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

Developed by the HHS Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission—
A Working Group of the Office of AIDS Research Advisory Council (OARAC)

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It is emphasized that concepts relevant to HIV management evolve rapidly. The Panel has a mechanism to update recommendations on a regular basis, and the most recent information is available on the AIDSinfo website (http://aidsinfo.nih.gov).

What's New in the Guidelines

Use of Dolutegravir in Pregnant Women and Women Who Are Trying to Conceive

The Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission (the Panel) has updated recommendations regarding the use of dolutegravir (DTG) in pregnant women and women who are trying to conceive based on data available as of August 2019.

Restrictions on use of DTG during the first trimester and in women who are trying to conceive have been removed. DTG is now a *Preferred* antiretroviral (ARV) drug throughout pregnancy and an *Alternative* ARV drug for women who are trying to conceive. Panel members weighed not only the updated data about DTG-associated risk of infant neural tube defects (NTDs) in Botswana, but also the important lack of comparable data about the risk of NTDs when using DTG in other settings, and what is known about the risk of NTDs and other adverse pregnancy outcomes, such as preterm birth, when using other *Preferred* and *Alternative* ARV drugs and drug combinations. The Panel has emphasized the importance of counseling and informed decision-making regarding all ARV regimens for people with HIV, and has added a guide to assist health care providers in counseling patients about the use of DTG.

The sections listed below were revised to include updated data, recommendations, and guidance about the use of DTG in pregnant women and in women who are trying to conceive:

- Teratogenicity
- Recommendations for Use of Antiretroviral Drugs During Pregnancy
  - Table 6. What to Start: Initial Combination Regimens for Antiretroviral-Naive Pregnant Women
  - Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs in Pregnant Women and Nonpregnant Women Who Are Trying to Conceive
- Pregnant Women Living with HIV Who Have Never Received Antiretroviral Drugs
- Pregnant Women Living with HIV Who are Currently Receiving Antiretroviral Therapy
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- Appendix D. Dolutegravir Counseling Guide for Health Care Providers

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Members of the Panel on Treatment of Pregnant Woman with HIV Infection and Prevention of Perinatal Transmission (Last updated December 7, 2018; last reviewed December 7, 2018)

Revisions to the November 14, 2017 *Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal Transmission in the United States* have been made by the Department of Health and Human Services (HHS) Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission (a Working Group of the Office of AIDS Research Advisory Council).

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Key to Acronyms: DSMB = Data Safety Monitoring Board; CC = Panel Co-Chairs; ES = Executive Secretary; ExOM = *Ex Officio* Member; HHS = Member from Department of Health and Human Services; M = Member; N/A = Not applicable; NVO = Nonvoting Observer

Introduction (Last updated December 7, 2018; last reviewed December 7, 2018)

Recommendations regarding HIV screening in pregnancy, treatment of pregnant women who are living with HIV, and the use of antiretroviral (ARV) drugs for prevention of perinatal transmission of HIV have evolved considerably in the United States since the mid-1990s, reflecting changes in both the epidemic and also in the science of prevention and treatment. With the implementation of recommendations for universal prenatal HIV counseling and testing, antiretroviral treatment (ART) for all pregnant women living with HIV, scheduled cesarean delivery for women with plasma HIV RNA >1,000 copies/mL near delivery, appropriate infant ARV management, and avoidance of breastfeeding, the rate of perinatal transmission of HIV has dramatically diminished to 1% or less in the United States and Europe.[1,2] In 2013, only 69 infants were born with HIV infection in the United States; the estimated incidence of perinatally acquired HIV infection was 1.8 out of 100,000 live births.[1] In response to this success, the Centers for Disease Control and Prevention has developed a goal of eliminating perinatal HIV transmission in the United States, defined as reducing perinatal transmission to an incidence of <1 infection per 100,000 live births and to a rate of <1% among HIV-exposed infants.[3]

It is estimated that approximately 5,000 women living with HIV give birth annually in the United States.[4] The best way to prevent HIV infection in infants is to focus on appropriate overall medical care for women living with HIV; this includes comprehensive reproductive health, family planning and preconception care services, optimization of HIV treatment, and maintenance of care between pregnancies. A critical component of preventing perinatal HIV transmission is ensuring the use of ART that maximally suppresses viral replication as early as possible during pregnancy or, ideally, prior to conception.

A critical role of Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission (the Panel) is to evaluate the many ARV drugs that are available for adults and assess the risks and benefits of using these drugs in pregnant women. The Office of AIDS Research Advisory Committee (OARAC)-sponsored Panel on Antiretroviral Guidelines for Adults and Adolescents primarily considers efficacy and safety evidence when making recommendations for preferred ART regimens. Secondary considerations include adherence-promoting tolerability and convenience characteristics, such as whether a regimen is available as a fixed-dose combination with once-daily dosing. When considering which ARV drugs to recommend for use in pregnant women (or women who may become pregnant), the Panel generally uses data from efficacy studies performed in nonpregnant adults; however, because drug exposure can change in pregnancy, data from direct pharmacokinetic (PK) studies in pregnant women are required.

In addition to considering direct evidence about short-term safety in pregnant women, the Panel must also make judgments about fetal safety. The Panel makes an initial assessment based on data from preclinical animal studies, analyses from reports to the Antiretroviral Pregnancy Registry, and all available post-marketing surveillance data. When there is strong evidence of fetal (or maternal) harm or unacceptable drug exposure, it is straightforward for the Panel to make recommendations against the use of a specific drug; however, this situation is unusual. More often, the Panel is faced with making recommendations for an ARV drug for which there are insufficient PK data in pregnant women and/or inadequate fetal safety information regarding exposure early in pregnancy or during the periconception period. To ensure that pregnant women are not denied the best available ART regimens—while acknowledging that some drugs have not yet been sufficiently evaluated for evidence of fetal or maternal harm—the Panel uses a graded approach to making recommendations for ART regimens to use during pregnancy:

- ART regimens with the most complete information on safety and PKs during pregnancy are designated *Preferred* initial regimens in pregnant women.
- Preferred ART regimens for nonpregnant adults that do not meet the above criteria can be considered as options for *Alternative* regimens in pregnant women when available data in pregnancy are incomplete, but there are no specific safety or PK concerns.

- Caution should be used when considering the use of regimens that contain drugs with little or no pregnancy data for evaluation. These regimens are considered to have *Insufficient Data to Recommend* for initiation in pregnancy, but there are no specific data to recommend discontinuing these regimens in women who become pregnant while taking them.

- Some drugs are designated as *Not Recommended Except in Special Circumstances* because the Panel recognizes that there may be situations in which treatment-experienced pregnant women may need to initiate or continue drugs with limited safety and efficacy data or specific safety concerns to reach or maintain viral suppression.

For all drugs, the Panel systematically reviews all new information from Antiretroviral Pregnancy Registry, published studies, and other sources to update their drug recommendations. The Panel also coordinates with the Panel on Antiretroviral Guidelines for Adults and Adolescents when there are concerns related to drug safety in pregnancy.

These guidelines update the November 2017 Perinatal Guidelines. The Panel, a working group of the National Institutes of Health (NIH) OARAC, develops these guidelines. The Panel works in close collaboration with the companion NIH OARAC Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV to jointly develop recommendations in overlapping areas (e.g., Maternal HIV Testing and Identification of Perinatal HIV Exposure, Diagnosis of HIV Infection in Infants and Children, Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV), as well as to ensure general harmony between the guidelines. The guidelines provide health care providers with information to discuss with pregnant women who are living with HIV to enable collaborative, informed decision-making regarding the use of ARV drugs during pregnancy, the use of scheduled cesarean delivery to reduce perinatal transmission of HIV, and decision-making around the use of ARV drugs in infants exposed to HIV. The recommendations in these guidelines are accompanied by discussions of various circumstances that commonly occur in clinical practice and the factors that influence treatment considerations. The Panel recognizes that strategies to prevent perinatal transmission and concepts related to management of HIV in pregnant women are rapidly evolving, and the Panel will consider new evidence and adjust recommendations accordingly. The updated guidelines are available from the AIDS*info* website. The National Perinatal HIV Hotline (1-888-448-8765) is a federally funded service that provides free clinical consultation to providers caring for women who are living with HIV or who are at risk for HIV and their children, and it serves as a resource for obtaining expert consultation for individual cases.

The Panel supports recommendations to ensure that women receive the full benefit of ART for their own health and for prevention of perinatal transmission. However, the Panel recognizes the right of women to make informed choices about treatment during pregnancy, even when their choices differ from a health care provider's recommendations.

The current guidelines have been structured to reflect the management of an individual mother-child pair and are organized into a brief discussion of preconception care followed by principles for managing the care of a woman and her infant during the antepartum, intrapartum, and postpartum periods. Although perinatal transmission of HIV occurs worldwide, these recommendations have been developed for use in the United States. Alternative strategies may be appropriate in other countries.

Guidelines Development Process

Table 1. Outline of the Guidelines Development Process

Topic	Comment
Goal of the Guidelines	Provide guidance to HIV care practitioners in the United States on the optimal use of antiretroviral (ARV) agents in pregnant women who are living with HIV for treatment of HIV infection and for prevention of perinatal transmission of HIV, as well as management of HIV-exposed infants.
Panel Members	The Panel is composed of approximately 30 voting members who have expertise in managing the care of pregnant women living with HIV (e.g., training in obstetrics/gynecology, infectious diseases, or women's health), pharmacology of ARV drugs during pregnancy, and interventions for prevention of perinatal transmission (e.g., specialized training in pediatric HIV infection), as well as community representatives with knowledge of HIV infection in pregnant women and interventions for prevention of perinatal transmission. The U.S. government representatives, appointed by their agencies, include at least one representative from each of the following Department of Health and Human Services agencies: the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), the Health Resources and Services Administration, and the National Institutes of Health (NIH). Members who do not represent U.S. government agencies are selected by Panel members after an open announcement to call for nominations. Each member serves on the Panel for a 3-year period, with an option for re-appointment. The Panel may also include liaison members from the Perinatal HIV Hotline, the American Academy of Pediatrics' Committee on Pediatric AIDS, and the American College of Obstetricians and Gynecologists. A list of all Panel members can be found in the Guidelines Panel Members section.
Financial Disclosures	All members of the Panel submit an annual written financial disclosure that reports any association with manufacturers of ARV drugs or diagnostics used for management of HIV infections. See Financial Disclosure for a list of the latest disclosures.
Users of the Guidelines	Providers of care to pregnant women who are living with HIV and to infants who have been exposed to HIV
Developer	The Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission—a working group of the Office of AIDS Research Advisory Council (OARAC)
Funding Source	Office of AIDS Research, NIH
Evidence for Recommendations	The recommendations in these guidelines are generally based on studies published in peer-reviewed journals. On some occasions, particularly when new information may affect patient safety, unpublished data that was presented at major conferences or prepared by the FDA and/or manufacturers as warnings to the public may be used as evidence to revise the guidelines.
Recommendation Grading	See Table 2.
Method of Synthesizing Data	Each section of the guidelines is assigned to a small group of Panel members with expertise in the area of interest. A structured literature search is conducted by a technical assistance consultant and provided to the Panel working group. The members review and synthesize the available data and propose recommendations to the entire Panel. The Panel discusses all proposals during monthly teleconferences. Proposals are modified based on Panel discussions and then distributed, with ballots, to all Panel members for concurrence and additional comments. If there are substantive comments or votes against approval, the recommended changes and areas of disagreement are brought back to the full Panel (via email or teleconference) for additional review, discussion, and further modification to reach a final version that is acceptable to all Panel members. The recommendations in these final versions represent endorsement from a consensus of members and are included in the guidelines as official Panel recommendations.
Other Guidelines	These guidelines focus on pregnant women living with HIV and their infants. Other guidelines (all of which are available on the AIDS*info* website) outline the use of ARV agents in nonpregnant adults and adolescents with HIV; use of ARV agents in infants and children with HIV; treatment and prevention of opportunistic infections (OIs) in adults and adolescents with HIV, including pregnant women; treatment and prevention of OIs in children who have been exposed to HIV or who have HIV infection; and treatment of people who experience occupational or nonoccupational exposure to HIV. Preconception management for nonpregnant women of reproductive age is briefly discussed in this document. However, for a more detailed discussion of the issues surrounding the treatment of nonpregnant adults, the Working Group defers to the designated expertise offered by the Panels that have developed those guidelines.

Guidelines Development Process

Table 1. Outline of the Guidelines Development Process, cont'd

Topic	Comment
Update Plan	The Panel meets monthly by teleconference to review data that may require modification of the guidelines. Updates may be prompted by new drug approvals (or new indications, new dosing formulations, and/or changes in dosing frequency), significant new safety or efficacy data, or other information that may have a significant impact on the clinical care of patients. In the event of significant new data that may affect patient safety, the Panel may issue a warning announcement and accompanying recommendations on the AIDS*info* website until the guidelines can be updated with appropriate changes.
Public Comments	A 2-week public comment period follows release of the updated guidelines on the AIDS*info* website. The Panel reviews these comments to determine whether additional revisions to the guidelines are indicated. The public may also submit comments to the Panel at any time at contactus@aidsinfo.nih.gov.

Basis for Recommendations

Recommendations in these guidelines are based on scientific evidence and expert opinion. Each recommended statement is rated with a letter of **A**, **B**, or **C** that represents the strength of the recommendation and with a numeral **I**, **II**, or **III** that represents the quality of evidence.

Table 2. Rating Scheme for Recommendations

Strength of Recommendation	Quality of Evidence for Recommendation
A: Strong recommendation for the statement **B:** Moderate recommendation for the statement **C:** Optional recommendation for the statement	**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

References

1. Nesheim SR, Wiener J, Fitz Harris LF, Lampe MA, Weidle PJ. Brief report: estimated incidence of perinatally acquired HIV infection in the United States, 1978–2013. *J Acquir Immune Defic Syndr*. 2017;76(5):461-464. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28991886.
2. Peters H, Francis K, Sconza R, et al. UK mother-to-child HIV transmission rates continue to decline: 2012–2014. *Clin Infect Dis*. 2017;64(4):527-528. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28174911.
3. Nesheim S, Taylor A, Lampe MA, et al. A framework for elimination of perinatal transmission of HIV in the United States. *Pediatrics*. 2012;130(4):738-744. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22945404.
4. Nesheim SR, FitzHarris LF, Lampe MA, Gray KM. Reconsidering the number of women with HIV infection who give birth annually in the United States. *Public Health Rep*. 2018;133(6):637-643. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30265616.

Maternal HIV Testing and Identification of Perinatal HIV Exposure

(Last updated April 16, 2019; last reviewed April 16, 2019)

Panel's Recommendations

- HIV testing is recommended as standard of care for all sexually active women and should be a routine component of preconception care **(AII)**.
- All pregnant women should be tested as early as possible during each pregnancy (see Laboratory Testing for the Diagnosis of HIV Infection: Updated Recommendations and Recommended Laboratory HIV Testing Algorithm for Serum or Plasma Specimens) **(AII)**.
- Partners of pregnant women should be encouraged to undergo HIV testing when their status is unknown **(AIII)**.
- Repeat HIV testing in the third trimester is recommended for pregnant women with negative initial HIV antibody tests who are at increased risk of acquiring HIV, including those who are receiving care in facilities that have an HIV incidence of ≥1 case per 1,000 pregnant women per year, those who reside in jurisdictions with elevated HIV incidence, or those who reside in states that require third-trimester testing (see Revised Recommendations for HIV Testing of Adults, Adolescents, and Pregnant Women in Health-Care Settings **(AII)**.
- Expedited HIV testing at the time of labor or delivery should be performed for any woman with undocumented HIV status; testing should be available 24 hours a day, and results should be available within 1 hour **(AII)**. If results are positive, intrapartum antiretroviral (ARV) prophylaxis should be initiated immediately **(AI)**, and infants should receive an ARV regimen that is appropriate for infants who are at higher risk of perinatal HIV transmission as soon as possible, pending results of supplemental HIV testing **(AII)**. See Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV for guidance.
- Women who have not been tested for HIV before or during labor should undergo expedited HIV antibody testing during the immediate postpartum period (or their newborns should undergo expedited HIV antibody testing) **(AII)**. If the results for the mother or infant are positive, an appropriate infant ARV drug regimen should be initiated immediately, and the mother should not breastfeed unless supplemental HIV testing is negative **(AII)**. Infants with initial positive HIV viral tests (RNA, DNA) should have their ARV regimen modified, if necessary, to a three-drug combination of ARV drugs at treatment doses (see Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV) **(AII)**.
- Results of maternal HIV testing should be documented in the newborn's medical record and communicated to the newborn's primary care provider **(AIII)**.
- HIV testing to determine HIV status is recommended for infants and children in foster care and adoptees for whom maternal HIV status is unknown **(AIII)**.

Rating of Recommendations: A = Strong; B = Moderate; C = Optional

Rating of Evidence: I = One or more randomized trials in children† with clinical outcomes and/or validated endpoints; I* = One or more randomized trials in adults with clinical outcomes and/or validated laboratory endpoints with accompanying data in children† from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies in children† with long-term outcomes; II* = One or more well-designed, nonrandomized trials or observational studies in adults with long-term clinical outcomes with accompanying data in children† from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion

† Studies that include children or children/adolescents, but not studies limited to post-pubertal adolescents

HIV Testing in Pregnancy

HIV infection should be identified prior to pregnancy (see Preconception Counseling and Care for Women of Childbearing Age Living with HIV) or as early in pregnancy as possible. This provides the best opportunity to improve maternal health and pregnancy outcomes, to prevent infant acquisition of HIV, and to identify HIV infection and start therapy as soon as possible in infants who acquire HIV. Universal voluntary HIV testing is recommended as the standard of care for all pregnant women in the United States by the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV and the Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission (the Panels), the Centers for Disease Control and Prevention (CDC), the American Academy of Pediatrics, the American College of Obstetricians and Gynecologists, and the U.S. Preventive Services Task Force.[1-5] All HIV testing should be performed in a manner that is consistent with state and local laws. The CDC recommends the "opt-out" approach, which involves notifying pregnant women that HIV testing will be performed as part of routine care unless they choose not to be tested for HIV.[2] The "opt-out" approach during pregnancy is allowed

in some jurisdictions.[6] The "opt-in" approach involves obtaining specific consent before testing, and this approach has been associated with lower testing rates.[7,8] The mandatory newborn HIV testing approach, adopted by several states, involves testing newborns for perinatal HIV exposure with or without maternal consent if the mother has declined prenatal or intrapartum testing.

Partners of pregnant women should also be encouraged to undergo HIV testing when their status is unknown, consistent with the 2006 CDC recommendations for HIV testing of all individuals in the United States. Testing will facilitate linkage to care if a partner is found to have HIV infection. Because women are more susceptible to HIV acquisition during pregnancy and the postpartum period,[9] clinicians can also initiate a discussion about preventative interventions, including pre-exposure prophylaxis, if the pregnant woman is uninfected. In addition, clinicians should assess the risk of acute HIV infection, particularly in late in pregnancy, because a pregnant woman may receive a negative result by expedited or rapid HIV testing when she is in the window period. However, during this period she would be viremic with high risk of perinatal transmission to her newborn. See Acute HIV Infection for more information.

Providers should be aware that gaps in maternal HIV testing do occur and can contribute to missed opportunities for preventing perinatal HIV transmission.[10-13] As discussed in the following sections, maternal HIV testing should be performed as early as possible during pregnancy, with repeat HIV testing in the third trimester for women who are at increased risk of acquiring HIV or who are living in areas of high HIV incidence. Women with unknown or undocumented HIV status should be tested during labor or after delivery.[10-13] Determining antenatal maternal HIV status enables:

- Women living with HIV to receive appropriate antiretroviral therapy (ART) and prophylaxis against opportunistic infections;
- Initiation of treatment in the identified women, which may also decrease the risk of transmission to their partners;[2,14,15]
- Referral of partners without HIV for preventative interventions;
- Provision of ART to the mother during pregnancy and labor, and provision of antiretroviral (ARV) drug prophylaxis to the newborn to reduce the risk of perinatal transmission;
- Counseling of women living with HIV about the indications for (and potential benefits of) scheduled elective cesarean delivery to reduce the risk of perinatal transmission of HIV;[16-18]
- Counseling of women living with HIV about the risks of HIV transmission through breast milk (breastfeeding is not recommended for women with HIV living in the United States);[19] *and*
- Early diagnostic evaluation of infants exposed to HIV (see Diagnosis of HIV Infection in Infants and Children), as well as testing of partners and other children, to permit prompt initiation of ART and any indicated prophylaxis.[1,20-22]

Technological improvements have resulted in an increased ability to detect early HIV infection and reduced performance time for laboratory-based assays; assays can now be completed in <1 hour. Accordingly, the Panels now incorporate CDC's 2014 Laboratory Testing for the Diagnosis of HIV Infection: Updated Recommendations.[23] The guidelines recommend that clinicians initiate HIV testing with an immunoassay that is capable of detecting HIV-1 antibodies, HIV-2 antibodies, and HIV-1 p24 antigen (referred to as an antigen/antibody combination immunoassay). Individuals with a reactive antigen/antibody combination immunoassay should be tested further with an HIV-1/HIV-2 antibody differentiation assay (referred to as supplemental testing). Individuals with a reactive antigen/antibody combination immunoassay and a nonreactive differentiation test should be tested with a Food and Drug Administration-approved HIV nucleic acid test (NAT) to establish diagnosis of acute HIV infection (see the CDC's Recommended Laboratory HIV Testing Algorithm for Serum or Plasma Specimens).

The antigen/antibody combination immunoassay is the test of choice and can be done quickly (referred to as an expedited test), but it requires trained laboratory staff and therefore may not be available in some hospitals 24 hours a day. When this test is unavailable, then initial testing should be performed by the most sensitive expedited or rapid test available. Every delivery unit needs to have access to an HIV test that can be done rapidly (i.e., in <1 hour) 24 hours a day. If the test result is positive, the test to confirm HIV infection should be done as soon as possible (as with all initial assays with positive results). Older antibody tests have lower sensitivity in the context of recent acquisition of HIV than antigen/antibody combination immunoassays. Therefore, testing that follows the 2014 CDC algorithm should be considered if HIV risk cannot be ruled out. Results of maternal HIV testing should be documented in the newborn's medical record and communicated to the newborn's primary care provider.

Repeat HIV Testing in the Third Trimester

Repeat HIV testing during the third trimester, before 36 weeks' gestation, is recommended (see Acute HIV Infection)[24] for pregnant women with negative results on their initial HIV antibody tests who:[5]

- Are known to be at high risk of acquiring HIV (e.g., those who are injection drug users or partners of injection drug users, those who exchange sex for money or drugs, those who are sex partners of individuals with HIV, those who have had a new sex partner or more than one sex partner during the current pregnancy, or those who have been diagnosed with a new sexually transmitted disease during pregnancy. Additionally, an analysis of 2013 National HIV Behavioral Surveillance data found that the prevalence of risk-related sexual behaviors was higher in recently incarcerated women than in those who were never incarcerated);[25] *or*
- Are receiving health care in facilities in which prenatal screening identifies one or more pregnant woman with HIV per 1,000 women screened, or who reside in a jurisdiction that has a high incidence of HIV or AIDS in women between the ages of 15 and 45 years (a list of jurisdictions where such screening is recommended is found in the 2006 CDC recommendations; a more up-to-date list is forthcoming), or who reside in states that require third-trimester testing; *or*
- Have signs or symptoms of acute HIV (e.g., fever, lymphadenopathy, skin rash, myalgia, headaches, oral ulcers, leukopenia, thrombocytopenia, elevated transaminase levels).[2,26-28]

Women who decline testing earlier in pregnancy should be offered testing again during the third trimester. In these cases, an antigen/antibody combination immunoassay should be used, as these tests have a higher sensitivity in the setting of acute HIV infection than older antibody tests.[23,29] When acute HIV infection is suspected during pregnancy, during the intrapartum period, or while breastfeeding, a plasma HIV RNA test result should be performed in conjunction with an antigen/antibody combination immunoassay (see Acute and Recent [Early] HIV Infection in the Adult and Adolescent Antiretroviral Guidelines).

