequences for dose adjustment. *J Antimicrob Chemother*. 2009;63(6):1223-1232. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19389715.

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

65. Ford N, Shubber Z, Pozniak A, et al. Comparative safety and neuropsychiatric adverse events associated with efavirenz use in first-line antiretroviral therapy: A systematic review and meta-analysis of randomized trials. *J Acquir Immune Defic Syndr*. 2015;69(4):422-429. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25850607.

66. Jones DL, Rodriguez VJ, Alcaide ML, Weiss SM, Peltzer K. The use of efavirenz during pregnancy is associated with suicidal ideation in postpartum women in rural South Africa. *AIDS Behav*. 2019;23(1):126-131. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29959721.

67. Mills AM, Antinori A, Clotet B, et al. Neurological and psychiatric tolerability of rilpivirine (TMC278) vs. efavirenz in treatment-naive, HIV-1-infected patients at 48 weeks. *HIV Med*. 2013;14(7):391-400. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23298380.

68. Ford N, Calmy A, Mofenson L. Safety of efavirenz in the first trimester of pregnancy: an updated systematic review and meta-analysis. *AIDS*. 2011;25(18):2301-2304. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21918421.

69. Ford N, Shubber Z, Jao J, Abrams EJ, Frigati L, Mofenson L. Safety of cotrimoxazole in pregnancy: a systematic review and meta-analysis. *J Acquir Immune Defic Syndr*. 2014;66(5):512-521. Available at:

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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http://www.ncbi.nlm.nih.gov/pubmed/24853309.

70. Zash R, Makhema J, Shapiro RL. Neural-tube defects with dolutegravir treatment from the time of conception. *N Engl J Med.* 2018;379(10):979-981. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30037297.

71. Martinez de Tejada B, European Pregnancy Paediatric HIV Cohort Collaboration Study Group. Birth defects after exposure to efavirenz-based antiretroviral therapy at conception/first trimester of pregnancy: a multicohort analysis. *J Acquir Immune Defic Syndr.* 2019;80(3):316-324. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30570524.

72. Bhattacharya D, Gupta A, Tierney C, et al. Hepatotoxicity and liver-related mortality in women of child-bearing potential living with HIV and high CD4 counts initiating efavirenz-containing regimens. *Clin Infect Dis.* 2020;ciaa244. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32161944.

73. Efavirenz (Sustiva) [package insert]. Food and Drug Administration. 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020972s057,021360s045lbl.pdf.

74. British HIV Association. British HIV association guidelines for the management of HIV in pregnancy and postpartum 2018 (2020 third interim update). 2020. Available at: https://www.bhiva.org/pregnancy-guidelines

75. Williams PL, Yildirim C, Chadwick EG, et al. Association of maternal antiretroviral use with microcephaly in children who are HIV-exposed but uninfected (SMARTT): a prospective cohort study. *Lancet HIV.* 2019;7(1):e49-e58. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31740351.

76. Schalkwijk S, Colbers A, Konopnicki D, et al. Lowered rilpivirine exposure during third trimester of pregnancy in HIV-1-positive women. *Clin Infect Dis.* 2017;65(8):1335-1341. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28595298.

77. Ramgopal M, Osiyemi O, Zorrilla C, et al. Pharmacokinetics of total and unbound etravirine in HIV-1-infected pregnant women. *J Acquir Immune Defic Syndr.* 2016;73(3):268-274. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27159225.

78. Colbers A, Best B, Schalkwijk S, et al. Maraviroc pharmacokinetics in HIV-1-infected pregnant women. *Clin Infect Dis.* 2015;61(10):1582-1589. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26202768.

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