Providers should be proactive in assessing a woman's HIV acquisition risk and implementing third-trimester HIV retesting in areas where it is not routine, when indicated. A recent study in Baltimore found that only 28% of women were retested for HIV despite the high incidence of HIV in Maryland and a high frequency of clinical risk factors.[13,30] A study of data from 2007 to 2014 on Florida children with perinatal HIV exposure found that perinatal HIV transmission was associated with poor or late prenatal care, diagnosis of maternal HIV during labor and delivery or after birth, and, in some, acute maternal infection (as indicated by negative results for initial tests). In addition, the study noted that third-trimester HIV tests were not performed in a portion of the patients.[30]

HIV Testing During Labor in Women with Unknown HIV Status

Women in labor whose HIV status is undocumented should undergo HIV testing in order to identify HIV infection in the mothers and HIV exposure in their infants. HIV testing during labor has been found to

be feasible, accurate, timely, and useful both in ensuring prompt initiation of intrapartum maternal ARV prophylaxis (see Intrapartum Antiretroviral Therapy/Prophylaxis) and in developing an appropriate ARV regimen for infants who are at high risk of perinatal transmission (see Table 11).[1-3,20,27,31,32]

Policies and procedures must be in place to ensure that staff are prepared to provide patient education and expedited HIV testing, that appropriate ARV drugs are available whenever needed, and that follow-up procedures are in place for women who receive an HIV diagnosis and their infants.

If the antigen/antibody combination immunoassay is not available, initial testing should be performed by the most sensitive expedited test available.

A positive expedited HIV test result must be followed by a supplemental test.[23] Immediate initiation of maternal intravenous intrapartum zidovudine is recommended to prevent perinatal transmission of HIV pending the supplemental result after an initial positive expedited HIV test result (see Intrapartum Antiretroviral Therapy/Prophylaxis).[1-4,20,27] Pending results of supplemental maternal testing, infants should receive an ARV regimen that is appropriate for infants who are at higher risk of perinatal HIV transmission as soon as possible, (see Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV). No further testing is required for specimens that are nonreactive (negative) on the initial immunoassay, unless acute HIV infection is suspected.[23]

HIV Testing During the Postpartum Period

Women who have not been tested for HIV before or during labor should be offered expedited testing during the immediate postpartum period. When mothers are unavailable for testing, their newborns should undergo expedited HIV testing, using the antigen/antibody combination immunoassay.[1,20,27] Maternal testing should be done using the antigen/antibody combination immunoassay to screen for established and acute HIV; results should be obtained in <1 hour. If acute HIV infection is a possibility, then a plasma HIV NAT test should be sent as well. Expedited HIV assays should be used to identify infants who have been exposed to HIV, because postnatal ARV drugs need to be initiated as soon as possible—ideally ≤6 hours after birth—to be effective in preventing perinatal transmission. When an initial HIV test is positive in mother or infant, it is strongly recommended that clinicians initiate an ARV regimen that is appropriate for infants who are at higher risk of perinatal HIV transmission and counsel the mother against breastfeeding. Both actions can be taken before the results of supplemental maternal HIV tests have confirmed the presence of HIV (see Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV). Breast milk can be expressed while supplemental HIV diagnostic testing is being completed, but it should not be given to the infant until testing confirms that the mother is HIV negative. If supplemental test results are negative and acute HIV is excluded, infant ARV drugs can be discontinued. In the absence of ongoing maternal HIV exposure, breastfeeding can be initiated.

Infant HIV Testing when Maternal HIV Test Results are Unavailable

When maternal HIV test results are unavailable (e.g., for infants and children who are in foster care) or their accuracy cannot be evaluated (e.g., for infants and children who were adopted from countries where results are not reported in English), HIV testing is indicated to identify HIV in those infants or children.[1] Mechanisms should be developed to facilitate prompt HIV screening for infants who have been abandoned and are in the custody of the state. The choice of test will vary based on the age of the child (see Diagnosis of HIV Infection in Infants and Children).

Acute Maternal HIV Infection During Pregnancy or Breastfeeding

Women are more susceptible to HIV infection during pregnancy and the early postpartum period.[9] Risk of HIV exposure should be assessed in all women who are considering becoming pregnant, as well as in all pregnant women who previously tested HIV negative. Women with risk factors for HIV acquisition should

receive prevention counseling and appropriate interventions, including pre-exposure prophylaxis if indicated (see Preconception Counseling and Care for Women of Childbearing Age Living with HIV). The risk of perinatal transmission of HIV is increased in infants born to women who have acute HIV during pregnancy or lactation.[24,33-36] The antigen/antibody combination immunoassay will detect acute infection more quickly than other immunoassays, within approximately 10 days. When acute HIV infection is suspected, a plasma HIV RNA test should be sent as well, because virologic tests can detect the presence of HIV earlier than the antigen/antibody combination immunoassay. Women with possible acute HIV infection who are breastfeeding should cease breastfeeding immediately until HIV infection is confirmed or excluded.[19] Expressing breast milk can be recommended while HIV diagnostic testing is completed. Breastfeeding can resume if HIV infection is excluded and there is no ongoing maternal exposure to HIV. Care of pregnant or breastfeeding women with acute or early HIV and their infants should follow the recommendations in the Perinatal Guidelines (see Acute HIV Infection and Guidance for Counseling and Managing Women Living with HIV in the United States Who Desire to Breastfeed).

Other Issues

Clinicians should be aware of public health surveillance systems and regulations that may exist in their jurisdictions for reporting infants who have been exposed to HIV; this is in addition to mandatory reporting of persons with HIV, including infants. Reporting infants who have been exposed to HIV allows the appropriate public health functions to be accomplished.

References

1. American Academy of Pediatrics Committee on Pediatric AIDS. HIV testing and prophylaxis to prevent mother-to-child transmission in the United States. *Pediatrics*. 2008;122(5):1127-1134. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18977995.

2. Branson BM, Handsfield HH, Lampe MA, et al. Revised recommendations for HIV testing of adults, adolescents, and pregnant women in health-care settings. *MMWR Recomm Rep*. 2006;55(RR-14):1-17; quiz CE11-14. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16988643.

3. Chou R, Cantor AG, Zakher B, Bougatsos C. Screening for HIV in pregnant women: systematic review to update the 2005 U.S. Preventive services task force recommendation. *Ann Intern Med*. 2012;157(10):719-728. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23165663.

4. U.S. Preventive Services Task Force. Screening for HIV: recommendation statement. 2013. Available at: http://www.uspreventiveservicestaskforce.org/uspstf/uspshivi.htm.

5. American College of Obstetrics and Gynecology: Committee on Obstetric Practice, HIV Expert Work Group. ACOG Committee Opinion No. 752: Prenatal and perinatal Human Immunodeficiency Virus testing. *Obstet Gynecol*. 2018;132(3):e138-e142. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30134428.

6. Clinical Consultation Center. Compendium of state HIV testing laws. Perinatal quick reference guide: a guide to states' perinatal HIV testing laws for clinicians. 2011. Available at: http://nccc.ucsf.edu/wp-content/uploads/2014/03/State_HIV_Testing_Laws_Perinatal_Quick_Reference.pdf.

7. Boer K, Smit C, van der Flier M, de Wolf F, Athena cohort study group. The comparison of the performance of two screening strategies identifying newly-diagnosed HIV during pregnancy. *Eur J Public Health*. 2011;21(5):632-637. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21051473.

8. Yudin MH, Moravac C, Shah RR. Influence of an "opt-out" test strategy and patient factors on human immunodeficiency virus screening in pregnancy. *Obstet Gynecol*. 2007;110(1):81-86. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17601900.

9. Thomson KA, Hughes J, Baeten JM, et al. Increased risk of HIV acquisition among women throughout pregnancy and during the postpartum period: a prospective per-coital-act analysis among women with HIV-infected partners. *J Infect Dis*. 2018;218(1):16-25. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29514254.

10. Whitmore SK, Taylor AW, Espinoza L, Shouse RL, Lampe MA, Nesheim S. Correlates of mother-to-child transmission

of HIV in the United States and Puerto Rico. *Pediatrics*. 2012;129(1):e74-81. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22144694.

11. Ezeanolue EE, Pharr JR, Hunt A, Patel D, Jackson D. Why are children still being infected with HIV? Impact of an integrated public health and clinical practice intervention on mother-to-child HIV transmission in Las Vegas, Nevada, 2007–2012. *Ann Med Health Sci Res*. 2015;5(4):253-259. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26229713.

12. Taylor AW, Nesheim SR, Zhang X, et al. Estimated perinatal HIV infection among infants born in the United States, 2002–2013. *JAMA Pediatr*. 2017;171(5):435-442. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28319246.

13. Liao C, Golden WC, Anderson JR, Coleman JS. Missed opportunities for repeat HIV testing in pregnancy: implications for elimination of mother-to-child transmission in the United States. *AIDS Patient Care STDS*. 2017;31(1):20-26. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27936863.

14. Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med*. 2011;365(6):493-505. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21767103.

15. Baggaley RF, White RG, Hollingsworth TD, Boily MC. Heterosexual HIV-1 infectiousness and antiretroviral use: systematic review of prospective studies of discordant couples. *Epidemiology*. 2013;24(1):110-121. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23222513.

16. Jamieson DJ, Read JS, Kourtis AP, Durant TM, Lampe MA, Dominguez KL. Cesarean delivery for HIV-infected women: recommendations and controversies. Am J *Obstet Gynecol*. 2007;197(3 Suppl):S96-100. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17825656.

17. Tubiana R, Le Chenadec J, Rouzioux C, et al. Factors associated with mother-to-child transmission of HIV-1 despite a maternal viral load <500 copies/ml at delivery: a case-control study nested in the French perinatal cohort (EPF-ANRS CO1). *Clin Infect Dis*. 2010;50(4):585-596. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20070234.

18. Townsend CL, Cortina-Borja M, Peckham CS, de Ruiter A, Lyall H, Tookey PA. Low rates of mother-to-child transmission of HIV following effective pregnancy interventions in the United Kingdom and Ireland, 2000-2006. *AIDS*. 2008;22(8):973-981. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18453857.

19. Committee On Pediatric AIDS. Infant feeding and transmission of human immunodeficiency virus in the United States. *Pediatrics*. 2013;131(2):391-396. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23359577.

20. Havens PL, Mofenson LM, American Academy of Pediatrics Committee on Pediatric AIDS. Evaluation and management of the infant exposed to HIV-1 in the United States. *Pediatrics*. 2009;123(1):175-187. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19117880.

21. Hegazi A, Forsyth S, Prime K, Bashh Adolescent Special Interest Group. Testing the children of HIV-infected parents: 6 years on from 'don't forget the children'. *Sex Transm Infect*. 2015;91(2):76-77. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25316913.

22. Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. 2018. Available at: http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf.

23. Branson BM, Owen SM, Wesolowski LG, et al. Laboratory testing for the diagnosis of HIV infection: updated recommendations. Centers for Disease Control and Prevention. 2014. Available at: https://www.medbox.org/laboratory-testing-for-the-diagnosis-of-hiv-infection-updated-recommendations/download.pdf.

24. Birkhead GS, Pulver WP, Warren BL, Hackel S, Rodriguez D, Smith L. Acquiring human immunodeficiency virus during pregnancy and mother-to-child transmission in New York: 2002–2006. *Obstet Gynecol*. 2010;115(6):1247-1255. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20502297.

25. Wise A, Finlayson T, Nerlander L, Sionean C, Paz-Bailey G, NHBS Study Group. Incarceration, sexual risk-related behaviors, and HIV infection among women at increased risk of HIV infection, 20 United States cities. *J Acquir Immune Defic Syndr*. 2017;75 Suppl 3:S261-S267. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28604426.

26. Sansom SL, Jamieson DJ, Farnham PG, Bulterys M, Fowler MG. Human immunodeficiency virus retesting during

pregnancy: costs and effectiveness in preventing perinatal transmission. *Obstet Gynecol*. 2003;102(4):782-790. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14551009.

27. American College of Obstetrics: Gynecology Committee on Obstetric Practice. ACOG committee opinion no. 418: prenatal and perinatal human immunodeficiency virus testing: expanded recommendations. *Obstet Gynecol*. 2008;112(3):739-742. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18757690.

28. Richey LE, Halperin J. Acute human immunodeficiency virus infection. *Am J Med Sci*. 2013;345(2):136-142. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23095473.

29. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV. 2018. Available at: http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf.

30. Trepka MJ, Mukherjee S, Beck-Sague C, et al. Missed opportunities for preventing perinatal transmission of human immunodeficiency virus, Florida, 2007-2014. *South Med J*. 2017;110(2):116-128. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28158882.

31. Yee LM, Miller ES, Statton A, et al. Sustainability of statewide rapid HIV testing in labor and delivery. *AIDS Behav*. 2018;22(2):538-544. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28986656.

32. Scott RK, Crochet S, Huang CC. Universal rapid human immunodeficiency virus screening at delivery: a cost-effectiveness analysis. *Infec Dis Obstet Gynecol*. 2018;2018:6024698. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29731602.

33. Lockman S, Creek T. Acute maternal HIV infection during pregnancy and breast-feeding: substantial risk to infants. *J Infect Dis*. 2009;200(5):667-669. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19627246.

34. Taha TE, James MM, Hoover DR, et al. Association of recent HIV infection and in-utero HIV-1 transmission. *AIDS*. 2011;25(11):1357-1364. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21572305.

35. Humphrey JH, Marinda E, Mutasa K, et al. Mother to child transmission of HIV among Zimbabwean women who seroconverted postnatally: prospective cohort study. *BMJ*. 2010;341:c6580. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21177735.

36. Drake AL, Wagner A, Richardson B, John-Stewart G. Incident HIV during pregnancy and postpartum and risk of mother-to-child HIV transmission: a systematic review and meta-analysis. *PLoS Med*. 2014;11(2):e1001608. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24586123.

Preconception Counseling and Care for Women of Childbearing Age Living with HIV (Last updated December 7, 2018; last reviewed December 7, 2018)

Panel's Recommendations
• Discuss reproductive desires with all women of childbearing age on an ongoing basis throughout the course of their care **(AIII)**.
• Provide information about effective and appropriate contraceptive methods to reduce the likelihood of unplanned pregnancy **(AI)**.
• During preconception counseling, provide information on safe sex and encourage the elimination of alcohol, tobacco, and other drugs of abuse; if elimination is not feasible, clinicians should provide appropriate treatment (e.g., methadone or buprenorphine) or counsel patients on how to manage health risks (e.g., use of syringe services program) **(AII)**.
• All women living with HIV who are contemplating pregnancy should be receiving antiretroviral therapy (ART) and have a plasma viral load below the limit of detection prior to conception **(AII)**.
• When selecting or evaluating ART for women of childbearing age living with HIV, consider a regimen's effectiveness, a woman's hepatitis B status, teratogenic potential of the drugs in the ART regimen, and possible adverse outcomes for the mother and fetus **(AII)**.
• HIV infection does not preclude the use of any contraceptive method; however, drug-drug interactions between hormonal contraceptives and ART should be considered **(AII)**.
Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*
Rating of Evidence: *I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

Overview

The Centers for Disease Control and Prevention (CDC), the American College of Obstetricians and Gynecologists (ACOG), and other national organizations recommend offering all women of childbearing age comprehensive family planning and the opportunity to receive preconception counseling and care as a component of routine primary medical care. The purpose of preconception care is to improve the health of each woman before conception by identifying risk factors for adverse maternal or fetal outcomes, providing education and counseling tailored to patients' individual needs, and treating or stabilizing medical conditions to optimize maternal and fetal outcomes.[1] Preconception care is not something that occurs in a single clinical visit; rather, it is a process of ongoing care and interventions integrated into primary care to address the needs of women during the different stages of reproductive life. It is important that comprehensive family planning and preconception care be integrated into routine health visits, because almost half of all pregnancies in the United States are unplanned.[2-10] Providers should initiate and document a nonjudgmental conversation with all women of reproductive age concerning their reproductive desires, because women may be reluctant to bring this up themselves.[11-14] Health care providers who routinely care for women of reproductive age who are living with HIV play an important role in promoting preconception health and informed reproductive decisions. However, even among providers who offer primary care to women living with HIV, the delivery of comprehensive reproductive counseling often falls short of the current guidelines.[15]

The fundamental principles of preconception counseling and care are outlined in the CDC Preconception Care Work Group's Recommendations to Improve Preconception Health and Health Care. In addition to the general components of preconception counseling and care that are appropriate for all women of reproductive age, women living with HIV have specific needs that should be addressed.[16-19] Health care providers should:

- Discuss reproductive options, actively assess women's pregnancy intentions on an ongoing basis throughout the course of care, and, when appropriate, make referrals to experts in HIV and women's health, including experts in reproductive endocrinology and infertility when necessary.[11,20]
- The primary treatment goal for women who are on ART and planning a pregnancy should be sustained suppression of plasma viral load (below the limit of) detection prior to conception. This is important for the

health of the woman and to decrease the risk of both perinatal transmission and sexual transmission to a partner without HIV (see Reproductive Options).

- Counsel women on safer sex practices (including condoms and ART) that prevent HIV transmission to sexual partners, protect women from acquiring sexually transmitted infections, and reduce the risk of acquiring resistant strains of HIV (see Reproductive Options).
- Encourage sexual partners to receive HIV counseling and testing so that they can seek HIV care if they have HIV or seek advice about oral pre-exposure prophylaxis (PrEP) and other measures to prevent HIV acquisition if they do not have HIV.
- Counsel women on eliminating the use of alcohol, tobacco, and other drugs of abuse. Appropriately treat (e.g., with methadone or buprenorphine) and manage (e.g., provide access to syringe services program) the use of these drugs when elimination is not feasible.
- Counsel women contemplating pregnancy to take a daily multivitamin that contains 400 mcg of folic acid to help prevent certain birth defects. Women who are at higher risk of having a child with neural tube defects than the baseline population are candidates for higher (1 to 4 mg) dose folic acid supplementation.
- Educate and counsel women about risk factors for perinatal transmission of HIV, strategies to reduce those risks, potential effects of HIV or of antiretroviral (ARV) drugs given during pregnancy on pregnancy course and outcomes, and the recommendation that women living with HIV in the United States not breastfeed because of the risk of transmission of HIV to their infants and the availability of safe and sustainable infant feeding alternatives.
- When prescribing antiretroviral therapy (ART) to women of childbearing age, consider the regimen's effectiveness, an individual's hepatitis B virus (HBV) status, the potential for teratogenicity, and possible adverse outcomes for mother and fetus.[21-23]
- Provide counseling about the potential risk of neural tube defects when dolutegravir is taken during conception to patients who are currently receiving dolutegravir as part of their ARV regimen or who wish to be started on dolutegravir, see Interim Recommendations about the Use of Dolutegravir at the Time of Conception and During Pregnancy in Teratogenicity and Recommendations for the Use of Antiretroviral Drugs During Pregnancy.
- Use the preconception period to modify the ART regimen of women who are contemplating pregnancy to optimize virologic suppression and minimize potential adverse effects, see Recommendations for Use of Antiretroviral Drugs in Pregnancy and Table 7.
- Recognize that women with perinatally acquired HIV may have special needs[24] (see Women with Perinatal HIV Infection).
- Evaluate and manage therapy-associated side effects (e.g., hyperglycemia, anemia, hepatotoxicity) that may adversely impact maternal-fetal health outcomes.
- Administer all vaccines as indicated, (see Guidance for Vaccine Recommendations for Pregnant and Breastfeeding Women and 2013 IDSA Clinical Practice Guideline for Vaccination of the Immunocompromised Host) including vaccines for influenza, pneumococcus, HBV, and tetanus. All women, including those with HIV, should receive Tdap vaccination during each pregnancy.
- Offer all women who do not currently desire pregnancy effective and appropriate contraceptive methods to reduce the likelihood of unintended pregnancy. Women living with HIV can use all available contraceptive methods, including hormonal contraception (e.g., pill, patch, ring, injection, implant) and

intrauterine devices (IUDs).[25] Providers should be aware of potential interactions between ARV drugs and hormonal contraceptives that could lower contraceptive efficacy (see Table 3 below).

- Offer emergency contraception as appropriate, including emergency contraceptive pills and the copper IUD (see The ACOG Practice Bulletin on Emergency Contraception). Concerns about drug interactions between ARV drugs and emergency contraceptive pills containing estrogen and a progestin, or containing levonorgestrel only, may be similar to concerns when those formulations are used for regular contraception.[26] There are no data on potential interactions between ARV drugs and ulipristal acetate, a progesterone receptor modulator; however, ulipristal acetate is predominantly metabolized by cytochrome P450 (CYP) 3A4, so interactions may be expected (see the HIV Drug Interaction Checker).
- Optimize the woman's health prior to conception (e.g., ensure appropriate folate intake, test for **all** sexually transmitted infections and treat as indicated, consider the teratogenic potential of **all** prescribed medications, and consider switching to safer medications).

Drug-Drug Interactions Between Hormonal Contraceptives and Antiretroviral Therapy

Data on drug interactions between ARV agents and hormonal contraceptives primarily come from drug labels and limited studies.[26-42] The contraceptive effectiveness of the levonorgestrel IUD (Mirena) is largely through local (i.e., intrauterine) release of levonorgestrel, not through systemic absorption. The CDC's U.S. Medical Eligibility Criteria for Contraceptive Use list the levonorgestrel IUD (Mirena) as category 1 (no restrictions) in drug interactions with all ARVs in women who already have an IUD and category 1/2 (benefits outweigh risk) for those initiating use of an IUD.

Hormonal contraceptives can be used with ART in women without other contraindications. Additional or alternative methods of contraception may be recommended when drug interactions are known. For women using ritonavir-boosted protease inhibitors (PI/r) who are also on combination hormonal contraceptives (e.g., pills, patches, rings) or progestin-only pills, use of an alternative or additional method of contraception may be considered, since the AUC of hormones may be decreased in some PI/r (i.e., darunavir/ritonavir [DRV/r], fosamprenavir/ritonavir, and lopinavir/ritonavir [LPV/r]) but not in others (see Table 3). Depot medroxyprogesterone acetate (DMPA) can be used without restriction because of its relatively higher dose than other progesterone-based contraception, and limited studies have shown no significant interaction between DMPA and ARV drugs.[28,30,40,43] Nucleoside reverse transcriptase inhibitors have no effect on hormonal contraceptive doses.

While contraceptive implants (e.g., etonogestrel/levonorgestrel) generally can be used in women on ART, both pharmacokinetic (PK) and clinical data suggest that these implants have decreased efficacy when used with efavirenz-based regimens.[38,44-46] Scarsi et al. reported on three groups of Ugandan women living with HIV (those who were not on ART [17 women], those taking nevirapine-based ART [20 women], and those taking efavirenz-based ART [20 women]) who had levonorgestrel implants placed and had levonorgestrel PK levels assessed at 1, 4, 12, 24, 36, and 48 weeks post-insertion. The geometric mean ratio of levonorgestrel (patients taking efavirenz-based ART vs. ART-naive patients) was 0.53 at 24 weeks and 0.43 at 48 weeks. Three pregnancies (3/20, 15%) occurred in the efavirenz group between weeks 36 and 48, whereas no pregnancies occurred in the ART-naive or nevirapine groups.[42]

In a study of 570 women with HIV in Swaziland who had levonorgestrel implants (i.e., Jadelle), none of the women on nevirapine- or LPV/r-based regimens (n = 208 and n = 13, respectively) became pregnant, whereas 15 women on efavirenz (n = 121; 12.4%) became pregnant.[38] Because of their overall efficacy, implants remain equally effective as or more effective than oral and injectable contraceptives among women with HIV who are using efavirenz, and all hormonal contraceptives remain more effective than no contraception among these women.[45,47] A study collected data from 5,153 women with HIV who were followed prospectively for 1 to 3 years. During the follow-up period, 9% of the women used implants (mostly levonorgestrel), 40% used injectables, and 14% used oral contraceptives; 31% of these women took ART during the follow-up period, mostly nevirapine (75%) or efavirenz (15%). Among women not using

contraception, pregnancy rates were 13.2 per 100 person-years for those who were on ART and 22.5 per 100 person-years for those who were not on ART. Implants greatly reduced the incidence of pregnancy among women on ART (adjusted hazard ratio[aHR] 0.06; 95% CI, 0.01–0.45) and not on ART (aHR 0.05; 95% CI, 0.02–0.11). Injectables and oral contraceptives also reduced pregnancy risk, though to lesser degrees. ART use did not significantly diminish contraceptive effectiveness, although all methods showed nonstatistically significant reduced contraceptive effectiveness when a woman was using efavirenz concurrently.[47]

Because data are limited on pregnancy rates among women on different hormonal contraceptives and ARV drugs, the dosing recommendations in Table 3 are based on consensus expert opinion. Whenever possible, the recommendations are based on available data regarding PK interactions between ARV drugs and combined hormonal methods, DMPA, and levonorgestrel and etonogestrel implants. The smallest decrease in PK for which an alternative method was recommended was a 14% decrease in norethindrone (with DRV/r). For women using atazanavir without ritonavir boosting (ethinyl estradiol increase 48%, norethindrone increase 110%), the Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission (the Panel) recommends use of oral contraceptives containing ≤30 µg ethinyl estradiol. The Panel does not recommend any change in ethinyl estradiol dose for etravirine (ethinyl estradiol increase 22%), rilpivirine (ethinyl estradiol increase 14%), or indinavir (ethinyl estradiol increase 25%, norethindrone increase 26%).

Table 3. Drug Interactions Between Antiretroviral Agents and Hormonal Contraceptives (page 1 of 8)
Note: All recommendations in the following table are based on consensus expert opinion. More details can be found in the CDC's U.S. Medical Eligibility Criteria for Contraceptive Use, 2016.

ARV Drug	Effect on Contraceptive Drug Levels and Contraceptive's Effects on ART and HIV	Clinical Studies	Dosing Recommendation/ Clinical Comment for COC/P/R	Dosing Recommendation/ Clinical Comment POPs	Dosing Recommendation/ Clinical Comment for DMPA[a]	Dosing Recommendation/ Clinical Comment for Etonogestrel Implants	Justification/ Evidence for Recommendation
NNRTIs							
EFV	COC: • No effect on EE concentrations • ↓ active metabolites of norgestimate LN AUC ↓ 83%; norelgestromin AUC ↓ 64%[31] • Etonogestrel (in COC) C_{24h} ↓ 61%[37] DMPA: • No effect on DMPA levels[28,30] Etonogestrel Implant: • Etonogestrel AUC ↓ 63% to 82%[46,48] LN Implant: • LN AUC ↓ 47%[42] • LN (emergency contraception) AUC ↓ 58%[26] Changes in ARV Levels and/or Effects on HIV *COC:* • No effect on EFV concentrations[31] • EFV C_{12h} ↓ 22%; was under therapeutic threshold in 3/16 subjects[37] *DMPA:* • No effect on HIV disease progression[28,49,50] • No effect on EFV concentrations[28]	COC: • No difference in pregnancy rates[47] • Pregnancy rate higher (13%) in women using COCs and EFV than COCs alone[45,51] • Progesterone >3 ng/mL (a surrogate for ovulation) in 3/16 women[52] • No ovulations[31] DMPA: • No increase in pregnancy rates[28,45,47,50] • Low progesterone[28,30,50] Etonogestrel Implant: • Pregnancy rate higher with EFV compared with no ART, but still lower than other hormonal methods of contraception[45] • Presumptive ovulation in 5%[48] LN Implant: • 12% pregnancy rate[38] • 15% pregnancy rate[42] • Pregnancy rate higher with EFV compared with no ART, but still lower than other hormonal methods of contraception[45]	Consider an alternative method (or a reliable method of barrier contraception) in addition to this method.	Consider an alternative method (or a reliable method of barrier contraception) in addition to this method.	No additional contraceptive protection is needed.	Consider an alternative method (or a reliable method of barrier contraception) in addition to this method.	For COCs, some studies suggest higher pregnancy rate and ovulation rate and decreased progestin levels. EFV may decrease, but clinical significance unclear. For DMPA, evidence does not show effects on pregnancy rate, ovulation, or DMPA levels. Also, no effect on HIV disease progression or EFV levels. For implants, some studies suggest higher pregnancy rate and decreased hormone levels.

Table 3. Drug Interactions Between Antiretroviral Agents and Hormonal Contraceptives (page 2 of 8)

ARV Drug	Effect on Contraceptive Drug Levels and Contraceptive's Effects on ART and HIV	Clinical Studies	Dosing Recommendation/ Clinical Comment for COC/P/R	Dosing Recommendation/ Clinical Comment POPs	Dosing Recommendation/ Clinical Comment for DMPA[a]	Dosing Recommendation/ Clinical Comment for Etonogestrel Implants	Justification/ Evidence for Recommendation
NNRTIs, continued							
EFV, continued	LN Implant: • No effect on HIV disease progression[42]	No increase in pregnancy rate[47]					
ETR	EE AUC ↑ 22%[53] NE: • No significant effect[53]	COC: • No ovulations[53]	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	For COCs, 1 study found no ovulations and no significant change in progestin levels. No evidence on POPs.
NVP	EE AUC ↓ 29%;[54] no change in EE AUC[55] NE AUC ↓ 18%[54] Etonogestrel (in COC) C_{24h} ↓ 22%[37] DMPA: • No significant change[28] LN Implant: • LN AUC ↑ 35%[42] Changes in ARV Levels and/or Effects on HIV *COC:* • No significant effect on NVP levels[52,54,56] *DMPA:* • No effect on HIV disease progression[28,49,50,57] *LN Implant:* • No effect on HIV disease progression[42,58]	COC: • No increase in pregnancy rate[45,47,51,59,60] • No ovulations[52,55,60] DMPA: • No increase in pregnancy rate[45,47,50,59] • No ovulations[28] Etonogestrel Implant: • No increase in pregnancy rate[45] LN Implant: • No increase in pregnancy rate[38,42,45,47,58]	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	No additional contraceptive protection is needed	For COCs, evidence does not show effects on pregnancy rate or ovulations. Evidence demonstrated small decrease in progestin levels. Also, no effect on NVP levels. For DMPA, evidence does not show effects on pregnancy rate, ovulation, or DMPA levels. Also, no effect on HIV disease progression. For implants, evidence does not show effects on pregnancy rate or HIV disease progression.

Table 3. Drug Interactions Between Antiretroviral Agents and Hormonal Contraceptives (page 3 of 8)

ARV Drug	Effect on Contraceptive Drug Levels and Contraceptive's Effects on ART and HIV	Clinical Studies	Dosing Recommendation/ Clinical Comment for COC/P/R	Dosing Recommendation/ Clinical Comment POPs	Dosing Recommendation/ Clinical Comment for DMPA[a]	Dosing Recommendation/ Clinical Comment for Etonogestrel Implants	Justification/ Evidence for Recommendation
NNRTIs, continued							
RPV	EE AUC ↑ 14%[36] NE: • No significant change[36] Changes in ARV Levels and/or Effects on HIV *COC:* • No change in RPV levels compared to historical controls[36]	COC: • No change in progesterone[36]	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	For COCs, evidence does not show effects on ovulation or progestin levels. Also, no change in RPV levels. No evidence on POPs.
RTV-Boosted PIs							
ATV/r	EE AUC ↓ 19%[61] Norgestimate AUC ↑ 85%[61] POP: • NE AUC ↑ 50%[62]	N/A	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	For COCs, increase in progestin levels seen in only 1 study. For POPs, increase in progestin levels seen in only 1 study. RTV inhibits CYP3A4, which may increase contraceptive hormone levels.
DRV/r	EE AUC ↓ 44%[63] NE AUC ↓ 14%[63]	N/A	Can consider an alternative method (or a reliable method of barrier contraception) in addition to this method.	Can consider an alternative method (or a reliable method of barrier contraception) in addition to this method.	No additional contraceptive protection is needed.	Can consider an alternative method (or a reliable method of barrier contraception) in addition to this method.	For COCs, small decrease in progestin levels. No evidence on POPs.
FPV/r	EE AUC ↓ 37%[64] NE AUC ↓ 34%[64] No change in FPV/r levels[64]	N/A	Can consider an alternative method (or a reliable method of barrier contraception) in addition to this method.	Can consider an alternative method (or a reliable method of barrier contraception) in addition to this method.	No additional contraceptive protection is needed.	Can consider an alternative method (or a reliable method of barrier contraception) in addition to this method.	For COCs, decrease in progestin levels. No evidence on POPs.

Table 3. Drug Interactions Between Antiretroviral Agents and Hormonal Contraceptives (page 4 of 8)

ARV Drug	Effect on Contraceptive Drug Levels and Contraceptive's Effects on ART and HIV	Clinical Studies	Dosing Recommendation/ Clinical Comment for COC/P/R	Dosing Recommendation/ Clinical Comment POPs	Dosing Recommendation/ Clinical Comment for DMPA[a]	Dosing Recommendation/ Clinical Comment for Etonogestrel Implants	Justification/ Evidence for Recommendation
RTV-Boosted PIs, continued							
LPV/r	EE AUC ↓ 55%[27] NE AUC ↓ 17% Patch: • EE AUC ↓ 45%[27] • Norelgestromin AUC ↑ 83%[27] DMPA: • DMPA AUC ↑ 46%[40] Etonogestrel Implant: • Etonogestrel AUC ↑ 52%[48] Changes in ARV Levels and/or Effects on HIV *Patch:* • LPV/r level ↓ 19%[27] *DMPA:* • No effect on HIV disease progression[40] • No change in LPV/r levels[40]	COC: • Increased pregnancy rate, but CIs overlap[45] Patch: • No ovulations[27] DMPA: • No pregnancies, no ovulations[40] • Increased pregnancy rate, but CIs overlap[45] Etonogestrel Implant: • No increase in pregnancy rate[45] LN Implant: • No increase in pregnancy rate.[38,45]	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	For COCs, nonsignificant increase in pregnancy rate. Small decrease in progestin level. For patch, no ovulations and progestin levels increased. For DMPA, evidence shows no effect on pregnancy rate or ovulations and progestin levels increased. For implants, evidence shows no effect on pregnancy rate and progestin levels increased.
SQV/r	↓ EE[65] Changes in ARV Levels and/or Effects on HIV *COC:* • No change in SQV/r levels[66]	N/A	Can consider an alternative method (or a reliable method of barrier contraception) in addition to this method.	Can consider an alternative method (or a reliable method of barrier contraception) in addition to this method.	No additional contraceptive protection is needed.	Can consider an alternative method (or a reliable method of barrier contraception) in addition to this method.	No information on progestin levels for CHCs or POPs. RTV inhibits CYP3A4, which may increase contraceptive hormone levels. However, some PI/r cause decreases in progestin levels, so there are theoretical concerns about contraceptive effectiveness.

Table 3. Drug Interactions Between Antiretroviral Agents and Hormonal Contraceptives (page 5 of 8)

ARV Drug	Effect on Contraceptive Drug Levels and Contraceptive's Effects on ART and HIV	Clinical Studies	Dosing Recommendation/ Clinical Comment for COC/P/R	Dosing Recommendation/ Clinical Comment POPs	Dosing Recommendation/ Clinical Comment for DMPA[a]	Dosing Recommendation/ Clinical Comment for Etonogestrel Implants	Justification/ Evidence for Recommendation
RTV-Boosted PIs, continued							
TPV/r	EE AUC ↓ 48%[67] NE: • No significant change[67] Changes in ARV Levels and/or Effects on HIV: • No change in TPV levels[67]	N/A	Can consider an alternative method (or a reliable method of barrier contraception) in addition to this method.	Can consider an alternative method (or a reliable method of barrier contraception) in addition to this method.	No additional contraceptive protection is needed.	Can consider an alternative method (or a reliable method of barrier contraception) in addition to this method.	For COCs, no significant change in progestin levels but only from product label. No evidence on POPs. RTV inhibits CYP3A4, which may increase contraceptive hormone levels. However, some PI/r cause decreases in progestin levels, so there are theoretical concerns about contraceptive effectiveness.
COBI-Boosted PIs							
ATV/c	Drospirenone AUC ↑ 2.3-fold; EE AUC ↓ 22%[68]	N/A	**Contraindicated** with drospirenone-containing hormonal contraceptives due to potential for hyperkalemia. Consider alternative or additional contraceptive method.	Consider an alternative method, due to safety concerns.	Consider an alternative method, due to safety concerns.	Consider an alternative method, due to safety concerns.	No evidence on POPs.

Table 3. Drug Interactions Between Antiretroviral Agents and Hormonal Contraceptives (page 6 of 8)

ARV Drug	Effect on Contraceptive Drug Levels and Contraceptive's Effects on ART and HIV	Clinical Studies	Dosing Recommendation/ Clinical Comment for COC/P/R	Dosing Recommendation/ Clinical Comment POPs	Dosing Recommendation/ Clinical Comment for DMPA[a]	Dosing Recommendation/ Clinical Comment for Etonogestrel Implants	Justification/ Evidence for Recommendation
COBI-Boosted PIs, continued							
DRV/c	Drospirenone AUC ↑ 1.6-fold; EE AUC ↓ 30%[68]	N/A	In combination with drospirenone-containing COCs, clinical monitoring is recommended due to the potential for hyperkalemia. Consider alternative or additional contraceptive method.	Consider an alternative method, due to safety concerns.	Consider an alternative method, due to safety concerns.	Consider an alternative method, due to safety concerns.	No evidence on POPs.
PIs without RTV							
ATV	COC: • EE AUC ↑ 48%[69] • NE AUC ↑ 110%[69]	N/A	Prescribe oral contraceptive that contains no more than 30 mcg of EE, or recommend alternative contraceptive method.	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	For COCs, increased concentrations of estrogen and progestin, but only data available are from the product label. No evidence on POPs.
FPV	COC *APV:* • No change in EE AUC; C_{min} ↑ 32% • NE AUC ↑ 18%; C_{min} ↑ 45%[64] FPV with EE/Norethindrone: • APV AUC ↓ 22% and C_{min} 20%)[64]	N/A	Use alternative contraceptive method.	Can consider an alternative method (or a reliable method of barrier contraception) in addition to this method.	Can consider an alternative method (or a reliable method of barrier contraception) in addition to this method.	Can consider an alternative method (or a reliable method of barrier contraception) in addition to this method.	Use of FPV alone with ethinyl estradiol/ norethindrone may lead to loss of virologic response. No evidence on POPs.

Table 3. Drug Interactions Between Antiretroviral Agents and Hormonal Contraceptives (page 7 of 8)

ARV Drug	Effect on Contraceptive Drug Levels and Contraceptive's Effects on ART and HIV	Clinical Studies	Dosing Recommendation/ Clinical Comment for COC/P/R	Dosing Recommendation/ Clinical Comment POPs	Dosing Recommendation/ Clinical Comment for DMPA[a]	Dosing Recommendation/ Clinical Comment for Etonogestrel Implants	Justification/ Evidence for Recommendation
PIs without RTV, continued							
IDV	COC: • EE AUC ↑ 22% • NE AUC ↑ 26%[70]	COC: • No pregnancies among women taking IDV and COCs[51]	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	For COCs, small increases in EE and progestin have been observed, and 1 clinical study did not suggest any efficacy concerns. No evidence on POPs.
NFV	COC: • EE AUC ↓ 47% • NE AUC ↓ 18%[71] DMPA: • No change[28] NFV: • AUC ↓ 18%	COC: • 1 small study suggested that women using COCs and NFV may have had higher pregnancy rates than those using COCs alone[51] DMPA: • No pregnancies, no ovulations[28,50] • CD4 count/HIV RNA: no change[28,50]	Can consider an alternative method (or a reliable method of barrier contraception) in addition to this method.	Can consider an alternative method (or a reliable method of barrier contraception) in addition to this method.	No additional contraceptive protection is needed.	Can consider an alternative method (or a reliable method of barrier contraception) in addition to this method.	For COCs, a small decrease in progestin and a decrease in estrogen have been observed; 1 small clinical study suggests possible higher pregnancy rate with COC and NFV use. DMPA, PK, and clinical data demonstrate no change. However, NFV AUC slightly decreased. No evidence on POPs or implants.
CCR5 Antagonist							
MVC	COC: • No significant effect on EE or LN[72]	N/A	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	For COCs, no change in EE or progestin. No clinical data. No evidence on POPs.

Table 3. Drug Interactions Between Antiretroviral Agents and Hormonal Contraceptives (page 8 of 8)

ARV Drug	Effect on Contraceptive Drug Levels and Contraceptive's Effects on ART and HIV	Clinical Studies	Dosing Recommendation/ Clinical Comment for COC/P/R	Dosing Recommendation/ Clinical Comment POPs	Dosing Recommendation/ Clinical Comment for DMPA[a]	Dosing Recommendation/ Clinical Comment for Etonogestrel Implants	Justification/ Evidence for Recommendation
Integrase Inhibitors							
BIC/FTC/ TAF	No significant drug interactions with EE or norgestimate.	N/A	No additional contraceptive protection is needed	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	No clinical data.
DTG	COC: • No significant effect on norgestimate or EE • DTG AUC no change[41]	N/A	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	COCs, no change in EE or progestin. No clinical data No evidence on POPs.
EVG/c	EVG/COBI *COC:* • Norgestimate AUC ↑ 126% EE AUC ↓ 25%[74]	N/A	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	When administered as the 4-drug regimen EVG/COBI/FTC/TDF, increases in P and small decrease in EE were observed. No clinical data. No evidence on POPs.
RAL	COC: • EE no change • Norgestimate AUC ↑ 14%[73]	N/A	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	For COCs, no change in EE and small increase in progestin. No clinical data. No evidence on POPs.

[a] Because the hormonal levels achieved with DMPA are substantially higher than are required for contraception, any small reduction in hormonal level due to ARVs is unlikely to reduce contraceptive effectiveness.

Key to Symbols:

↑ = increase ↓ = decrease

Key to Acronyms: ART = antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; AUC = area under the curve; BIC = bictegravir; CD4 = CD4 T lymphocyte; CHC = combination hormonal contraceptives; CI = confidence interval; C_{min} = minimum plasma concentration; COBI = cobicistat; COC/P/R =combined oral contraceptives/patch/ring; CYP = cytochrome P450 3A4; DMPA = depot medroxyprogesterone acetate; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EE = ethinyl estradiol; EFV = efavirenz; ETR = etravirine; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FPV = fosamprenavir; FPV/r = fosamprenavir/ritonavir; FTC = emtricitabine; IDV =

Table 3. Drug Interactions Between Antiretroviral Agents and Hormonal Contraceptives

indinavir; LN =levonorgestrel; LPV/r = lopinavir/ritonavir; MVC = maraviroc; NE = norethindrone; NFV = nelfinavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NVP = nevirapine; P = progestin; PI = protease inhibitor; PI/r = ritonavir-boosted protease inhibitor; PK = pharmacokinetic; POP = progesterone-only oral contraceptive pills; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SQV/r = saquinavir/ritonavir; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TPV/r = tipranavir/ritonavir

Source: Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV. Department of Health and Human Services. Tables 15a, 15b, and 15d.

References

1. American College of Obstetricians Gynecologists. ACOG Committee Opinion number 313, September 2005. The importance of preconception care in the continuum of women's health care. *Obstet Gynecol*. 2005;106(3):665-666. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16135611.
2. Johnson K, Posner SF, Biermann J, et al. Recommendations to improve preconception health and health care--United States. A report of the CDC/ATSDR Preconception Care Work Group and the Select Panel on Preconception Care. *MMWR Recomm Rep*. 2006;55(RR-6):1-23. Available at:http://www.ncbi.nlm.nih.gov/pubmed/16617292.
3. Cohn SE, Umbleja T, Mrus J, Bardeguez AD, Andersen JW, Chesney MA. Prior illicit drug use and missed prenatal vitamins predict nonadherence to antiretroviral therapy in pregnancy: adherence analysis A5084. *AIDS Patient Care STDS*. 2008;22(1):29-40. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18442305.
4. Elgalib A, Hegazi A, Samarawickrama A, et al. Pregnancy in HIV-infected teenagers in London. *HIV Med*. 2011;12(2):118-123. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20807252.
5. Kost K, Finer LB, Singh S. Variation in state unintended pregnancy rates in the United States. *Perspect Sex Reprod Health*. 2012;44(1):57-64. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22405153.
6. Sun M, Peipert JF, Zhao Q, et al. Trends in contraceptive use among women with human immunodeficiency virus. *Obstet Gynecol*. 2012;120(4):783-790. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22996095.
7. Sutton MY, Patel R, Frazier EL. Unplanned pregnancies among HIV-infected women in care-United States. *J Acquir Immune Defic Syndr*. 2014;65(3):350-358. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24189153.
8. Finer LB, Zolna MR. Shifts in intended and unintended pregnancies in the United States, 2001-2008. *Am J Public Health*. 2014;104 Suppl 1:S43-48. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24354819.
9. Salters K, Loutfy M, de Pokomandy A, et al. Pregnancy incidence and intention after HIV diagnosis among women living with HIV in Canada. *PLoS One*. 2017;12(7):e0180524. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28727731.
10. Guttmacher Institute. Unintended pregnancy in the United States. 2016. Available at: https://www.guttmacher.org/fact-sheet/unintended-pregnancy-united-states.
11. Finocchario-Kessler S, Dariotis JK, Sweat MD, et al. Do HIV-infected women want to discuss reproductive plans with providers, and are those conversations occurring? *AIDS Patient Care STDS*. 2010;24(5):317-323. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20482467.
12. Finocchario-Kessler S, Sweat MD, Dariotis JK, et al. Childbearing motivations, pregnancy desires, and perceived partner response to a pregnancy among urban female youth: does HIV-infection status make a difference? *AIDS Care*. 2012;24(1):1-11. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21777077.
13. Finger JL, Clum GA, Trent ME, Ellen JM, Adolescent Medicine Trials Network for HIV AIDS Interventions. Desire for pregnancy and risk behavior in young HIV-positive women. *AIDS Patient Care STDS*. 2012;26(3):173-180. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22482121.
14. Rahangdale L, Stewart A, Stewart RD, et al. Pregnancy intentions among women living with HIV in the United States. *J Acquir Immune Defic Syndr*. 2014;65(3):306-311. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24525467.
15. Gokhale RH, Bradley H, Weiser J. Reproductive health counseling delivered to women living with HIV in the United States. *AIDS Care*. 2017;29(7):928-935. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28114813.
16. Lampe MA. Human immunodeficiency virus-1 and preconception care. *Matern Child Health J*. 2006;10(5 Suppl):S193-195. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16832609.
17. Aaron EZ, Criniti SM. Preconception health care for HIV-infected women. *Top HIV Med*. 2007;15(4):137-141.

Available at: http://www.ncbi.nlm.nih.gov/pubmed/17721000.

18. Anderson J. Women and HIV: motherhood and more. *Curr Opin Infect Dis*. 2012;25(1):58-65. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22156896.
19. Jones D, Chakhtoura N, Cook R. Reproductive and maternal healthcare needs of HIV infected women. *Curr HIV/AIDS Rep*. 2013;10(4):333-341. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23918674.
20. Gosselin JT, Sauer MV. Life after HIV: examination of HIV serodiscordant couples' desire to conceive through assisted reproduction. *AIDS Behav*. 2011;15(2):469-478. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20960049.
21. Cotter AM, Garcia AG, Duthely ML, Luke B, O'Sullivan MJ. Is antiretroviral therapy during pregnancy associated with an increased risk of preterm delivery, low birth weight, or stillbirth? *J Infect Dis*. 2006;193(9):1195-1201. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16586354.
22. Tuomala RE, Shapiro DE, Mofenson LM, et al. Antiretroviral therapy during pregnancy and the risk of an adverse outcome. *N Engl J Med*. 2002;346(24):1863-1870. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12063370.
23. Stek AM. Antiretroviral medications during pregnancy for therapy or prophylaxis. *Curr HIV/AIDS Rep*. 2009;6(2):68-76. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19358777.
24. Byrne L, Sconza R, Foster C, Tookey PA, Cortina-Borja M, Thorne C. Pregnancy incidence and outcomes in women with perinatal HIV infection. *AIDS*. 2017;31(12):1745-1754. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28590327.
25. Centers for Disease C, Prevention. Update to CDC's U.S. medical eligibility criteria for contraceptive use, 2010: revised recommendations for the use of hormonal contraception among women at high risk for HIV infection or infected with HIV. *MMWR Morb Mortal Wkly Rep*. 2012;61(24):449-452. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22717514.
26. Carten ML, Kiser JJ, Kwara A, Mawhinney S, Cu-Uvin S. Pharmacokinetic interactions between the hormonal emergency contraception, levonorgestrel (Plan B), and Efavirenz. *Infect Dis Obstet Gynecol*. 2012;2012:137192. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22536010.
27. Vogler MA, Patterson K, Kamemoto L, et al. Contraceptive efficacy of oral and transdermal hormones when co-administered with protease inhibitors in HIV-1-infected women: pharmacokinetic results of ACTG trial A5188. *J Acquir Immune Defic Syndr*. 2010;55(4):473-482. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20842042.
28. Cohn SE, Park JG, Watts DH, et al. Depo-medroxyprogesterone in women on antiretroviral therapy: effective contraception and lack of clinically significant interactions. *Clin Pharmacol Ther*. 2007;81(2):222-227. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17192768.
29. Hoyt MJ, Storm DS, Aaron E, Anderson J. Preconception and contraceptive care for women living with HIV. *Infect Dis Obstet Gynecol*. 2012;2012:604183. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23097595.
30. Nanda K, Amaral E, Hays M, Viscola MA, Mehta N, Bahamondes L. Pharmacokinetic interactions between depot medroxyprogesterone acetate and combination antiretroviral therapy. *Fertil Steril*. 2008;90(4):965-971. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17880953.
31. Sevinsky H, Eley T, Persson A, et al. The effect of efavirenz on the pharmacokinetics of an oral contraceptive containing ethinyl estradiol and norgestimate in healthy HIV-negative women. *Antivir Ther*. 2011;16(2):149-156. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21447863.
32. Robinson JA, Jamshidi R, Burke AE. Contraception for the HIV-positive woman: a review of interactions between hormonal contraception and antiretroviral therapy. *Infect Dis Obstet Gynecol*. 2012;2012:890160. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22927715.
33. Tseng A, Hills-Nieminen C. Drug interactions between antiretrovirals and hormonal contraceptives. *Expert Opin Drug Metabol Toxicol*. 2013. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23425052.
34. Landolt NK, Phanuphak N, Ubolyam S, et al. Efavirenz, in contrast to nevirapine, is associated with unfavorable progesterone and antiretroviral levels when co-administered with combined oral contraceptives. *J Acquir Immune Defic Syndr*. 2012. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23187949.
35. Atrio J, Stanczyk FZ, Neely M, Cherala G, Kovacs A, Mishell DR, Jr. Effect of protease inhibitors on steady-state pharmacokinetics of oral norethindrone contraception in HIV-infected women. *J Acquir Immune Defic Syndr*. 2014;65(1):72-77. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24025339.
36. Crauwels HM, van Heeswijk RP, Buelens A, Stevens M, Hoetelmans RM. Lack of an effect of rilpivirine on the pharmacokinetics of ethinylestradiol and norethindrone in healthy volunteers. *Int J Clin Pharmacol Ther*.

2014;52(2):118-128. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24161160.

37. Landolt NK, Phanuphak N, Ubolyam S, et al. Significant decrease of ethinylestradiol with nevirapine, and of etonogestrel with efavirenz in HIV-positive women. *J Acquir Immune Defic Syndr*. 2014;66(2):e50-52. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24608892.
38. Perry SH, Swamy P, Preidis GA, Mwanyumba A, Motsa N, Sarero HN. Implementing the jadelle implant for women living with HIV in a resource-limited setting in sub-Saharan Africa: concerns for drug interactions leading to unintended pregnancies. *AIDS*. 2014. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24401645.
39. Thurman AR, Anderson S, Doncel GF. Effects of hormonal contraception on antiretroviral drug metabolism, pharmacokinetics and pharmacodynamics. *Am J Reprod Immunol*. 2014;71(6):523-530. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24521428.
40. Luque AE, Cohn SE, Park JG, et al. Depot medroxyprogesterone acetate in combination with a twice-daily lopinavir-ritonavir-based regimen in HIV-infected women showed effective contraception and a lack of clinically significant interactions, with good safety and tolerability: results of the ACTG 5283 study. *Antimicrob Agents Chemother*. 2015;59(4):2094-2101. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25624326.
41. Song IH, Borland J, Chen S, Wajima T, Peppercorn AF, Piscitelli SC. Dolutegravir has no effect on the pharmacokinetics of oral contraceptives with norgestimate and ethinyl estradiol. *Ann Pharmacother*. 2015;49(7):784-789. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25862012.
42. Scarsi KK, Darin KM, Nakalema S, et al. Unintended pregnancies observed with combined use of the levonorgestrel contraceptive implant and efavirenz-based antiretroviral therapy: a three-Arm pharmacokinetic evaluation over 48 weeks. *Clin Infect Dis*. 2016;62(6):675-682. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26646680.
43. Weinberg A, Park JG, Bosch R, et al. Effect of depot medoxyprogesterone acetate on immune functions and inflammatory markers of HIV-infected women. *J Acquir Immune Defic Syndr*. 2016;71(2):137-145. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26413850.
44. Leticee N, Viard JP, Yamgnane A, Karmochkine M, Benachi A. Contraceptive failure of etonogestrel implant in patients treated with antiretrovirals including efavirenz. *Contraception*. 2012;85(4):425-427. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22036046.
45. Patel RC, Onono M, Gandhi M, et al. Pregnancy rates in HIV-positive women using contraceptives and efavirenz-based or nevirapine-based antiretroviral therapy in Kenya: a retrospective cohort study. *Lancet HIV*. 2015;2(11):e474-482. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26520927.
46. Chappell CA, Lamorde M, Nakalema S, et al. Efavirenz decreases etonogestrel exposure: a pharmacokinetic evaluation of implantable contraception with antiretroviral therapy. *AIDS*. 2017;31(14):1965-1972. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28692531.
47. Pyra M, Heffron R, Mugo NR, et al. Effectiveness of hormonal contraception in HIV-infected women using antiretroviral therapy. *AIDS*. 2015;29(17):2353-2359. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26544706.
48. Vieira CS, Bahamondes MV, de Souza RM, et al. Effect of antiretroviral therapy including lopinavir/ritonavir or efavirenz on etonogestrel-releasing implant pharmacokinetics in HIV-positive women. *J Acquir Immune Defic Syndr*. 2014;66(4):378-385.
49. Polis CB, Curtis KM. Use of hormonal contraceptives and HIV acquisition in women: a systematic review of the epidemiological evidence. *Lancet Infect Dis*. 2013;13(9):797-808. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23871397.
50. Watts DH, Park JG, Cohn SE, et al. Safety and tolerability of depot medroxyprogesterone acetate among HIV-infected women on antiretroviral therapy: ACTG A5093. *Contraception*. 2008;77(2):84-90. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18226670.
51. Clark RA, Theall K. Population-based study evaluating association between selected antiretroviral therapies and potential oral contraceptive failure. *J Acquir Immune Defic Syndr*. 2004;37(1):1219-1220.
52. Landolt NK, Phanuphak N, Ubolyam S, et al. Efavirenz, in contrast to nevirapine, is associated with unfavorable progesterone and antiretroviral levels when coadministered with combined oral contraceptives. *J Acquir Immune Defic Syndr*. 2013;62(5):534-539.
53. Scholler-Gyure M, Kakuda TN, Woodfall B, et al. Effect of steady-state etravirine on the pharmacokinetics and pharmacodynamics of ethinylestradiol and norethindrone. *Contraception*. 2009;80(1):44-52. Available at: https://www.sciencedirect.com/science/article/pii/S0010782409000262.
54. Mildvan D, Yarrish R, Marshak A, et al. Pharmacokinetic interaction between nevirapine and ethinyl estradiol/

norethindrone when administered concurrently to HIV-infected women. *J Acquir Immune Defic Syndr*. 2002;29(5):471-477.

55. Stuart GS, Moses A, Corbett A, et al. Combined oral contraceptives and antiretroviral PK/PD in Malawian women: pharmacokinetics and pharmacodynamics of a combined oral contraceptive and a generic combined formulation antiretroviral in Malawi. *J Acquir Immune Defic Syndr*. 2011;58(2):e40-43.
56. Muro E, Droste JA, Hofstede HT, Bosch M, Dolmans W, Burger DM. Nevirapine plasma concentrations are still detectable after more than 2 weeks in the majority of women receiving single-dose nevirapine: implications for intervention studies. *J Acquir Immune Defic Syndr*. 2005;39(4):419-421. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16010163.
57. Day S, Graham SM, Masese LN, et al. A prospective cohort study of the effect of depot medroxyprogesterone acetate on detection of plasma and cervical HIV-1 in women initiating and continuing antiretroviral therapy. *J Acquir Immune Defic Syndr*. 2014;66(4):452-456.
58. Hubacher D, Liku J, Kiarie J, et al. Effect of concurrent use of anti-retroviral therapy and levonorgestrel sub-dermal implant for contraception on CD4 counts: a prospective cohort study in Kenya. *J Int AIDS Soc*. 2013;16:18448.
59. Myer L, Carter RJ, Katyal M, Toro P, El-Sadr WM, Abrams EJ. Impact of antiretroviral therapy on incidence of pregnancy among HIV-infected women in Sub-Saharan Africa: a cohort study. *PLoS Med*. 2010;7(2):e1000229. Available at: http://www.plosmedicine.org/article/fetchObject.action?uri=info:doi/10.1371/journal.pmed.1000229&representation=PDF.
60. Nanda K, Delany-Moretlwe S, Dube K, et al. Nevirapine-based antiretroviral therapy does not reduce oral contraceptive effectiveness. *AIDS*. 2013;27 Suppl 1:S17-25.
61. Zhang J, Chung E, Yones C, et al. The effect of atazanavir/ritonavir on the pharmacokinetics of an oral contraceptive containing ethinyl estradiol and norgestimate in healthy women. *Antivir Ther*. 2011;16(2):157-164.
62. DuBois BN, Atrio J, Stanczyk FZ, Cherala G. Increased exposure of norethindrone in HIV+ women treated with ritonavir-boosted atazanavir therapy. *Contraception*. 2015;91(1):71-75. Available at: https://www.sciencedirect.com/science/article/pii/S0010782414006398.
63. Sekar VJ, Lefebvre E, Guzman SS, et al. Pharmacokinetic interaction between ethinyl estradiol, norethindrone and darunavir with low-dose ritonavir in healthy women. *Antivir Ther*. 2008;13(4):563-569.
64. Fosamprenavir calcium [package insert]. Food and Drug Administration. 2016. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021548s037,022116s021lbl.pdf.
65. Dolutegravir [package insert]. Food and Drug Administration. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/204790Orig1s008lbl.pdf.
66. Frohlich M, Burhenne J, Martin-Facklam M, et al. Oral contraception does not alter single dose saquinavir pharmacokinetics in women. *Br J Clin Pharmacol*. 2004;57(3):244-252.
67. Tipranavir [package insert]. Food and Drug Administration. 2015. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021814s011lbl.pdf.
68. Majeed SR, West SK, Jiang S, et al. Confirmation of the drug-drug interaction (DDI) potential between cobicistat-boosted antiretroviral regimens and hormonal contraceptives. Presented at: 18th International Workshop on Clinical Pharmacology of Antiviral Therapy. 2017. Chicago, IL.
69. Atazanavir [package insert]. Food and Drug Administration. 2015. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/206352s003,021567s038lbl.pdf.
70. Indinavir sulfate [package insert]. Food and Drug Administration. 2015. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/020685s077lbl.pdf.
71. Nelfinavir [package insert]. Food and Drug Administration. 2015. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/020778s040,020779s061,021503s023lbl.pdf.
72. Abel S, Russell D, Whitlock LA, Ridgway CE, Muirhead GJ. Effect of maraviroc on the pharmacokinetics of midazolam, lamivudine/zidovudine, and ethinyloestradiol/levonorgestrel in healthy volunteers. *Br J Clin Pharmacol*. 2008;65 Suppl 1:19-26. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18333862.
73. Anderson MS, Hanley WD, Moreau AR, et al. Effect of raltegravir on estradiol and norgestimate plasma pharmacokinetics following oral contraceptive administration in healthy women. *Br J Clin Pharmacol*. 2011;71(4):616-620. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21395656.
74. Elvitegravir/cobicitstat/emtricitabine/tenofovir disaproxil fumarate [package insert]. Food and Drug Administration. 2017. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/203100s030lbl.pdf.

Reproductive Options for Couples in Which One or Both Partners are Living with HIV (Last updated December 7, 2018; last reviewed December 7, 2018)

Panel's Recommendations

For Couples Who Want to Conceive When One or Both Partners are Living with HIV:

- Expert consultation is recommended to tailor guidance to couples' specific needs **(AIII)**.
- Partners should be screened and treated for genital tract infections before attempting to conceive **(AII)**.
- Partners living with HIV should attain maximum viral suppression before attempting conception to prevent HIV sexual transmission **(AI)** and, for women living with HIV, to minimize the risk of HIV transmission to the infant **(AII)**.
- For couples with differing HIV statuses, **when the partner living with HIV is on ART and has achieved sustained viral suppression**, sexual intercourse without a condom limited to the 2 to 3 days before and the day of ovulation (peak fertility) is an approach to conception with effectively no risk of sexual HIV transmission to the partner without HIV **(BII)**.
- For couples with differing HIV statuses who attempt conception via sexual intercourse without a condom (despite counseling) **when the partner living with HIV has not been able to achieve viral suppression or when the viral suppression status is not known**, administration of antiretroviral pre-exposure prophylaxis (PrEP) to the partner without HIV is recommended to reduce the risk of sexual transmission of HIV **(AI)**. Couples should still be counseled to limit sex (without condoms) to the period of peak fertility **(AIII)**.
- When the woman is living with HIV, assisted insemination at home or in a provider's office with semen from a partner without HIV during the periovulatory period is an option for conception that eliminates the risk of HIV transmission to the partner without HIV **(AIII)**.
- When the man is living with HIV, the use of donor sperm from a man without HIV is an option for conception that eliminates the risk of HIV transmission to the partner without HIV **(BIII)**.
- For couples with differing HIV statuses who attempt conception (sexual intercourse without a condom limited to peak fertility) when the partner living with HIV has achieved viral suppression, it is unclear whether administering PrEP to the partner without HIV further reduces the risk of sexual transmission **(CIII)**.

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*

The objective of this section is to provide guidance for safe conception and pregnancy while maximizing efforts to prevent HIV transmission to partners and infants. For couples who want to conceive while one or both partners are living with HIV, expert consultation is recommended so that approaches can be tailored to their specific needs.

For couples in which one or both partners are living with HIV, couples should be counseled to only attempt conception after the partners living with HIV have initiated antiretroviral therapy (ART) and have achieved sustained suppression of plasma viral load below the limits of detection.

Before attempting to conceive, both partners should be screened for genital tract infections. Treatment of such infections is important, because genital tract inflammation is associated with genital tract shedding of HIV.[1-6]

Couples with Differing HIV Statuses

Before attempting conception, the partner living with HIV should be on ART and have achieved sustained suppression of plasma viral load below the limits of detection. HPTN 052 was a randomized clinical trial designed to evaluate whether immediate initiation of ART in people with CD4 T lymphocyte (CD4) cell counts of 350 to 550 cells/mm^3 could prevent sexual transmission of HIV among couples with differing HIV statuses more effectively than delaying ART. Most of the participants were from Africa (54%), with 30% from Asia and 16% from North and South America. This study showed that earlier initiation of ART led to a 93% reduction in sexual transmission of HIV to the partner. Of 46 cases of HIV infection documented to be genetically linked to the partner living with HIV, 43 cases occurred among the 877 couples in which the partner living with HIV delayed initiation of ART until the CD4 cell count fell below 250 cells/mm^3, and three cases of HIV infection occurred among the 886 couples in which a partner living with HIV began

immediate ART. Thus, this randomized trial clearly demonstrated that provision of treatment to persons living with HIV can reduce the risk of transmission of HIV to their sexual partners.[7] In addition, the PARTNERS trial—which studied 1,166 couples of differing HIV statuses (both heterosexual couples and men who have sex with men) where the partner with HIV was on suppressive ART and had sex without using a condom—had no cases of transmission after 1.3 years.[8]

Among 161 couples with differing HIV statuses (133 couples included a male partner living with HIV) where the partner living with HIV received suppressive ART and the couple opted for natural conception, a total of 144 natural pregnancies occurred and 107 babies were born. No cases of sexual (to partner) or vertical (to infant) transmission occurred.[9]

It is important to recognize that no single method (including treatment of the partner living with HIV) is fully protective against transmission of HIV, though the risk appears to approach zero when the partner living with HIV maintains a consistently undetectable plasma viral load on ART.[10] Effective ART that decreases plasma viral load to undetectable levels is also associated with decreased concentration of virus in genital secretions. However, discordance between plasma and genital viral loads has been reported, and individuals with an undetectable plasma viral load may have detectable genital tract virus.[11-15] In addition, antiretroviral (ARV) drugs vary in their ability to penetrate the genital tract.[16] In a prospective study of 2,521 African couples with differing HIV statuses, higher genital HIV RNA concentrations were associated with greater risk of heterosexual HIV-1 transmission, and this effect was independent of plasma HIV concentrations.[17] Each $\log_{10}$ increase in genital HIV-1 RNA levels increased the risk of female-to-male or male-to-female HIV transmission by 1.7-fold.[17] However, there were no cases of transmission in the context of undetectable plasma viral load but detectable genital tract HIV.

In addition to reducing the risk of HIV transmission between partners, starting ART before conception in women living with HIV may also further reduce the risk of perinatal transmission.[18] Evidence suggests that early and sustained control of HIV may decrease the risk of perinatal transmission,[19,20] but it does not completely eliminate the risk of perinatal transmission.[20] In addition, reports are mixed on the possible effects of ART on prematurity and low birthweight, with some, but not all, data suggesting that such outcomes may be more frequent in women on ART at conception.[21-23]

The implications of initiating therapy before conception and the need for strict adherence to achieve plasma viral load below the limits of detection should be discussed with the couple. Consultation with an expert in HIV care is strongly recommended.

Options for Safer Conception

When a woman living with HIV is in a serodiscordant relationship, assisted insemination during the periovulatory period at home or in a provider's office with semen from a partner without HIV infection is an option for conception that eliminates the risk of HIV transmission to her partner.

When a man living with HIV is in a serodiscordant relationship, the use of donor sperm from a man without HIV is an option for conception that eliminates the risk of HIV transmission to the partner without HIV.

However, as described above, studies have shown that the risk of HIV infection to the partner without HIV is very low when the partner living with HIV is on ART and has demonstrated sustained plasma viral load below the limits of detection. For couples with differing HIV statuses, where the partner living with HIV is on ART and has achieved sustained viral suppression, sexual intercourse without a condom that occurs only during the 2 to 3 days before ovulation and on the day of ovulation (peak fertility) is an approach to conception with effectively no risk of sexual HIV transmission to the partner without HIV. The use of an ovulation kit is the optimal method for identifying the most fertile time of the cycle.

When a man living with HIV is in a serodiscordant relationship, the use of sperm preparation techniques coupled with either intrauterine insemination or *in vitro* fertilization with intracytoplasmic sperm injection has been reported. However, the appropriate role of semen preparation techniques in the current context is

unclear, particularly given their expense and technical requirements. These sperm preparation techniques were largely developed before studies had demonstrated the efficacy of ART and pre-exposure prophylaxis (PrEP) in decreasing transmission to sexual partners without HIV. Sperm preparation techniques may be useful in cases of male infertility.

Pre-Exposure Prophylaxis Provision and Monitoring in Couples with Differing HIV Statuses

For serodiscordant couples who attempt conception via sexual intercourse without a condom (despite counseling) when the partner living with HIV has not been able to achieve viral suppression or when viral suppression status is not known, administration of antiretroviral PrEP to the partner without HIV is recommended to reduce the risk of sexual transmission of HIV. PrEP is the use of ARV medications by an individual who is HIV negative to maintain blood and genital drug levels sufficient to prevent acquisition of HIV. Only daily dosing of a combination of tenofovir disoproxil fumarate (TDF) and emtricitabine is currently Food and Drug Administration-approved for use as PrEP. **Adherence is critical.** Couples should still be counseled to limit sex without a condom to the period of peak fertility. If conception does not occur 6 months providers should pursue a workup for infertility, including a semen analysis. HIV, and possibly ART, may be associated with a higher prevalence of sperm abnormalities, such as low sperm count, low motility, a higher rate of abnormal forms, and low semen volume. Early evaluation is indicated to limit periods of unprotected sex in the context of infertility.[24-28]

Sun et al. reported on 91 serodiscordant couples (43 with men living with HIV and 48 with women living with HIV) in which the partner with HIV was on effective ART, the partner without HIV received PrEP (or post-exposure prophylaxis), and intercourse was timed to maximally reduce the risk of HIV transmission. There were 196 acts of intercourse without a condom, 100 natural conceptions, and 97 live births. There were no cases of HIV seroconversion in the sexual partner without HIV.[29]

One study followed 1,013 Kenyan and Ugandan serodiscordant couples (67% of couples involved women living with HIV) who had a high risk of sexual transmission. After an integrated ART and PrEP strategy for HIV prevention was implemented, there were no HIV transmissions to male partners among these couples. Only two incident infections were observed in the women (HIV incidence of 0.2 per 100 person years). These two infections occurred in the absence of ART or PrEP.[30]

Many studies have demonstrated that PrEP reduces the risk of HIV acquisition in both men and women, with minimal risk of incident ARV resistance. Other trials failed to demonstrate PrEP efficacy, likely because of suboptimal levels of adherence.[7,31-36] Table 4 summarizes clinical trials of PrEP.[37]

Table 4. Clinical Trials of Pre-Exposure Prophylaxis

Trial	Study Population	Location	Intervention	Outcome	Comments
TDF2	1,219 sexually active adults; 55% male, 45% female; 94% unmarried; approximately 90% aged 21–29 years	Botswana	Daily oral TDF/FTC	63% protection	>30% did not complete study; cannot draw definitive conclusions for women and men separately.
PIP	4,758 serodiscordant heterosexual couples; 38% HIV-negative female partner, 62% HIV-negative male partner; 98% married; median age 33 years	Botswana, Kenya, Rwanda, South Africa, Tanzania, Uganda, Zambia	Daily oral TDF or TDF/FTC	67% protection with TDF alone; 75% protection with TDF/FTC	Serodiscordant couples may be a distinct, unique population.
FEM-PrEP	1,951 heterosexual women aged 18–35 years and at high risk of infection	Kenya, South Africa, Tanzania	Daily oral TDF/FTC	Trial discontinued for futility in April 2011	Adherence assessment with monthly clinical samples to measure drug concentration is pending.
VOICE MTN-003	5,029 heterosexual women aged 18–45 years in areas with a high prevalence of HIV	Uganda, South Africa, Zimbabwe	Daily oral TDF or daily oral TDF/FTC or daily topical TFV gel	No study drug significantly reduced the risk of HIV acquisition. Estimates of effectiveness were <0 for TDF and TDF/FTC daily oral dosing (negative 48.8% and negative 4.2% TDF/FTC, respectively), and reduced risk of HIV infection of 14.7% for TFV gel.	Adherence to study drugs was low; TFV was detected in 30% of the oral TDF arm, 29% in the oral TDF/FTC arm, and 25% in the TFV gel arm.

Adapted from: Kashuba et al., Pre-exposure prophylaxis for HIV prevention: how to predict success: Table Antiretroviral-based HIV prevention studies. *Lancet*. 2012;379(9835): 2409-2411.

Key to Acronyms: FTC = emtricitabine; TDF = tenofovir disoproxil fumarate; TFV = tenofovir

Pregnancy and breastfeeding are not contraindications to PrEP.[38-43] There is no evidence of an increase in congenital anomalies among children born to women exposed to TDF or to emtricitabine during the first trimester.[44] Data from studies of infants born to mothers living with HIV and exposed to TDF through breast milk suggest limited drug exposure.[45-48] Condom use should be encouraged during pregnancy, because several studies have reported increased incidence of HIV acquisition during pregnancy, which may also lead to increased perinatal transmission.

For couples with differing HIV status who attempt conception (sexual intercourse without a condom limited to periods of peak fertility) when the partner living with HIV has achieved viral suppression, it is unclear if PrEP for the partner without HIV further reduces the risk of sexual transmission. A modeling study analyzed the utility of PrEP under different conditions. In an analysis by Hoffman et al., PrEP provided little added benefit when the male partner was on ART, had a suppressed viral load, limited sex without a condom to the ovulation window, and optimized other modifiable transmission risks.[49]

If clinicians elect to prescribe PrEP in couples with differing HIV status, couples should be educated about the potential risks and benefits and all available alternatives for safer conception. The Centers for Disease Control and Prevention (CDC) has issued guidelines for the use of PrEP in sexually active heterosexual adults. The CDC recommends that an individual who does not have HIV and is planning a pregnancy with a partner who does have HIV start daily oral TDF plus emtricitabine beginning 1 month before conception is attempted and continuing for 1 month after conception is attempted.[50] Recommended laboratory testing should include

HIV diagnostic testing at baseline and then every 3 months, renal function testing at baseline and then every 6 months, and pregnancy testing at baseline and then every 3 months. Testing for hepatitis B virus (HBV) infection should be performed before initiating PrEP. Individuals without HBV infection should be vaccinated if they have not received HBV vaccination or they lack immunity to HBV. Individuals receiving PrEP should be educated about symptoms associated with acute HIV infection and advised to contact their providers immediately for further evaluation if symptoms occur. Partners who are HIV negative should undergo frequent HIV testing to detect HIV infection quickly. If HIV infection is documented, the PrEP ARV agents should be discontinued to minimize selection of drug-resistant virus, measures should be instituted to prevent perinatal transmission if pregnancy has occurred and attempts at conception should be stopped if pregnancy has not occurred, and the patient should be referred to an HIV specialist immediately. Individuals with chronic HBV should be monitored for possible hepatitis flares when PrEP is stopped.[51] Clinicians are strongly encouraged to register women who become pregnant while receiving PrEP with the Antiretroviral Pregnancy Registry.

Couples Where Both Partners are Living with HIV

Both partners should be on ART with maximum viral suppression before attempting conception. Periovulatory unprotected intercourse (with use of condoms at all other times) is a reasonable option for monogamous couples. The risk of HIV superinfection or infection with a resistant virus is negligible when both partners are on ART and have fully suppressed plasma viral loads.[52]

Monitoring of Pregnant Women Without HIV who have Partners with HIV

Women without HIV who present during pregnancy and indicate that their partners are living with HIV should, like all pregnant women, be notified that HIV screening is recommended and that they will receive an HIV test as part of the routine panel of prenatal tests unless they decline (i.e., "op-out strategy"). Pregnant women without HIV should also be counseled to always use condoms to reduce the risk of HIV acquisition and informed that their partners with HIV should have attained virologic suppression on ART. These women should be tested for HIV at least once per trimester, or more often if the partner's viral load is not known. Acute HIV infection during pregnancy increases the risk of transmitting HIV to the fetus (see Acute Infection). A woman who presents in labor with suspicion of acute seroconversion should be screened with an expedited HIV test and offered zidovudine during labor. If results are not received until after delivery, the infant can also start ARV drug(s) until a negative test is obtained. If at any time during pregnancy a clinician suspects that a pregnant woman may be in the "window" period of seroconversion (i.e., she has signs or symptoms consistent with acute HIV infection), then a plasma HIV RNA test should be used in conjunction with an HIV antigen/antibody fourth-generation test. If the plasma HIV RNA is negative, it should be repeated in 2 weeks. Pregnant women who do not have HIV but who have partners who are living with HIV should be counseled on methods to prevent acquisition of HIV, including suppressive ART for her partner, PrEP, and condom use. Women should be counseled regarding the symptoms of acute retroviral syndrome (i.e., fever, pharyngitis, rash, myalgia, arthralgia, diarrhea, and headache) and the importance of seeking medical care and testing if they experience such symptoms.

Women who test HIV seropositive on either conventional or rapid HIV tests should receive appropriate evaluation and interventions to reduce perinatal transmission of HIV, including immediate initiation of appropriate ART and consideration of elective cesarean delivery according to established guidelines (see Transmission and Mode of Delivery). In cases where confirmatory test results are not readily available, such as with rapid testing during labor, it is still appropriate to initiate interventions to reduce perinatal transmission (see Infant Antiretroviral Therapy/Prophylaxis).

Women who test HIV seronegative and have partners who are living with HIV should continue to be regularly counseled regarding consistent condom use to decrease their risk of sexual transmission of HIV. They should also be counseled on the importance of their partners' adherence to ART and the need for achievement of sustained virologic suppression to reduce the risk of sexual transmission of HIV. Women with primary HIV infection during pregnancy or lactation are at high risk of transmitting HIV to their infants.[53,54]

Coordination of care across multiple disciplines, including HIV primary care, Ob/Gyn, family planning, case management, and peer support, is advised. Integration of reproductive health counseling, including pregnancy desires and/or prevention, is recommended.

Monitoring of Men Without HIV Who Have Female Partners with HIV

Men who are HIV seronegative and are attempting pregnancy with women partners who are living with HIV should continue to be regularly counseled regarding consistent condom use to decrease the risk of sexual transmission of HIV. They should also be counseled on the importance of their partners' adherence to ART and the need to achieve sustained virologic suppression to reduce the risk of sexual transmission of HIV. They should be tested for HIV every 3 months while attempting conception without condoms.

The National Perinatal HIV Hotline (1-888-448-8765) is a resource for a list of institutions offering reproductive services for HIV concordant/serodiscordant couples.

References

1. Mitchell C, Hitti J, Paul K, et al. Cervicovaginal shedding of HIV type 1 is related to genital tract inflammation independent of changes in vaginal microbiota. *AIDS Res Hum Retroviruses*. 2011;27(1):35-39. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20929397.
2. Johnson LF, Lewis DA. The effect of genital tract infections on HIV-1 shedding in the genital tract: a systematic review and meta-analysis. *Sex Transm Dis*. 2008;35(11):946-959. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18685546.
3. Anderson BL, Firnhaber C, Liu T, et al. Effect of trichomoniasis therapy on genital HIV viral burden among African women. *Sex Transm Dis*. 2012;39(8):638-642. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22797689.
4. Blish CA, McClelland RS, Richardson BA, et al. Genital inflammation predicts HIV-1 shedding independent of plasma viral load and systemic inflammation. *J Acquir Immune Defic Syndr*. 2012;61(4):436-440. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22878424.
5. Homans J, Christensen S, Stiller T, et al. Permissive and protective factors associated with presence, level, and longitudinal pattern of cervicovaginal HIV shedding. *J Acquir Immune Defic Syndr*. 2012;60(1):99-110. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22517416.
6. Wall KM, Kilembe W, Vwalika B, et al. Risk of heterosexual HIV transmission attributable to sexually transmitted infections and non-specific genital inflammation in Zambian discordant couples, 1994-2012. *Int J Epidemiol*. 2017;46(5):1593-1606. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28402442.
7. Cohen MS, Chen YQ, McCauley M, et al. Antiretroviral therapy for the prevention of HIV-1 transmission. *N Engl J Med*. 2016;375(9):830-839. Available at: http://www.ncbi.nlm.nih.gov/pubmed/27424812.
8. Rodger AJ, Cambiano V, Bruun T, et al. Sexual activity without condoms and risk of HIV transmission in serodifferent couples when the HIV-positive partner Is using suppressive antiretroviral therapy. *JAMA*. 2016;316(2):171-181. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27404185.
9. Del Romero J, Baza MB, Rio I, et al. Natural conception in HIV-serodiscordant couples with the infected partner in suppressive antiretroviral therapy: a prospective cohort study. *Medicine (Baltimore)*. 2016;95(30):e4398. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27472733.
10. Eshleman SH, Hudelson SE, Redd AD, et al. Treatment as prevention: characterization of partner infections in the HIV prevention trials network 052 trial. *J Acquir Immune Defic Syndr*. 2017;74(1):112-116. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27532476.
11. Sheth PM, Kovacs C, Kemal KS, et al. Persistent HIV RNA shedding in semen despite effective antiretroviral therapy. *AIDS*. 2009;23(15):2050-2054. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19710596.
12. Cu-Uvin S, DeLong AK, Venkatesh KK, et al. Genital tract HIV-1 RNA shedding among women with below detectable plasma viral load. *AIDS*. 2010;24(16):2489-2497. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20736815.
13. Politch JA, Mayer KH, Welles SL, et al. Highly active antiretroviral therapy does not completely suppress HIV in semen of sexually active HIV-infected men who have sex with men. *AIDS*. 2012. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22441253.
14. King CC, Ellington SR, Davis NL, et al. Prevalence, magnitude, and correlates of HIV-1 genital shedding in women on antiretroviral therapy. *J Infect Dis*. 2017;216(12):1534-1540. Available at: https://www.ncbi.nlm.nih.gov/

pubmed/29240922.

15. Pasquier C, Walschaerts M, Raymond S, et al. Patterns of residual HIV-1 RNA shedding in the seminal plasma of patients on effective antiretroviral therapy. *Basic Clin Androl*. 2017;27:17. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28904798.

16. Taylor S, Davies S. Antiretroviral drug concentrations in the male and female genital tract: implications for the sexual transmission of HIV. *Curr Opin HIV AIDS*. 2010;5(4):335-343. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20543610.

17. Baeten JM, Kahle E, Lingappa JR, et al. Genital HIV-1 RNA predicts risk of heterosexual HIV-1 transmission. *Sci Transl Med*. 2011;3(77):77ra29. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21471433.

18. Mandelbrot L, Tubiana R, Le Chenadec J, et al. No perinatal HIV-1 transmission from women with effective antiretroviral therapy starting before conception. *Clin Infect Dis*. 2015;61(11):1715-1725. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26197844.

19. Townsend CL, Cortina-Borja M, Peckham CS, de Ruiter A, Lyall H, Tookey PA. Low rates of mother-to-child transmission of HIV following effective pregnancy interventions in the United Kingdom and Ireland, 2000-2006. *AIDS*. 2008;22(8):973-981. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18453857.

20. Tubiana R, Le Chenadec J, Rouzioux C, et al. Factors associated with mother-to-child transmission of HIV-1 despite a maternal viral load <500 copies/mL at delivery: a case-control study nested in the French perinatal cohort (EPF-ANRS CO1). *Clin Infect Dis*. 2010;50(4):585-596. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20070234.

21. Kourtis AP, Schmid CH, Jamieson DJ, Lau J. Use of antiretroviral therapy in pregnant HIV-infected women and the risk of premature delivery: a meta-analysis. *AIDS*. 2007;21(5):607-615. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17314523.

22. Rudin C, Spaenhauer A, Keiser O, et al. Antiretroviral therapy during pregnancy and premature birth: analysis of Swiss data. *HIV Med*. 2011;12(4):228-235. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20726902.

23. Jao J, Abrams EJ. Metabolic complications of *in utero* maternal HIV and antiretroviral exposure in HIV-exposed Infants. *Pediatr Infect Dis J*. 2014;33(7):734-740. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24378947.

24. Garrido N, Meseguer M, Remohi J, Simon C, Pellicer A. Semen characteristics in human immunodeficiency virus (HIV)- and hepatitis C (HCV)-seropositive males: predictors of the success of viral removal after sperm washing. *Hum Reprod*. 2005;20(4):1028-1034. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15608027.

25. Dulioust E, Du AL, Costagliola D, et al. Semen alterations in HIV-1 infected men. *Hum Reprod*. 2002;17(8):2112-2118. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12151446.

26. Cardona-Maya W, Velilla P, Montoya CJ, Cadavid A, Rugeles MT. Presence of HIV-1 DNA in spermatozoa from HIV-positive patients: changes in the semen parameters. *Curr HIV Res*. 2009;7(4):418-424. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19601777.

27. Bujan L, Sergerie M, Moinard N, et al. Decreased semen volume and spermatozoa motility in HIV-1-infected patients under antiretroviral treatment. *J Androl*. 2007;28(3):444-452. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17215546.

28. Jeronimo A, Baza MB, Rio I, et al. Factors associated with seminal impairment in HIV-infected men under antiretroviral therapy. *Hum Reprod*. 2017;32(2):265-271. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28007791.

29. Sun L, Wang F, Liu A, et al. Natural conception may be an acceptable option in HIV-serodiscordant couples in resource limited settings. *PLoS One*. 2015;10(11):e0142085. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26540103.

30. Baeten JM, Heffron R, Kidoguchi L, et al. Integrated delivery of antiretroviral treatment and pre-exposure prophylaxis to HIV-1-serodiscordant couples: a prospective implementation study in Kenya and Uganda. *PLoS Med*. 2016;13(8):e1002099. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27552090.

31. Abdool Karim Q, Abdool Karim SS, Frohlich JA, et al. Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. *Science*. 2010;329(5996):1168-1174. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20643915.

32. Grant RM, Lama JR, Anderson PL, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *N Engl J Med*. 2010;363(27):2587-2599. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21091279.

33. Thigpen MC, Kebaabetswe PM, Paxton LA, et al. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. *N Engl J Med*. 2012. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22784038.

34. Aaron E, Cohan D. Preexposure prophylaxis for the prevention of HIV transmission to women. *AIDS*. 2013;27(1):F1-5.

Available at: http://www.ncbi.nlm.nih.gov/pubmed/22914582.

35. Baeten J, Celum C. Oral antiretroviral chemoprophylaxis: current status. *Curr Opin HIV AIDS*. 2012;7(6):514-519. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22964886.

36. Marrazzo JM, Ramjee G, Richardson BA, et al. Tenofovir-based preexposure prophylaxis for HIV pnfection among African women. *N Engl J Med*. 2015;372:509-518. Available at: http://www.nejm.org/doi/full/10.1056/NEJMoa1402269#t=article.

37. Kashuba AD, Patterson KB, Dumond JB, Cohen MS. Pre-exposure prophylaxis for HIV prevention: how to predict success. *Lancet*. 2012;379(9835):2409-2411. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22153566.

38. Gray RH, Li X, Kigozi G, et al. Increased risk of incident HIV during pregnancy in Rakai, Uganda: a prospective study. *Lancet*. 2005;366(9492):1182-1188. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16198767.

39. Morrison CS, Wang J, Van Der Pol B, Padian N, Salata RA, Richardson BA. Pregnancy and the risk of HIV-1 acquisition among women in Uganda and Zimbabwe. *AIDS*. 2007;21(8):1027-1034. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17457097.

40. Moodley D, Esterhuizen TM, Pather T, Chetty V, Ngaleka L. High HIV incidence during pregnancy: compelling reason for repeat HIV testing. *AIDS*. 2009;23(10):1255-1259. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19455017.

41. Moodley D, Esterhuizen T, Reddy L, et al. Incident HIV infection in pregnant and lactating women and its effect on mother-to-child transmission in South Africa. *J Infect Dis*. 2011;203(9):1231-1234. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21398393.

42. Taha TE, James MM, Hoover DR, et al. Association of recent HIV infection and *in utero* HIV-1 transmission. *AIDS*. 2011;25(11):1357-1364. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21572305.

43. Mofenson LM, Baggaley RC, Mameletzis I. Tenofovir disoproxil fumarate safety for women and their infants during pregnancy and breastfeeding. *AIDS*. 2017;31(2):213-232. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27831952.

44. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral pregnancy registry international interim report for 1 January 1989–31 January 2018. Wilmington, NC: Registry Coordinating Center. 2018. Available at: http://www.apregistry.com/.

45. Johnson LF, Stinson K, Newell ML, et al. The contribution of maternal HIV seroconversion during late pregnancy and breastfeeding to mother-to-child transmission of HIV. *J Acquir Immune Defic Syndr*. 2012;59(4):417-425. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22193774.

46. Benaboud S, Pruvost A, Coffie PA, et al. Concentrations of tenofovir and emtricitabine in breast milk of HIV-1-infected women in Abidjan, Cote d'Ivoire, in the ANRS 12109 tEmAA study, step 2. *Antimicrob Agents Chemother*. 2011;55(3):1315-1317. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21173182.

47. Mirochnick M, Best BM, Clarke DF. Antiretroviral pharmacology: special issues regarding pregnant women and neonates. *Clinics in Perinatology*. 2010;37(4):907-927, xi. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21078458.

48. Waitt C, Olagunju A, Nakalema S, et al. Plasma and breast milk pharmacokinetics of emtricitabine, tenofovir and lamivudine using dried blood and breast milk spots in nursing African mother-infant pairs. *J Antimicrob Chemother*. 2018;73(4):1013-1019. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29309634.

49. Hoffman RM, Jaycocks A, Vardavas R, et al. Benefits of PrEP as an adjunctive method of HIV prevention during attempted conception between HIV-uninfected women and HIV-infected male partners. *J Infect Dis*. 2015. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26092856.

50. Centers for Disease Control and Prevention. Preexposure prophylaxis for the prevention of HIV infection in the United States. 2017. Available at: https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2017.pdf.

51. Lampe MA, Smith DK, Anderson GJ, Edwards AE, Nesheim SR. Achieving safe conception in HIV-discordant couples: the potential role of oral preexposure prophylaxis (PrEP) in the United States. *Am J Obstet Gynecol*. 2011;204(6):488 e481-488. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21457911.

52. Waters L, Smit E. HIV-1 superinfection. *Curr Opin Infect Dis*. 2012;25(1):42-50. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22156898.

53. Marinda ET, Moulton LH, Humphrey JH, et al. *In utero* and intra-partum HIV-1 transmission and acute HIV-1 infection during pregnancy: using the BED capture enzyme-immunoassay as a surrogate marker for acute infection. *Int J Epidemiol*. 2011;40(4):945-954. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21471020.

54. Humphrey JH, Marinda E, Mutasa K, et al. Mother to child transmission of HIV among Zimbabwean women who

seroconverted postnatally: prospective cohort study. *BMJ*. 2010;341:c6580. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21177735.

Antepartum Care (Last updated December 7, 2018; last reviewed December 7, 2018)

General Principles Regarding Use of Antiretroviral Drugs during Pregnancy

Panel's Recommendations

- Initial evaluation of pregnant women living with HIV should include an assessment of HIV disease status and plans to initiate, continue, or modify antiretroviral therapy (ART) **(AI)**. The National Perinatal HIV Hotline (888-448-8765) provides free clinical consultation on all aspects of perinatal HIV care.
- All pregnant women living with HIV should initiate ART as early in pregnancy as possible, regardless of their plasma HIV RNA copy number or CD4 T lymphocyte count, to prevent perinatal transmission **(AI)**. It is recommended that the HIV viral load be maintained below the limit of detection throughout pregnancy and lifetime of the individual living with HIV **(AII)**.
- To minimize the risk of perinatal transmission, antiretroviral (ARV) drugs should be administered at all time points (including antepartum and intrapartum) to the woman as well as postnatally to the neonate **(AI)**.
- The known benefits and potential risks of all medications, including ARV drugs used during pregnancy and postpartum, should be discussed with all women living with HIV **(AIII)**.
- The importance of adherence to ARV drug regimens should be emphasized during patient counseling **(AII)**.
- ARV drug-resistance genotype studies should be performed before starting ARV drug regimens in women who are ARV-naive **(AII)** or ARV-experienced **(AIII)** and before modifying ARV drug regimens **(AII)** in women whose HIV RNA levels are above the threshold for resistance testing (i.e., >500 to 1,000 copies/mL).
- In pregnant women who are not already receiving ART, ART should be initiated before results of drug-resistance testing are available, because **earlier viral suppression has been associated with lower risk of transmission**. If ART is initiated before results are available, the regimen should be modified, if necessary, based on resistance assay results **(BIII)**.
- Coordination of services among prenatal care providers, primary care and HIV specialty care providers, and, when appropriate, mental health and drug abuse treatment services, intimate partner violence support services, and public assistance programs is essential to help ensure that women living with HIV adhere to their ARV drug regimens **(AII)**.
- Providers should initiate counseling about key intrapartum and postpartum considerations during pregnancy, including mode of delivery, maternal lifelong HIV therapy, family planning and contraceptive options, infant feeding, infant ARV prophylaxis, timing of infant diagnostic testing, and neonatal circumcision **(AIII)**.

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*

In addition to the standard antenatal assessments for all pregnant women, the initial evaluation of women living with HIV should include an assessment of HIV disease status and recommendations for HIV-related medical care. This initial assessment should include the following:

- Review of prior HIV-related illnesses and past CD4 T lymphocyte (CD4) cell counts and plasma HIV RNA levels;
- Current CD4 cell count;
- Current plasma HIV RNA level;
- Assessment of the need for prophylaxis against opportunistic infections, such as *Pneumocystis jirovecii* pneumonia and *Mycobacterium avium* complex (see the Adult and Adolescent Opportunistic Infections Guidelines);
- Screening for hepatitis A virus (HAV), hepatitis C virus, and tuberculosis in addition to standard screening for hepatitis B virus (HBV) infection;
- Screening for and treatment of sexually transmitted infections (STIs), such as syphilis, *Chlamydia trachomatis*, and *Neisseria gonorrhea*;[1-3]
- Assessment of the need for HAV, HBV, influenza, pneumococcus, and Tdap immunizations;[4,5]

- Complete blood cell count and renal and liver function testing;
- HLA-B*5701 testing if abacavir use is anticipated (see Table 10);
- History of prior and current antiretroviral (ARV) drug use, including prior ARV use for prevention of perinatal transmission or treatment of HIV and history of adherence problems;
- Results of prior and current ARV drug-resistance tests;
- History of adverse effects or toxicities caused by previous ARV regimens;
- Screening for depression and anxiety and an assessment of the need for supportive care (e.g., mental health services, substance abuse treatment, smoking cessation), as well as support to help ensure lifelong antiretroviral therapy (ART);[6]
- Screening for intimate partner violence and assessment of the need for related supportive care;
- Referral of sexual partner(s) for HIV testing and ARV treatment or prophylaxis; *and*
- Referral of children for HIV testing

The National Perinatal HIV Hotline

The National Perinatal HIV Hotline (888-448-8765) is a federally funded service provides free clinical consultation to providers caring for women living with HIV and their infants.

How Antiretrovirals Prevent Perinatal Transmission and Improve Maternal Health

All pregnant women living with HIV should receive ART early in pregnancy, regardless of their viral load or CD4 cell count, for their own health and for the prevention of perinatal HIV transmission. ARV drugs are important for maintaining maternal health because they decrease the rate of HIV disease progression and reduce the risk of opportunistic disease and the risk of maternal death. ARV drugs reduce the risk of perinatal transmission of HIV in all pregnant women, regardless of their CD4 cell counts and HIV RNA levels. ARV drugs can reduce perinatal transmission through several mechanisms. Antenatal drug administration decreases maternal viral load in blood and genital secretions.[7-9] Strict adherence to an ARV regimen is needed to achieve rapid viral suppression and minimize the risk of perinatal transmission. Although the risk of perinatal transmission in women with undetectable plasma HIV RNA levels appears to be extremely low, perinatal transmission has been reported among women on ART (see Recommendations for Use of Antiretroviral Drugs During Pregnancy).[10-13] Low-level cervicovaginal HIV RNA and DNA shedding has been detected even in women treated with ART who have undetectable plasma viral loads.[14-16] Penetration of ARV drugs into the female genital tract varies by drug.[17-20]

Infant pre-exposure prophylaxis should also be used to prevent perinatal transmission, as maternal viremia is not the only risk factor for HIV transmission. Pre-exposure prophylaxis is achieved by administering ARV drugs to the mother that cross the placenta and produce adequate systemic drug levels in the fetus. In addition, infant post-exposure prophylaxis is achieved by administering drugs to the infant after birth, providing protection from cell-free or cell-associated virus that may have entered the fetal/infant systemic circulation during labor and delivery. The importance of the pre- and post-exposure components of prophylaxis in reducing perinatal transmission is demonstrated by the reduced efficacy of interventions that involve administration of ARVs only during labor and/or to the newborns.[21-28] Therefore, combined preconception ART, confirmation of antepartum plasma viral load suppression, scheduled surgical delivery (if indicated, based on most recent maternal plasma viral load), intrapartum continuation of the current regimen with the addition of intravenous zidovudine (if indicated, based on the most recent maternal plasma viral load), and infant ARV prophylaxis are all recommended to prevent perinatal transmission of HIV.

General Principles of Drug Selection

In general, the guidelines for the use of ART in pregnant women are the same as those for women who are not pregnant. However, the Perinatal Guidelines may differ from the Adult and Adolescent Guidelines in

some instances where regimen selection has been modified based on concerns about specific drugs or limited experience with newer drugs during pregnancy (see Table 6 and Recommendations for Use of Antiretroviral Drugs During Pregnancy).

The benefits and potential risks of ARV drug use during pregnancy should be considered and discussed with women (see Table 10 and Supplement: Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy). Potential risks of these drugs should be placed into perspective by reviewing the substantial benefits of ARV drugs for maternal health and for reducing the risk of transmission of HIV to infants. Counseling of pregnant women about ARV use should be directive and noncoercive, and providers should help women make informed decisions regarding the use of ARV drugs.

Discussions with women about initiation of ART regimens should include information about:

- Maternal risk of disease progression and the benefits and risks of therapy for maternal health;
- Benefits of ART for preventing perinatal transmission of HIV;[11]
- Benefits of therapy for reducing sexual transmission to partners who do not have HIV when viral suppression is maintained;[29]
- The need for strict adherence to the prescribed drug regimen to avoid resistance, optimize health outcomes, and minimize the risk of perinatal HIV transmission;
- Potential adverse effects of ARV drugs for mothers, fetuses, and infants, including potential interactions with other medications the women may already be receiving (see Recommendations for Use of Antiretroviral Drugs During Pregnancy);[30-32] *and*
- The limited long-term outcome data for infants who were exposed to ARV drugs *in utero*, especially for newer ARV drugs.

In pregnant women with HIV who are not currently receiving treatment, plasma HIV RNA levels should be measured, and ART should be initiated. In women with plasma HIV RNA levels above the threshold for resistance testing (i.e., >500 to 1,000 copies/mL), ARV drug-resistance testing should be sent off before starting ART; however, ART should be initiated before results of drug-resistance testing are available, because earlier viral suppression is associated with lower risk of perinatal transmission.[33,34] The ART regimen can be modified, if necessary, based on resistance assay results[35] (see Antiretroviral Drug Resistance and Resistance Testing in Pregnancy). Counseling should emphasize the importance of adherence to the ARV drug regimen to minimize the development of resistance and support the effectiveness of ART in achieving viral suppression. Women with poor adherence during pregnancy are more likely to have detectable viral load at delivery.[36]

Transplacental passage of ARV drugs is thought to be an important mechanism of infant pre-exposure prophylaxis. Thus, when selecting an ARV regimen for a pregnant woman, at least one nucleoside/nucleotide reverse transcriptase inhibitor agent with high placental transfer should be included as a component of the ART regimen (see Table 10).[37-41]

Patient Counseling and Coordination of Care

Coordination of services among prenatal care providers, primary care and HIV specialty care providers, mental health and drug abuse treatment services, and public assistance programs is essential to ensure that women living with HIV are well supported during all stages of their pregnancies and the postpartum period. Medical care of pregnant women living with HIV requires coordination and communication between HIV specialists and obstetric providers. General counseling should include current knowledge about risk factors for perinatal transmission. Risk of perinatal transmission of HIV has been associated with potentially modifiable factors, including cigarette smoking, illicit drug use, and genital tract infections. Besides improving maternal health, cessation of cigarette smoking and drug use and treatment of STIs and other genital tract infections may reduce the risk of perinatal transmission. Women should be assessed for mental health concerns and the risk of intimate partner violence and referred to services that are appropriate for each woman's individual circumstances.

In addition, providers should begin to counsel women living with HIV about what to expect during labor, delivery, and the postnatal period. This includes discussions about the mode of delivery and the possible use of intrapartum zidovudine, as well as family planning and contraceptive options during the postpartum period. Providers should also discuss the possibility of simplifying a woman's ARV regimen after delivery, which can help promote long-term adherence to ART. Discussions regarding the prevention of postnatal transmission to the neonate should also include recommendations about infant feeding, neonatal ARV prophylaxis, infant diagnostic HIV testing, and the avoidance of premastication of food.

References

1. Adachi K, Klausner JD, Bristow CC, et al. Chlamydia and gonorrhea in HIV-infected pregnant women and infant HIV transmission. *Sex Transm Dis*. 2015;42(10):554-565. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26372927.
2. American College of Obstetricians Gynecologists' Committee on Practice Bulletins-Obstetrics. Practice bulletin No. 170: critical care in pregnancy. *Obstet Gynecol*. 2016;128(4):e147-154. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27661653.
3. Sivarajah V, Venus K, Yudin MH, Murphy KE, Morrison SA, Tan DH. Does maternal HSV-2 coinfection increase mother-to-child transmission of HIV? a systematic review. *Sex Transm Infect*. 2017;93(8):535-542. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28600331.
4. Rubin LG, Levin MJ, Ljungman P, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. *Clin Infect Dis*. 2014;58(3):e44-100. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24311479.
5. Centers for Disease Control and Prevention. Guidelines for vaccinating pregnant women. 2017. Available at: https://www.cdc.gov/vaccines/pregnancy/hcp/guidelines.html.
6. American College of Obstetricians and Gynecologists. Screening for perinatal depression. 2015. Available at: https://www.acog.org/Clinical-Guidance-and-Publications/Committee-Opinions/Committee-on-Obstetric-Practice/Screening-for-Perinatal-Depression.
7. Pilotto JH, Velasque LS, Friedman RK, et al. Maternal outcomes after HAART for the prevention of mother-to-child transmission in HIV-infected women in Brazil. *Antivir Ther*. 2011;16(3):349-356. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21555817.
8. Becquet R, Bland R, Ekouevi DK, Dabis F, Newell ML. Universal antiretroviral therapy among pregnant and postpartum HIV-infected women would improve maternal health and decrease postnatal HIV transmission. *AIDS*. 2010;24(8):1239-1241. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20421749.
9. Becquet R, Ekouevi DK, Arrive E, et al. Universal antiretroviral therapy for pregnant and breast-feeding HIV-1-infected women: towards the elimination of mother-to-child transmission of HIV-1 in resource-limited settings. *Clin Infect Dis*. 2009;49(12):1936-1945. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19916796.
10. Warszawski J, Tubiana R, Le Chenadec J, et al. Mother-to-child HIV transmission despite antiretroviral therapy in the ANRS French Perinatal Cohort. *AIDS*. 2008;22(2):289-299. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18097232.
11. Tubiana R, Le Chenadec J, Rouzioux C, et al. Factors associated with mother-to-child transmission of HIV-1 despite a maternal viral load <500 copies/mL at delivery: a case-control study nested in the French perinatal cohort (EPF-ANRS CO1). *Clin Infect Dis*. 2010;50(4):585-596. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20070234.
12. European Collaborative Study. Mother-to-child transmission of HIV infection in the era of highly active antiretroviral therapy. *Clin Infect Dis*. 2005;40(3):458-465. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15668871.
13. Raffe SF, Savage C, Perry LA, et al. The management of HIV in pregnancy: a 10-year experience. *Eur J Obstet Gynecol Reprod Biol*. 2017;210:310-313. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28110176.
14. Launay O, Tod M, Tschope I, et al. Residual HIV-1 RNA and HIV-1 DNA production in the genital tract reservoir of women treated with HAART: the prospective ANRS EP24 GYNODYN study. *Antivir Ther*. 2011;16(6):843-852. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21900716.
15. Cu-Uvin S, DeLong AK, Venkatesh KK, et al. Genital tract HIV-1 RNA shedding among women with below detectable plasma viral load. *AIDS*. 2010;24(16):2489-2497. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20736815.
16. Henning TR, Kissinger P, Lacour N, Meyaski-Schluter M, Clark R, Amedee AM. Elevated cervical white blood cell

infiltrate is associated with genital HIV detection in a longitudinal cohort of antiretroviral therapy-adherent women. *J Infect Dis*. 2010;202(10):1543-1552. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20925530.

17. Yeh RF, Rezk NL, Kashuba AD, et al. Genital tract, cord blood, and amniotic fluid exposures of seven antiretroviral drugs during and after pregnancy in human immunodeficiency virus type 1-infected women. *Antimicrob Agents Chemother*. 2009;53(6):2367-2374. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19307360.

18. Dumond JB, Yeh RF, Patterson KB, et al. Antiretroviral drug exposure in the female genital tract: implications for oral pre- and post-exposure prophylaxis. *AIDS*. 2007;21(14):1899-1907. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17721097.

19. Else LJ, Taylor S, Back DJ, Khoo SH. Pharmacokinetics of antiretroviral drugs in anatomical sanctuary sites: the male and female genital tract. *Antivir Ther*. 2011;16(8):1149-1167. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22155899.

20. Drake A, Kinuthia J, Materno D, et al. Plasma and genital HIV decline on ART among pregnant/postpartum women with recent HIV infection. Paper presented at: International AIDS Conference. 2016. Durban, South Africa.

21. Jackson JB, Musoke P, Fleming T, et al. Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: 18-month follow-up of the HIVNET 012 randomised trial. *Lancet*. 2003;362(9387):859-868. Available at: http://www.ncbi.nlm.nih.gov/pubmed/13678973.

22. Petra Study Team. Efficacy of three short-course regimens of zidovudine and lamivudine in preventing early and late transmission of HIV-1 from mother to child in Tanzania, South Africa, and Uganda (Petra study): a randomised, double-blind, placebo-controlled trial. *Lancet*. 2002;359(9313):1178-1186. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11955535.

23. Moodley D, Moodley J, Coovadia H, et al. A multicenter randomized controlled trial of nevirapine versus a combination of zidovudine and lamivudine to reduce intrapartum and early postpartum mother-to-child transmission of human immunodeficiency virus type 1. *J Infect Dis*. 2003;187(5):725-735. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12599045.

24. Taha TE, Kumwenda NI, Gibbons A, et al. Short postexposure prophylaxis in newborn babies to reduce mother-to-child transmission of HIV-1: NVAZ randomised clinical trial. *Lancet*. 2003;362(9391):1171-1177. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14568737.

25. Gaillard P, Fowler MG, Dabis F, et al. Use of antiretroviral drugs to prevent HIV-1 transmission through breast-feeding: from animal studies to randomized clinical trials. *J Acquir Immune Defic Syndr*. 2004;35(2):178-187. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14722452.

26. Gray GE, Urban M, Chersich MF, et al. A randomized trial of two postexposure prophylaxis regimens to reduce mother-to-child HIV-1 transmission in infants of untreated mothers. *AIDS*. 2005;19(12):1289-1297. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16052084.

27. Nielsen-Saines K, Watts H, Veloso VG, et al. Three postpartum antiretroviral regimens to prevent intrapartum HIV infection. *N Engl J Med*. 2012;366(25):2368-79. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22716975.

28. Scott GB, Brogly SB, Muenz D, Stek AM, Read JS, IMPAACT P1025 Study Team. Missed opportunities for prevention of mother-to-child transmission of human immunodeficiency virus. *Obstet Gynecol*. 2017;129(4):621-628. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28277349.

29. Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med*. 2011;365(6):493-505. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21767103.

30. Grignolo S, Agnello R, Gerbaldo D, et al. Pregnancy and neonatal outcomes among a cohort of HIV-infected women in a large Italian teaching hospital: a 30-year retrospective study. *Epidemiol Infect*. 2017;145(8):1658-1669. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28325171.

31. Stringer E, Kendall M, Lockman S, et al. Pregnancy outcomes among HIV-infected women who conceived on antiretroviral therapy. Presented at: International AIDS Society. 2017. Paris, France.

32. Harrington B, Phulusa J, Melhado C, et al. Incidence of hepatotoxicity among HIV-positive pregnant women initiating efavirenz-based ART through option B+ in Malawi. Presented at: International AIDS Society; 2017; Paris, France.

33. Mandelbrot L, Tubiana R, Le Chenadec J, et al. No perinatal HIV-1 transmission from women with effective antiretroviral therapy starting before conception. *Clin Infect Dis*. 2015. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26197844.

34. Favarato G, Bailey H, Burns F, Prieto L, Soriano-Arandes A, Thorne C. Migrant women living with HIV in Europe: are they facing inequalities in the prevention of mother-to-child-transmission of HIV?: the European pregnancy and paediatric HIV cohort collaboration (EPPICC) study group in EuroCoord. *Eur J Public Health*. 2017. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28449111.

35. Tariq S, Townsend CL, Cortina-Borja M, et al. Use of zidovudine-sparing HAART in pregnant HIV-infected women in Europe: 2000-2009. *J Acquir Immune Defic Syndr*. 2011;57(4):326-333. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21499113.

36. Katz IT, Leister E, Kacanek D, et al. Factors associated with lack of viral suppression at delivery among highly active antiretroviral therapy-naive women with HIV: a cohort study. *Ann Intern Med*. 2015;162(2):90-99. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25599347.

37. Hirt D, Urien S, Rey E, et al. Population pharmacokinetics of emtricitabine in human immunodeficiency virus type 1-infected pregnant women and their neonates. *Antimicrob Agents Chemother*. 2009;53(3):1067-1073. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19104016.

38. Hirt D, Urien S, Ekouevi DK, et al. Population pharmacokinetics of tenofovir in HIV-1-infected pregnant women and their neonates (ANRS 12109). *Clin Pharmacol Ther*. 2009;85(2):182-189. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18987623.

39. Moodley D, Pillay K, Naidoo K, et al. Pharmacokinetics of zidovudine and lamivudine in neonates following coadministration of oral doses every 12 hours. *J Clin Pharmacol*. 2001;41(7):732-741. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11452705.

40. Wade NA, Unadkat JD, Huang S, et al. Pharmacokinetics and safety of stavudine in HIV-infected pregnant women and their infants: pediatric AIDS clinical trials group protocol 332. *J Infect Dis*. 2004;190(12):2167-2174. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15551216.

41. McCormack SA, Best BM. Protecting the fetus against HIV infection: a systematic review of placental transfer of antiretrovirals. *Clin Pharmacokinet*. 2014;53(11):989-1004. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25223699.

Teratogenicity (Last updated December 12, 2019; last reviewed December 12, 2019)

Panel's Recommendations

- All cases of antiretroviral (ARV) drug exposure during pregnancy should be reported to the Antiretroviral Pregnancy Registry **(AIII)**.
- Based on multiple studies indicating no difference in rates of total birth defects for first-trimester exposure compared with later ARV drug exposures, women can be counseled that ARV drugs during pregnancy generally do not increase the risk of birth defects **(BIII)**; a possible exception is a small increased risk of neural tube defects (NTDs) with dolutegravir (DTG) use during the periconception period. Providers should be aware that data on the risks of birth defects for many ARV drugs are limited.

Updated Panel Recommendations Regarding the Use of Dolutegravir at the Time of Conception and During Pregnancy:

- DTG exposure around the time of conception has been associated with a small but significant increase in the risk of infant NTDs in Botswana (0.3%), where food is not routinely fortified with folate. Although this risk was higher than the risk for NTDs in infants born to women who were receiving efavirenz (0.05%) and women without HIV (0.08%), there are not enough data to determine the risk of NTDs with preconception use of all *Preferred* and *Alternative* regimens, including DTG, in the United States. Based on the available evidence, the Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission (the Panel) recommends DTG as a ***Preferred* drug for pregnant women, irrespective of trimester (AII)**, and an ***Alternative* drug for women who are trying to conceive (AIII)**.
- The Panel emphasizes the importance of counseling and informed decision-making regarding all ARV regimens for people with HIV **(AIII)**. For additional information, see Appendix D: Dolutegravir Counseling Guide for Health Care Providers.
- Clinicians should discuss future reproductive plans and timing as well as the risks and benefits of conceiving on specific ARV medications and use of appropriate contraceptive options to prevent unintended pregnancy **(AIII)**.
- Folic acid is known to prevent NTDs in the general population. All pregnant women and women who might conceive should take at least 400 mcg of folic acid daily **(AI)**. There is no established link between the use of DTG and impaired folate metabolism, nor is there evidence that folate supplementation prevents DTG-associated NTDs.
- For additional information, see Updated Guidance about the Use of Dolutegravir in Pregnancy in Recommendations for Use of Antiretroviral Drugs During Pregnancy, Preconception Counseling and Care for Women of Childbearing Age Living with HIV, Pregnant Women Living with HIV Who Are Currently Receiving Antiretroviral Therapy, and Dolutegravir.

Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*

Rating of Evidence: *I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

Antiretroviral Pregnancy Registry Reporting

Health care providers who are caring for pregnant women with HIV and their newborns are strongly advised to report instances of prenatal exposure to antiretroviral (ARV) drugs (either single-drug exposure or exposure to a combination of ARV drugs) to the Antiretroviral Pregnancy Registry as early in pregnancy as possible. This registry is an epidemiologic project to collect observational, nonexperimental data regarding ARV drug exposure during pregnancy for the purpose of assessing the potential teratogenicity of these drugs. Registry data will be used to supplement animal toxicology studies and assist clinicians in weighing the potential risks and benefits of treatment for individual patients. The Antiretroviral Pregnancy Registry is a collaborative project of pharmaceutical manufacturers with an advisory committee that includes a teratologist, an infectious disease specialist, an epidemiologist, a biostatistician, and a group of obstetric, maternal-fetal medicine, and pediatric providers. The registry does not use patient names, and registry staff obtain birth outcome follow-up information from the reporting health care provider.

Referrals should be directed to:

Antiretroviral Pregnancy Registry
Research Park
1011 Ashes Drive
Wilmington, NC 28405
Telephone: 1-800-258-4263
Fax: 1-800-800-1052
http://www.APRegistry.com

Antiretroviral Drugs and Birth Defects

The potential harm to the fetus from maternal ingestion of a specific drug depends not only on the drug itself, but also on the dose ingested, the gestational age of the fetus at exposure, the duration of exposure, interactions with other agents to which the fetus is exposed, and, to an unknown extent, the genetic makeup of the mother and fetus.

Information regarding the safety of using certain drugs during pregnancy is derived from animal toxicity data, anecdotal experience, registry data, and clinical trials. Drug choice should be individualized and discussed with the woman before treatment begins. Clinicians must also consider available data from preclinical and clinical testing of the individual drugs. Preclinical data include results of in vitro and animal *in vivo* screening tests for carcinogenicity, clastogenicity/mutagenicity, and reproductive and teratogenic effects. However, the predictive value of such tests for adverse effects in humans is unknown.

Data continue to be collected on the placental passage, pharmacokinetics, and safety of Food and Drug Administration (FDA)-approved ARV drugs during pregnancy, in addition to data on the long-term safety in infants who were exposed to these drugs. However, the data remains somewhat limited, especially for newer drugs (see Supplement: Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy). When analyzing registry data, data on birth outcomes from 200 infants who were exposed to an ARV drug during the first trimester is viewed as sufficient to detect a 2.2-fold increase in the risk of overall birth defects associated with that drug compared to the general population. A cohort of 1,000 is sufficient to detect a 1.5-fold increase in the risk of birth defects. The general U.S. population birth defect prevalence is 2.8%.[1] However, data from a larger number of infants is required to detect an increased risk of specific birth defects with lower frequencies of occurrence, with the required number of infants who were exposed to an ARV drug increasing as the frequency of the defect in an unexposed population decreases.[2]

A recent report from the Surveillance Monitoring for ART Toxicities (SMARTT) study of the Pediatric HIV/AIDS Cohort Study (PHACS) network detected an increased rate of microcephaly in HIV-exposed but uninfected children with *in utero* efavirenz (EFV) exposure. The relative risk of microcephaly in infants with *in utero* EFV exposure was 2.56 (95% confidence interval [CI], 1.22–5.37). In this study, microcephaly was defined as a z-score of less than -2 between 6 and 36 months of age or head size below the second percentile after 36 months.[3] Only 4.7% of children had been exposed to EFV *in utero*. The relative risk of microcephaly was higher among children who had been exposed to EFV plus zidovudine (ZDV) and lamivudine (3TC) than among those who had been exposed to EFV plus tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC). Children with microcephaly had lower scores on neurodevelopmental assessments at ages 1 year and 5 years and a higher rate of neurodevelopmental impairment than those without microcephaly. Additional evaluation of the association between microcephaly and *in utero* EFV exposure is needed.

It is important to consider potential confounding factors in studies of ARV drugs and birth defects. Several factors that are associated with HIV may also increase the risk of birth defects, such as exposure to folate antagonists (e.g., trimethoprim-sulfamethoxazole),[4] nutritional and folate status,[5] and tobacco and alcohol use.[6] Clinicians should also be aware of indication bias, which can occur when a patient's reason for taking a particular ARV drug is associated with an increased risk of birth defects, such as older age or more advanced disease.

Several studies of birth defects in fetuses and infants of women who received ARV regimens during observational studies found no difference in rates of total birth defects between first-trimester drug exposures and later exposures.[7-11] The Antiretroviral Pregnancy Registry conducts a primary analysis of prospective cases of ARV drug exposure during pregnancy provided by health care providers. In this analysis, the prevalence of birth defects was 2.8 per 100 live births among women with a first-trimester exposure to any ARV drug (271 of 9,854 exposures; 95% CI, 2.4–3.1). The prevalence of defects is not significantly different from that seen in women with an initial exposure during the second and/or third trimester (2.8 per 100 live births; prevalence ratio 0.99, 95% CI, 0.83–1.18).[1] Though these studies are reassuring, an increased risk of specific abnormalities, particularly rare abnormalities, would not necessarily be detectable when looking only

at the total number of birth defects. Further, risk may be underestimated when defects are only ascertained after live births, as this does not include more severe defects that result in stillbirths and terminations. Another limitation is that an increased risk that is associated with a specific ARV drug may be obscured when the analysis unit combines all ARV drugs together.

Use of Dolutegravir at the Time of Conception and in Early Pregnancy

In May 2018, an unplanned interim evaluation of a National Institutes of Health-funded, observational surveillance study of birth outcomes among pregnant women on antiretroviral therapy (ART) in Botswana revealed four neural tube defects (NTDs) among infants born to 426 women (0.94%) who became pregnant while receiving a dolutegravir (DTG)-based regimen.[12] These data were updated in a planned analysis in May 2019. In the Tsepamo study, five NTDs were identified (0.30%) among 1,683 deliveries to women who were taking DTG around the time of conception; the defects included two instances of myelomeningocele, one of anencephaly, one of encephalocele, and one of iniencephaly. In comparison, 15 NTDs were found among 14,792 deliveries (0.10%) in which the mother was taking any ART that did not include DTG at conception, three NTDs were found among 7,959 deliveries (0.04%) in which the mother was taking EFV at conception, one NTD was found among 3,840 deliveries (0.03%) in which the mother started treatment with DTG during pregnancy, and 70 NTDs were found among 89,372 deliveries (0.08%) to mothers without HIV.[13] While the risk of NTDs in infants who were exposed to DTG around the time of conception was lower than initially reported, it remains significantly increased compared to all comparison groups.

Although there are limited data on the association between NTDs and DTG exposure, three studies that included an internal comparator group and assessments of NTDs in stillbirths and terminations have evaluated NTDs in infants who were exposed to DTG at conception in addition to the Botswana study. The first was a prospective study by the Ministry of Health and the Centers for Disease Control and Prevention at 22 additional sites in Botswana that were not included in the Tsepamo study. This study identified one NTD among infants born to 152 women (0.66%) who were receiving DTG at conception, compared to no NTDs among infants born to 381 women who were receiving other ARV drugs at conception and two NTDs among infants born to 2,328 women who did not have HIV (0.09%).[14] The second study included prospective data from the Antiretroviral Pregnancy Registry, and it is worth noting that 75% of the data in the registry comes from North America, Europe, and Latin America, where most countries require folate fortification for food. The study found one case of an NTD among 248 live births (0.4%) of infants with periconception DTG exposure and no NTDs among 217 live births of infants with periconception elvitegravir (EVG) exposure and 268 live births of infants with periconception raltegravir (RAL) exposure.[1] The third study was a retrospective study of women with periconception ARV drug exposure in a national cohort in Brazil; no NTDs were observed among 384 pregnancies in which infants were exposed to DTG (95% CI, 0–0.0099) or among 1,109 pregnancies in which infants were exposed to EFV or RAL (95% CI, 0–0.003).[15] Unlike Brazil and the United States, Botswana does not have mandated food folate fortification, which can decrease NTD prevalence by half. More data are needed to delineate the risks of NTDs among infants born to women living in other geographical regions and countries with mandated food folate fortification.

No mechanism has been identified to explain the observed association between DTG exposure and NTDs, though several studies have evaluated the role of folate. A substudy of the ADVANCE trial evaluated serum folate levels among women by randomized arm and found that folate deficiency occurred less often in women who were receiving DTG, with 13.7% of women in the DTG plus TDF plus FTC arm and 5.4% of women in the DTG plus tenofovir alafenamide (TAF) plus FTC arm experiencing folate deficiency compared with 30% of those who received EFV ($P < 0.001$).[16] Studies that have evaluated folate receptor antagonism by DTG in animal models and cell models have had conflicting results, and the clinical implications of these results is unclear. Additional studies are needed to clarify the role of folate and to explore other potential mechanisms.

The risk of NTDs decreases after early pregnancy, though it is not clear exactly when this period of increased risk ends. Most NTDs result from failure of neural tube closure. The neural tube closes by

approximately 4 weeks post-conception, or approximately 6 weeks after the last menstrual period in women with regular menses. Therefore, the risk period for a medication to cause NTDs is over by approximately 6 weeks gestational age. However, it is possible that one of the five defects observed in the Botswana study (encephalocele) may have occurred by a different mechanism (a post-neurulation event) slightly after the neural tube had closed. The exact timing of development of encephalocele in humans is not well described; however, extrapolating from animal data, it is likely to occur before 6 weeks post-conception (8 weeks gestational age). Determining when the risk period for defects is over also depends on accurately determining the gestational age and the date of the last menstrual period.

Data on Other Integrase Strand Transfer Inhibitors

Limited data are available on the association between other integrase strand transfer inhibitors and birth defects. A retrospective case series evaluated data from nine institutions on 140 pregnancies in which the woman received EVG during pregnancy, including 82 women who received the drug before conception and during the first trimester.[17] Two defects were noted: one case of hydronephrosis in which exposure began before conception, and one case of an encephalocele in which a woman with periconceptional exposure to TDF plus FTC plus darunavir/ritonavir was switched to atazanavir (ATV) plus EVG/cobicistat/FTC/TDF at 9 weeks due to drug side effects. Among 33 women who were exposed to EVG during the first trimester in the United Kingdom and Ireland, no defects were noted in 31 liveborn infants.[18] In the Antiretroviral Pregnancy Registry, defects were reported in six of 240 infants (2.5%; 95% CI, 0.9% to 5.4%) born after first-trimester exposure to EVG; this does not represent an increased risk compared to the overall rate of defects in the Registry.[1] A review of the Gilead safety database, which included an earlier data set from the Antiretroviral Pregnancy Registry, reported 155 prospective periconception exposures to EVG with no NTDs.[19] Review of a surveillance database in Canada found no NTDs among 28 infants with first-trimester exposures.[11]

Surveillance data from the United Kingdom and Ireland included 882 live births of infants with exposure to RAL, and birth defects were reported in 23 infants, a rate of 2.59% (95% CI, 1.65% to 3.86%); this rate is similar to that in the general population. No NTDs were reported.[18] Among the 222 infants with periconception exposure to RAL, five defects were noted, including two heart defects, two limb defects, and one unspecified defect. In the Antiretroviral Pregnancy Registry, birth defects were reported in nine of 327 infants (2.8%; 95% CI, 1.3% to 5.2%) with first-trimester exposure to RAL. This incidence is similar to the incidence seen in the overall population reported to the APR. A review performed by Merck researchers that included data from the company database; the previously noted Antiretroviral Pregnancy Registry data; and the United Kingdom, Ireland and French pregnancy cohorts reported 456 periconception exposures to RAL with no NTDs.[20]

The Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission has updated its recommendations regarding the use of DTG during pregnancy and at the time of conception in coordination with the Panel on Antiretroviral Guidelines for Adults and Adolescents (see Recommendations for Use of Antiretroviral Drugs During Pregnancy, Preconception Counseling and Care for Women of Childbearing Age Living with HIV, and the Adult and Adolescent Antiretroviral Guidelines). The potential risk of NTDs, the benefits of DTG-containing regimens, and the risks and benefits of alternative regimens should be discussed with women who need to initiate ART during the first trimester or who are planning to become pregnant (see Appendix D: Dolutegravir Counseling Guide for Health Care Providers). For additional guidance, please contact the National Perinatal HIV Hotline (1-888-448-8765).

Specific Drugs

Efavirenz

EFV use during pregnancy has received increased scrutiny because of the results of a small study in nonhuman primates. Significant malformations were observed in three of 20 infant cynomolgus monkeys that received EFV from gestational days 20 to 150 at a dose that produced plasma concentrations comparable to those seen in humans with systemic exposure to the therapeutic dose.[21] The malformations included

anencephaly and unilateral anophthalmia in one monkey, microphthalmia in another, and cleft palate in the third.

Increased scrutiny of outcomes after EFV exposure has provided reassuring data. Sufficient numbers of first-trimester exposures to EFV have been monitored in the Antiretroviral Pregnancy Registry to rule out at least a 1.5-fold increase in the risk of overall birth defects and a two-fold increase in risk of birth defects in the cardiovascular and genitourinary systems. Twenty-five of 1,061 infants (2.4%) with first-trimester exposures to EFV were found to have birth defects, including a single case of myelomeningocele and one case of anophthalmia and amniotic bands.[1] A meta-analysis that included data from 23 studies reporting on 2,026 first-trimester exposures to ARV drugs found no increased risk of overall birth defects for infants born to women who were on EFV during the first trimester compared with those who were on other ARV drugs during the first trimester (relative risk [RR] 0.78; 95% CI, 0.56–1.08). One NTD was observed, giving an incidence of 0.05% (95% CI, <0.01 to 0.28).[22] The number of reported first-trimester EFV exposures in this meta-analysis is sufficient to rule out a two-fold increase in low-incidence birth defects, such as NTDs. Incidence of NTDs in the general U.S. population is 0.02% to 0.2%.[2,22]

The Tsepamo study discussed above found three NTDs among 7,959 live births and stillbirths (0.04%) to women who were on EFV at conception. There is no difference between this incidence and the incidence for NTDs among infants born to women without HIV.[13] The study also found no increased risk of total major abnormalities identified on infant surface exam among women who were taking EFV around the time of conception compared to women without HIV (0.68% vs. 0.59%). In addition, a birth defect surveillance program in Uganda that used methods that were similar to those used in the Tsepamo study reported an NTD prevalence of 0.059% (95% CI, 0.001% to 0.118%) among infants born to women with HIV, 80% of whom were on EFV, and an NTD prevalence of 0.092% (95% CI, 0.068% to 0.116%) among infants born to women without HIV.[23] Thus, the findings in monkeys have not been confirmed by human data, underscoring the need for well-designed studies to rapidly provide data on the safety of new drugs for use in pregnancy.

The FDA advises women to avoid becoming pregnant while taking EFV and advises health care providers to avoid administering EFV during the first trimester of pregnancy, as fetal harm may occur. However, with the data from Botswana on over 7,900 periconception exposures, we can now rule out a three-fold or more increase in the risk of NTDs in infants who were exposed to EFV. 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 and World Health Organization guidelines for use of ARV drugs in pregnancy, both of which note that EFV can be used throughout pregnancy.[24,25] Importantly, women who become pregnant on EFV-containing regimens that are suppressive and tolerated should continue using those regimens.

Tenofovir Disoproxil Fumarate

TDF has not demonstrated teratogenicity in rodents or monkeys. Data from the Antiretroviral Pregnancy Registry showed that 91 of 3,851 infants born to women with first-trimester TDF exposure had birth defects. That means the birth defect incidence for infants exposed to TDF during the first trimester is 2.4%, similar to the incidence in the general population.[1] A more recent meta-analysis of TDF use among women with HIV found no increase in the risk of congenital anomalies associated with the use of TDF (RR 1.03; 95% CI, 0.83–1.28).[26]

No clinical studies have reported newborn outcomes associated with maternal use of TAF.

Zidovudine

In a study from France that included 13,124 live births that occurred between 1994 and 2010, first-trimester ARV drug exposure was found in 5,388 infants (42%). The authors reported a significant adjusted association between first-trimester ZDV exposure and congenital heart defects, primarily ventricular (58%) and atrial (18%) septal defects (adjusted odds ratio [aOR] 2.2; 95% CI, 1.3–3.7). Because fetal ultrasounds were conducted on all infants who were exposed to HIV, and because spontaneous closure of ventricular septal

defects after birth is common, the clinical significance of the cardiac findings is uncertain.[27] An analysis of 16,304 prospectively reported pregnancies compared the risk of ventricular septal defects and congenital heart defects in infants with prenatal exposure to ZDV-containing regimens and infants with prenatal exposure to ART regimens that did not contain ZDV. In contrast to the French study, this analysis found that the risk of these defects was similar between the two groups.[28] A recent study that combined a meta-analysis and data from a Medicaid database of ART prescriptions and infant outcomes did not detect a significant increase in overall defects or heart defects among infants who had first-trimester ZDV exposure compared to infants with exposure to other ART regimens during the first trimester (odds ratio [OR] for overall defects 1.11; 95% CI, 0.80–1.55; OR for cardiac defects 1.30; 95% CI, 0.63–2.71).[29] Additionally, one study investigated echocardiographic parameters of left ventricular function and structure in 417 infants. Some of the infants had been exposed to HIV and ARV drugs but had not contracted HIV, while others had not been exposed to either HIV or ARV drugs. When these children were tested at ages 2 to 7 years, no clinically significant differences in left ventricular function and structure were found between the exposed and unexposed groups.[6]

Atazanavir

In an analysis from the Pediatric HIV/AIDS Cohort Study that included 2,580 live births, first-trimester ARV drug exposure overall was not associated with an increased risk of birth defects.[30] First-trimester exposures to ATV were reported for 222 infants, and in adjusted analyses, ATV was the only individual ARV drug for which first-trimester exposure was associated with birth defects (primarily skin and musculoskeletal defects). However, in the Antiretroviral Pregnancy Registry, there was no increase in the risk of birth defects with first-trimester ATV exposure among 1,328 births.[1]

Other Antiretroviral Drugs

In the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposures have been monitored to detect at least a two-fold increase in the risk of overall birth defects for cobicistat, darunavir, didanosine (ddI), EVG, indinavir, RAL, rilpivirine, stavudine, and telbivudine; however, no such increases have been detected to date. For abacavir, ATV, EFV, FTC, 3TC, lopinavir, nelfinavir (NFV), nevirapine, ritonavir, TDF, and ZDV, sufficient numbers of first-trimester exposures have been monitored to detect at least a 1.5-fold increase in the risk of overall birth defects and a two-fold increase in the risk of birth defects in cardiovascular and genitourinary systems; no such increases have been detected to date. A modest (but statistically significant) increase in overall birth defect rates for ddI and NFV is observed when data from the Antiretroviral Pregnancy Registry are compared with the U.S. population-based Metropolitan Atlanta Congenital Defects Program (MACDP) surveillance data.[1] The lower bounds of the CIs for ddI and NFV (2.9% and 2.8%, respectively) are slightly above the higher bound (2.72%) for the MACDP rate, but rates are not elevated compared to the Texas Birth Defect Registry rate of 4.17%, an additional comparator now included in the Antiretroviral Pregnancy Registry. No specific pattern of defects has been detected with the use of either ddI or NFV, and the clinical relevance of this statistical finding is unclear. The Antiretroviral Pregnancy Registry will continue to monitor ddI and NFV for any signal or pattern of birth defects.

See Supplement: Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy for detailed information on individual drugs.

References

1. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral Pregnancy Registry international interim report for 1 January 1989–31 January 2019. Wilmington, NC: Registry Coordinating Center. 2019. Available at: http://www.apregistry.com.

2. Watts DH. Teratogenicity risk of antiretroviral therapy in pregnancy. *Curr HIV/AIDS Rep*. 2007;4(3):135-140. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17883999.

3. 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;S2352-3018(19)30340-6. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31740351.

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

5. Jungmann EM, Mercey D, DeRuiter A, et al. Is first trimester exposure to the combination of antiretroviral therapy and folate antagonists a risk factor for congenital abnormalities? *Sex Transm Infect*. 2001;77(6):441-443. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11714944.

6. Lipshultz SE, Williams PL, Zeldow B, et al. Cardiac effects of in-utero exposure to antiretroviral therapy in HIV-uninfected children born to HIV-infected mothers. *AIDS*. 2015;29(1):91-100. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25562493.

7. Watts DH, Huang S, Culnane M, et al. Birth defects among a cohort of infants born to HIV-infected women on antiretroviral medication. *J Perinat Med*. 2011;39(2):163-170. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21142844.

8. Knapp KM, Brogly SB, Muenz DG, et al. Prevalence of congenital anomalies in infants with *in utero* exposure to antiretrovirals. *Pediatr Infect Dis J*. 2012;31(2):164-170. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21983213.

9. da Costa TP, Machado ES, et al. Malformations among HIV vertically exposed newborns–results from a Brazilian cohort study. Presented at: 6th IAS Conference on HIV Pathogenesis and Treatment and Prevention. 2011. Rome, Italy.

10. Floridia M, Mastroiacovo P, Tamburrini E, et al. Birth defects in a national cohort of pregnant women with HIV infection in Italy, 2001-2011. *BJOG*. 2013;120(12):1466-1475. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23721372.

11. Money D, Lee T, O'Brien C, et al. Congenital anomalies following antenatal exposure to dolutegravir: a Canadian surveillance study. *BJOG*. 2019;126(11):1338-1345. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31188522.

12. 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.

13. 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.

14. Raesima M, Forhan S, Thomas V, Rabold E, et al. Addressing the safety signal with dolutegravir use at conception: Additional surveillance data from Botswana. Presented at: International AIDS Society Conference. 2019. Mexico City, Mexico.

15. Pereira G, Kim A, Jalil E, Fernandes F, Shepard B, Veloso V, et al. No occurrences of neural tube defects among 382 women on dolutegravir at pregnancy conception in Brazil. Presented at: International AIDS Society Conference. 2019. Mexico City, Mexico.

16. Chandiwana N, Hill A, Chersich M, et al. Serum folate and birth outcomes: DTG vs. EFV trial evidence in South Africa. Presented at: Conference on Retroviruses and Opportunistic Infections. 2019. Seattle, Washington.

17. 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.

18. Rasi V, Cortina-Borja M, Peters H, Sconza R, Thorne C. Brief report: surveillance of congenital anomalies after exposure to raltegravir or elvitegravir during pregnancy in the United Kingdom and Ireland, 2008-2018. *J Acquir Immune Defic Syndr*. 2019;80(3):264-268. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30531300.

19. 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.

20. Shamsuddin H, Raudenbush CL, Sciba BL, et al. Evaluation of neural tube defects (NTDs) after exposure to raltegravir during pregnancy. *J Acquir Immune Defic Syndr*. 2019;81(3):247-250. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30908331.

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

22. Ford N, Mofenson L, Shubber Z, et al. Safety of efavirenz in the first trimester of pregnancy: an updated systematic review and meta-analysis. *AIDS*. 2014;28 Suppl 2:S123-131. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24849471.

23. Barlow-Mosha L, Mumpe D, Williamson D, et al. Neural tube defects, HIV, and antiretrovirals: birth-defect surveillance in Uganda. Presented at: Conference on Retroviruses and Opportunistic Infections. 2019. Seattle, Washington.

24. de Ruiter A, Taylor GP, Clayden P, et al. British HIV Association guidelines for the management of HIV infection in pregnant women 2012 (2014 interim review). *HIV Med*. 2014;15 Suppl 4:1-77. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25604045.

25. British HIV Association. British HIV association guidelines for the management of HIV in pregnancy and postpartum 2018. *HIV Med*. 2019;20 Suppl 3:s2-s85. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30869192.

26. Nachega JB, Uthman OA, Mofenson LM, et al. Safety of tenofovir disoproxil fumarate-based antiretroviral therapy regimens in pregnancy for HIV-infected women and their Infants: a systematic review and meta-analysis. *J Acquir Immune Defic Syndr*. 2017;76(1):1-12. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28291053.

27. Mofenson LM, Watts DH. Safety of pediatric HIV elimination: the growing population of HIV- and antiretroviral-exposed but uninfected infants. *PLoS Med*. 2014;11(4):e1001636. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24781352.

28. Vannappagari V, Albano JD, Koram N, Tilson H, Scheuerle AE, Napier MD. Prenatal exposure to zidovudine and risk for ventricular septal defects and congenital heart defects: data from the antiretroviral pregnancy registry. *Eur J Obstet Gynecol Reprod Biol*. 2016;197:6-10. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26687320.

29. Rough K, Sun JW, Seage GR, 3rd, et al. Zidovudine use in pregnancy and congenital malformations. *AIDS*. 2017;31(12):1733-1743. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28537936.

30. Williams PL, Crain MJ, Yildirim C, et al. Congenital anomalies and *in utero* antiretroviral exposure in human immunodeficiency virus-exposed uninfected infants. *JAMA Pediatr*. 2015;169(1):48-55. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25383770.

Combination Antiretroviral Drug Regimens and Maternal and Neonatal Outcomes

(Last updated December 7, 2018; last reviewed December 7, 2018)

Panel's Recommendations
• Clinicians should be aware of a possible increased risk of adverse neonatal outcomes (e.g., preterm delivery) in pregnant women who are receiving antiretroviral therapy. However, given the clear benefits of such regimens for both a woman's health and the prevention of perinatal transmission, HIV treatment should not be withheld for fear of altering pregnancy outcomes **(All)**.
Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*
Rating of Evidence: *I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

Women with HIV taking antiretroviral therapy (ART) may be at increased risk for adverse pregnancy outcomes, including preterm birth or delivery (PTD) (i.e., delivery before 37 weeks' gestation), low birth weight (LBW) infants (<2,500 g), and small-for-gestational-age (SGA) infants (birth weight <10th percentile expected for gestational age). In this section, the Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission (the Panel) provides a summary of the published data regarding ART and adverse maternal and neonatal outcomes. There are limited data suggesting a potential association between hypertensive disorders of pregnancy (HDP) and maternal HIV.

We have reviewed and summarized studies from 1986 to 2018 that reported on maternal and neonatal outcomes in women with HIV. These studies were conducted in Europe, North America, sub-Saharan Africa, and Latin America. Study sizes and designs vary significantly; the number of participants in each study ranges from 183 to 10,592. The ART regimens evaluated in these studies differ, and may include:

- No ART
- Monotherapy, defined as the use of a single antiretroviral (ARV) drug
- Dual therapy, defined as the use of two ARV drugs
- Multidrug therapy, defined as the use of ≥3 ARV drugs: not specified (multi), nucleoside reverse transcriptase inhibitor-based regimens (multi-NRTI), non-nucleoside reverse transcriptase inhibitor-based regimens (multi-NNRTI), protease inhibitor (PI)-based regimens (multi-PI), non-PI-based regimens (multi-no PI), or specified ARVs

Table 5 lists the published, high-quality studies that reported potential effects of ART use on pregnancy outcomes. The studies' conclusions regarding PTD, LBW, and SGA are provided. Most of the studies present data regarding PTD, and fewer studies report instances of LBW, SGA, and stillbirth.

Pregnancy Outcomes

Preterm Delivery

Most of the studies reviewed in this section have reported outcomes related to PTD. Among the studies that report an association between ART use and PTD, the relative risks (RRs)/odds ratios (ORs) for PTD range from 1.2 to 3.4.[1-21] Conflicting findings regarding the association between PTD and ART use may be influenced by variability in the data available for analysis (e.g., for example, some studies have reported increased rates of PTD when ART is initiated before pregnancy or during early pregnancy compared to later in pregnancy). Maternal factors, such as HIV disease severity, may have affected the timing of ART initiation during pregnancy. These variables may be associated with PTD independent of ART use.[22-24] In order to control for medical or obstetrical factors associated with PTD, two studies have assessed spontaneous PTD alone. One study included women who initiated ART during pregnancy. Neither study reported an association

between ART use and PTD.[25,26] Two large meta-analyses of 11,224 and 37,877 women which included 14 and 17 studies, respectively, did not report an increased rate of PTD among women using ART during pregnancy.[4,27] In general, none of the studies reviewed in this section have comprehensively controlled for all potential factors that may be associated with PTD.

Preterm Delivery and Antiretroviral Therapy Exposure Before Pregnancy

Some studies report an association between ART initiation prior to pregnancy and PTD.[1,19-21,28,29] The reported RRs and ORs range from 1.20 to 2.05; the risk is attenuated in multivariate analysis.[14] These studies were conducted in Europe, Latin America, Africa, and North America and included various ART regimens (including no ART, single-drug, two-drug, and multidrug regimens). A retrospective cohort study that included >2,000 women on multidrug ART did not show an association between ART initiation before pregnancy and PTD.[29]

Antiretroviral Therapy Regimens Associated with Preterm Delivery

PI-Based Regimens

An association between PI-based ART and PTD has been investigated. These studies include populations in Europe, North America, and Africa. The risk of PTD ranges from 1.14 to 3.4.[1,3-6,8,15,17-19,21,25,30,31] Six studies did not demonstrate a significant association between PI-based ART and PTD.[15,25,30-33] The recent Promoting Maternal and Infant Survival Everywhere (PROMISE) trial study compared zidovudine alone to lopinavir/ritonavir (LPV/r) ART combined with a dual-NRTI backbone of either zidovudine/lamivudine or tenofovir disoproxil fumarate (TDF)/emtricitabine.[34] Compared to women receiving zidovudine alone, higher rates of extremely PTD (< 34 weeks) were reported in women receiving zidovudine/lamivudine/lopinavir/ritonavir ($P < 0.001$) but not TDF/emtricitabine/lopinavir/ritonavir ($P = 0.77$). In contrast, extremely PTD rates were higher among women receiving TDF/emtricitabine/lopinavir/ritonavir than among women receiving zidovudine/lamivudine/lopinavir/ritonavir ($P = 0.04$). These rates of extremely PTD were not significantly different than the rates among women receiving zidovudine alone ($P = 0.10$).

PI-based regimens boosted with ritonavir may be associated with PTD compared to non-boosted PI regimens. In a small, retrospective Canadian study, women taking non-boosted PI regimens did not have increased rates of PTD.[15] A study of >6,000 women in the UK and Ireland demonstrated increased rates of PTD among women with HIV who were taking PI-based ART before pregnancy, especially LPV/r. This effect was increased when the women had CD4 T lymphocyte (CD4) cell counts <350 cells/mm^3 (aOR = 1.99; 95% CI, 1.02–3.85).[21] A retrospective cohort study combining observations from the Surveillance Monitoring for ART Toxicities (SMARTT) study and International Maternal and Pediatric Adolescent AIDS Clinical Trials (IMPAACT) for a total of 4,646 live birth outcomes reported that rates of PTD and LBW were 19% among women taking PI-based regimens.[19] A small meta-analysis of 10 studies (eight prospective cohort studies, one randomized controlled trial, and one surveillance study) demonstrated an increased risk of PTD associated with the use of PI-based ART, with an adjusted odds ratio (aOR) of 1.32 (95% CI, 1.04–1.6) and $I^2 = 47\%$ (moderate heterogeneity). When evaluating the effects of initiating PI-based ART during the first and third trimesters of pregnancy, the pooled effect was nonsignificant.[35]

Non-PI-Based Regimens

Exposure to single NRTI ART (primarily zidovudine) was not associated with PTD.[1] South African women with HIV who were taking emtricitabine/TDF plus nevirapine had higher rates of PTD than women without HIV (aOR = 1.2; 95% CI, 1.0–1.5).[20] Other reports have found increased rates of PTD when multidrug ART is compared with dual-ARV regimens[9] and when NNRTI-based ART regimens are compared with other forms of ART.[23] A retrospective cohort study of South African women on efavirenz/emtricitabine/TDF did not show an increased risk of PTD, SGA, or LBW when these women were compared to women taking nevirapine-based ART or other multidrug regimens.[29] In a meta-analysis of 17 studies in which women with HIV (n = 37,877) who were taking ART that included TDF were compared to women who were taking ARV

regimens that did not contain tenofovir, TDF-based ART was associated with lower rates of PTD (RR = 0.9; 95% CI, 0.81–0.99, I^2 = 59%).[27]

Mechanism for Preterm Delivery

The potential mechanism of action by which PIs may increase a woman's risk of PTD is unknown. Papp et al. demonstrated in cell culture, in mouse models, and in pregnant women with HIV that exposure to PIs (except for darunavir) can decrease plasma progesterone levels. Low levels of plasma progesterone during pregnancy may potentially be associated with fetal loss, PTD, and LBW.[36] Papp et al. subsequently demonstrated that pregnant women with HIV who have low serum progesterone experience elevated levels of human placental 20-α-hydroxysteroid dehydrogenase, an enzyme that inactivates serum progesterone, after being exposed to PI-based ART. These women were also noted to have lower prolactin levels when compared to controls.[37]

Other Pregnancy Outcomes: Low Birth Weight, Small-for-Gestational-Age, and Stillbirth

In addition to evaluating the effect of ART use on PTD, some studies have assessed other pregnancy outcomes including LBW, SGA, and stillbirth. Reported rates of LBW range from 7.4% to 36%.[8,14,16,18-20,24,30,31,34,38-40] Six studies have demonstrated an association between any ART use and LBW infants.[16,20,33,34,39-41]

Some studies have demonstrated an association between ART use and SGA. The reported rates of SGA range from 7.3% to 31%.[11,14,16,18,20,21,24,29,32,33,42,43] In a study that compared the effects of initiating monotherapy during pregnancy to the effects of initiating multidrug ART before pregnancy and continuing ART during pregnancy, ART was associated with severe SGA (RR = 1.34; 95% CI, 0.98-1.84).[16] Three studies in Botswana reported a positive association between ART use (both non-PI-based and PI-based regimens) and SGA.[11,18,44] Continuation of ART that was initiated before pregnancy and initiation of ART during pregnancy may be associated with SGA (aOR = 1.8; 95% CI, 1.6–2.1 and aOR = 1.5; 95% CI, 1.2–1.9).[11] When compared to emtricitabine/TDF/efavirenz ART, both nevirapine-based and LPV/r-based ART were associated with increased incidence of SGA.[18] In contrast, a retrospective cohort of women with HIV who were taking TDF/emtricitabine/efavirenz, nevirapine-based ART, or other multidrug regimens before pregnancy did not show any association between these regimens and SGA.[29] Women in the Netherlands who were taking PI-based ART before pregnancy had a higher risk of SGA (OR = 1.35; 95% CI, 1.03–1.77) than women taking NNRTI-based ART.[33]

Eleven studies reported rates of stillbirth ranging from 0.5% to 11.4%.[7,11,12,14,18,24,28,31,39,40] Two studies have evaluated the association between continuing ART during pregnancy or starting ART during pregnancy and the risk of stillbirth, with data that include both non-PI-based and PI-based regimens. A greater risk of stillbirth was observed among women who continued ART during pregnancy (aOR = 1.5; 95% CI, 1.2–1.8) and among women who started ART during pregnancy (aOR = 2.5; 95% CI, 1.6–3.5) in one of those[11] and (aOR = 0.99; 95% CI, 0.69-1.42).[18] In the latter study, use of zidovudine/lamivudine/nevirapine was associated with a significantly increased rate of stillbirth compared to use of emtricitabine/TDF/efavirenz. The risk of perinatal mortality, which includes stillbirths and neonatal deaths, was noted to be higher among children born to South African women with HIV who were taking ART before pregnancy when compared to the children of women who started ART during pregnancy (OR = 3.25; 95% CI, 1.38–8.04). In a meta-analysis of 17 studies that included 37,877 women with HIV who were taking ART, three studies included stillbirth outcomes. Women with HIV who were taking TDF-based ART had a lower risk of stillbirth than those who were taking ART that did not include TDF (pooled RR= 0.6; 95% CI, 0.43–0.84, I^2 = 72%).[27]

Maternal Outcomes

Hypertensive Disorders of Pregnancy

Limited data suggest and association between HDP and maternal HIV. An earlier meta-analysis[45] reported an association between maternal HIV and HDP, but a more recent meta-analysis[46] did not reveal a clear association between maternal HIV and pregnancy-induced hypertension, preeclampsia, or eclampsia. An Italian study demonstrated an increased risk for both early-onset and late-onset preeclampsia (aOR = 2.50; 95% CI, 1.51–4.15 and aOR = 2.64; 95% CI, 1.82–3.85, respectively) as well as pre-eclampsia with severe

features (aOR = 2.03; 95% CI, 1.26–3.28) when comparing pregnant women with HIV to pregnant women without HIV.[47]

Few studies have evaluated whether the use of combination ART is associated with a higher risk of pre-eclampsia. No studies have evaluated the effect of specific ARV drugs on maternal hypertension. In the NISDI cohort, women exposed to ART in the first trimester had an increased risk of preeclampsia when compared to women who were not exposed to ART (aOR = 2.3; 95% CI, 1.1–4.9)[48,49] A secondary analysis of South African data revealed that amongst women with low CD4 cell counts (<200 cells/mm^3), there was an increased risk of maternal death from hypertensive disorders of pregnancy when comparing women who were taking combination ART to women who received no ART during pregnancy (RR = 1.15; 95% CI, 1.02–1.29).[50] A more recently published retrospective study on South African women with HIV demonstrated that those who were on ART before pregnancy and those who were not on ART before pregnancy had similar rates of HPD (15.7% and 14.9%, respectively). Women with HIV were less likely to have HDP than women without HIV (OR = 0.67; 95% CI, 0.48–0.93).[28] It is unclear whether the potential association between HIV and HDP reflects the fact that immune reconstitution associated with ART initiation plays a role in increasing inflammatory responses associated with preeclampsia/eclampsia or whether there is a direct effect of ART on this outcome.

Unknown Effects of Newer Antiretroviral Drugs on Pregnancy Outcomes

Data are insufficient regarding the effects of newer ARV drug classes on adverse pregnancy outcomes. Therefore, potential adverse pregnancy outcomes associated with these drug classes, which include integrase inhibitors, fusion inhibitors, and CCR5 antagonists, are not addressed in this section.

Summary

Clinicians should be aware of a possible increased risk of adverse maternal and neonatal outcomes with the use of ART for prevention of perinatal HIV infection. Given that ART has clear benefits for maternal health and reduces the risk of perinatal transmission, these agents should not be withheld due to concern for increased risk of adverse neonatal outcomes. Until more information is available, pregnant women with HIV who are receiving ART should continue their provider-recommended regimens. Additional monitoring for pregnancy complications, including PTD, should be considered.[51]

Table 5. Results of Studies Assessing the Association Between Antiretroviral Regimens and Preterm Delivery (page 1 of 8)

Study Location(s); Dates of Study	Total Number of Pregnancies/Total Number on ARV Drugs	Types of ARV Regimens Compared (Numbers)	Association Noted Between ARV Regimens and Preterm Delivery	Notes
European Collaborative Study and Swiss Mother and Child HIV Cohort Study; 1986–2000[1]	3,920/896	• Mono (573) • Multi-no PI (215) • Multi-PI (108)	• YES (compared with no ARV) • Multi: 1.82 (1.13–2.92) • Multi-PI: 2.60 (1.43–4.7)	• Increase in PTD if ARV was initiated before pregnancy versus in third trimester.
United States; 1990–1998[30]	3,266/2,123	• Mono (1,590) • Multi (396) • Multi-PI (137)	• NO (compared with mono) • Multi: 0.95 (0.60–1.48) • Multi-PI: 1.45 (0.81–2.50)	• 7 prospective clinical studies.
European Collaborative Study; 1986–2004[52]	4,372/2,033	• Mono (704) • Dual (254) • Multi (1,075)	• YES (compared with mono/dual) • Multi in pregnancy: 1.88 (1.34–2.65) • Multi pre-pregnancy: 2.05 (1.43–2.95)	• N/A

Table 5. Results of Studies Assessing the Association Between Antiretroviral Regimens and Preterm Delivery (page 2 of 8)

Study Location(s); Dates of Study	Total Number of Pregnancies/Total Number on ARV Drugs	Types of ARV Regimens Compared (Numbers)	Association Noted Between ARV Regimens and Preterm Delivery	Notes
United States; 1990–2002[41]	2,543/Not given	Early (≤25 Weeks): • Mono (621) • ≥2 ARVs without PI or NNRTI (198) • Multi-NNRTI or Multi-PI (357) Late (≥32 Weeks): • Mono (932) • ≥2 ARVs without PI or NNRTI (258) • Multi-NNRTI or Multi-PI (588)	• NO (compared with mono) • No association between any ARV and preterm delivery	• PTD decreased with receipt of any ARV, ART that contained ZDV, and other ARV regimens compared with no ARV.
United States; 1990–2002[3]	1,337/999	• Mono (492) • Multi-no PI (373) • Multi-PI (134)	• YES (compared with Mono and Multi-no PI) • Multi-PI: 1.8 (1.1–3.03)	• Multi-PI reserved for those with advanced disease and those who experienced virologic failure while on other multi-ARV regimens.
Brazil, Argentina, Mexico, Bahamas; 2002–2005[38]	681/681	• Mono/Dual NRTI (94) • Multi-NNRTI (257) • Multi-PI (330)	• NO (compared with Mono/Dual-NRTI) • No association between any ARV regimen and PTD	• All patients were on ARV for ≥28 days during pregnancy. • Pre-eclampsia/ eclampsia, cesarean delivery, diabetes, and low BMI were associated with PTD.
Meta-Analysis, Europe and United States; 1986–2004[4]	11,224/Not given	• Multi-no PI (including Dual) or Multi-PI (2,556)	• YES (only comparing Multi-PI with Multi-no PI) • PI vs. Multi-no PI: 1.35 (1.08–1.70)	• 14 studies, 5 in PTD ARV comparison. • No overall increase in PTD with antepartum ARV. • PTD increased in those on ARV pre-pregnancy and in first trimester compared with later use.
Italy; 2001–2006[5]	419/366	• Multi-PI second trimester (97) • Multi-PI third trimester (146)	• YES • Multi-PI second trimester: 2.24 (1.22–4.12) • Multi-PI third trimester: 2.81 (1.46–5.39)	• Multivariate association also with HCV.
United States; 1989–2004[6]	8,793/6,228	• Mono (2,621) • Dual (1,044) • Multi-no PI (1,781) • Multi-PI (782)	• YES (compared with Dual) • Multi-PI: 1.21 (1.04–1.40)	• Lack of antepartum ARV also associated with PTD. • PTD and LBW decreased over time.

Table 5. Results of Studies Assessing the Association Between Antiretroviral Regimens and Preterm Delivery (page 3 of 8)

Study Location(s); Dates of Study	Total Number of Pregnancies/Total Number on ARV Drugs	Types of ARV Regimens Compared (Numbers)	Association Noted Between ARV Regimens and Preterm Delivery	Notes
United Kingdom, Ireland; 1990–2005[7]	5,009/4,445	• Mono/Dual (1,061) • Multi-NNRTI or Multi-PI (3,384)	• YES (compared with Mono/Dual) • Multi-PI or Multi-NNRTI: 1.51 (1.19–1.93)	• Similar increased risk with Multi-PI or Multi-no PI. • No association with duration of ARV use.
Germany, Austria; 1995–2001[8]	183/183	• Mono (77) • Dual (31) • Multi-NNRTI (54) • Multi-PI (21)	• YES (compared with Mono) • Multi-PI: 3.40 (1.13–10.2)	N/A
United States; 2002–2007[25]	777/777	• Mono (6) • Dual (11) • Multi-no PI (202) • Multi-PI (558)	• NO (compared PI with all non-PI) • Multi-PI: 1.22 (0.70–2.12)	• All patients started ARV during pregnancy. • Study analyzed only spontaneous PTD.
Swiss Mother and Child HIV Cohort Study; 1985–2007[9]	1,180/941	• Mono (94) • Dual (53) • Multi-PI or Multi-no PI (409) • Multi-PI (385)	• YES (compared with no ARV) • Multi: 2.5 (1.4–4.3)	• No association of Mono/Dual with PTD compared with no ARV. • No confounding by duration of ARV or maternal risk factors.
Botswana; 2006–2008[10]	530/530	• Multi-NRTI, ABC plus ZDV plus 3TC (263) • Multi-PI, LPV/r plus ZDV plus 3TC (267)	• YES • Multi-PI vs. Multi-NRTI: 2.03 (1.26–3.27)	• Secondary analysis of data from randomized, controlled clinical trial of ARV begun at 26–34 weeks for prevention of perinatal transmission. • All CD4 cell counts >200 cells/mm^3
Botswana; 2007–2010[44]	4,347/3,659	• ARV, regimen unspecified (70) • Mono (2,473) • Multi (1,116), 91% Multi-NNRTI	• NO • No association between multi-ART and very PTD (<32 weeks' gestation)	• Observational; multi-ART before conception associated with very SGA and maternal hypertension during pregnancy.
Spain; 1986–2010[26]	519/371	• Mono/Dual NRTI (73) • All Multi (298) • Multi-PI (178)	• NO (compared with No ARV plus Mono/Dual) • Spontaneous PTD not associated with Multi ARV or Multi-PI before or during pregnancy	• PTD associated with Multi-ARV given in second half of pregnancy and with prior PTD.
Botswana; 2009–2011[11]	9,504/7,915	• Mono (4,625) • All Multi (3,290) • Multi-PI (312)	• YES (Multi-ARV before and during pregnancy compared with Mono): 1.2 (1.1–1.4) and 1.4 (1.2–1.8) • YES (Multi-PI compared with Multi-no PI before pregnancy): 2.0 (1.1–3.6)	• ART group classified by initiation before and during pregnancy.
France, ANRS French Perinatal Cohort; 1990–2009[12]	8,696/8,491	• Mono (950) • Dual (590) • Multi-PI (2,414)	• YES (Multi compared to Mono): 1.69 (1.38–2.07) • YES (before conception compared to during pregnancy): 1.31 (1.11–1.55)	• Patients on ART before and during pregnancy had increased rates of PTD.

Table 5. Results of Studies Assessing the Association Between Antiretroviral Regimens and Preterm Delivery (page 4 of 8)

Study Location(s); Dates of Study	Total Number of Pregnancies/Total Number on ARV Drugs	Types of ARV Regimens Compared (Numbers)	Association Noted Between ARV Regimens and Preterm Delivery	Notes
United States; 2000–2011[43]	183/183	• Multi-PI (183)	• NO (no control group without ART) • Rate of PTD: 18.6%	• SGA rate: 31.2% • Patients on NNRTI-based ART less likely to have SGA: 0.28 (0.1–0.75).
United States; 2007–2010[13]	1,869/1,810	• Mono/Dual (138) • Multi-NRTI (193) • Multi-NNRTI (160) • Multi-PI (1,319)	• YES (compared with no ARV in first trimester) • Multi-PI in first trimester vs. none in first trimester • PTD 1.55 (1.16–2.07); spontaneous PTD 1.59 (1.10–2.30)	N/A
Latin America; 2002–2012[14]	1,512/1,446	• No ART or ART <28 days (66) • Mono/Dual (130) • Multi-no PI (409) • Multi-PI (907)	• YES (when on ARVs at conception): PTD 1.53 (1.11–2.09)	• ART for treatment rather than prophylaxis was associated with increased rates of LBW (<2,500 g) infants: 1.8 (1.26–2.56). • Multi-no PI associated with decreased risk of LBW (0.33 [0.14–0.74]) and stillbirth (0.11 [0.04–0.34]). • Multi-PI associated with decreased risk of stillbirth: 0.14 (0.05–0.34).
Uganda; 2009–2012[53]	356/356	• Multi-NNRTI, EFV (177) • Multi-PI, LPV/r (179)	• NO (no control group without ART)	• Trend in increased incidence of PTD among women starting ART 24–28-week GA was NS: aOR = 1.76 (0.96–3.23).
Italy; 1997–2013[54]	158/158	• Mono/Dual (27) • Multi-no PI (17) • Multi-PI (114)	• NO (no control group without ART)	• PTD rate was 17% for this cohort. • Trend towards association of PTD with longer duration of ART: 2.82 (0.35–8.09).
Canada; 1988–2011[15]	589/530	• No ART (59) • Mono (77) • Multi-no PI (166) • Multi-non-boosted PI (220) • Multi-boosted PI with RTV (144)	• YES (Multi-boosted PI compared to Multi-non-boosted PI): 2.01 (1.02–3.97) • NO (non-PI regimens compared to Multi-non-boosted PI): 0.81 (0.4–1.66)	• Highest risk of PTD was among women not taking ART compared to non-boosted PI group: 2.7 (1.2–6.09).

Table 5. Results of Studies Assessing the Association Between Antiretroviral Regimens and Preterm Delivery (page 5 of 8)

Study Location(s); Dates of Study	Total Number of Pregnancies/Total Number on ARV Drugs	Types of ARV Regimens Compared (Numbers)	Association Noted Between ARV Regimens and Preterm Delivery	Notes
United Kingdom; 2007–2012[31]	493/493	• Multi-PI, LPV/r (306) • Multi-PI, ATV/r (187)	• NO (comparing 2 PI-based regimens): aOR = 1.87 (0.93–3.75)	• Rate of PTD was 13% among women who conceived on ART and 14% among women who started ART during pregnancy. • In a multivariate analysis, a history of PTD was associated with recurrent PTD: aOR = 5.23 (1.91–14.34).
Republic of the Congo; 2007–2012[39]	188/188	• Multi-no PI, EFV (31) • Multi-no PI, NVP (146)	• NO (comparing EFV 13% vs. NVP 10%)	• Rate of PTD was 11%, with no difference between study groups. • LBW increased in EFV group (33% vs. 16%, *P* = 0.04). • Stillbirth rate was 4% (8/188).
Tanzania; 2004–2011[16]	3,314/2,862	• No ART (452-excluded) • Mono (1,768) • Multi (1,094)	• YES (Multi before pregnancy vs. Mono): 1.24 (1.05–1.47) • Very PTD, YES (Multi before pregnancy vs. Mono):1.42 (1.02–1.99) • NO (Multi during pregnancy compared to Mono): 0.85 (0.7–1.02)	• Rate of PTD was 29%; women who conceived on ART were more likely to have PTD compared to women on ZDV monotherapy. • Pregnancy-induced hypertension associated with PTD: 1.25 (1.03–1.51).
67 Countries and US Territories, APR; 1989–2013[40]	14,684/14,684	• ARV with ZDV (12,780) • ARV without ZDV (1,904)	• NO (any ZDV-ARV vs. non-ZDV ARV exposure): 1.0 (0.9–1.2)	• PTD rate was 12%. • LBW rate was 16%; RR of LBW with ZDV ART vs. non-ZDV ART = 1.2 (1.0–1.3), *P* = 0.02. • Stillbirth rate: 1.5%, RR = 0.8 (0.5–1.1).
Texas, United States; 1984–2014[32]	1,004/792	• No ART (177) • Mono, Dual, or Multi-no PI (230) • Multi-PI (597)	• NO (no-PI ART vs. PI ART): 0.9 (0.5–1.5)	• Rate of PTD: 13% to 21%. • Rate of SGA: 19% to 23%, OR = 1.3 (0.8–1.9).

Table 5. Results of Studies Assessing the Association Between Antiretroviral Regimens and Preterm Delivery (page 6 of 8)

Study Location(s); Dates of Study	Total Number of Pregnancies/Total Number on ARV Drugs	Types of ARV Regimens Compared (Numbers)	Association Noted Between ARV Regimens and Preterm Delivery	Notes
India, Malawi, South Africa, Tanzania, Uganda, Zambia, Zimbabwe, PROMISE Trial; 2011–2014[34]	3,490/3,096	• Mono (1,386) • All Multi (2,710) • Multi-PI with ZDV (1,385) • Multi-PI with TDF (325)	• YES (Multi ≥14 weeks vs. Mono)	• Rate of PTD: 21% on Multi-PI with ZDV ART compared to ZDV-Mono ($P < 0.001$). • Rate of very PTD: 6% in Multi-PI with TDF ART and 3% in Multi-PI with ZDV ART ($P = 0.04$). • LBW was more common in Multi-PI with ZDV ART compared to ZDV Mono (23% vs. 12%, $P < 0.001$) and in Multi-PI with TDF compared to ZDV Mono (17% vs. 9%, $P = 0.004$).
United States and Puerto Rico, SMARTT; 2007–2016[17]	1,864/1,658	• Multi (1,658)	• YES: (Multi-PI vs. No ART): 1.59 (1.1–2.3)	• PI-based ART exposure in first trimester was associated with increased risk of spontaneous PTD compared with no first-trimester ART.
South Africa; 2011–2014[24]	3,723/3,547	• Dual (974) • Multi (2,573)	• NO • Dual: 0.2 (0.08–0.5) • Multi: 0.3 (0.1–0.9)	• PTD rate regardless of ART: 22% to 23%. • LBW rate on ART: 9% to 15%. Risk of LBW: Dual 0.06 (0.02–0.2) and Multi 0.12 (0.04–0.4). • SGA rate on ART: 7% to 9%. Risk of SGA: Dual 0.37 (0.1 to 1.5) and Multi 0.3 (0.07 to 0.9). • Stillbirth rate on Dual (1.2%) and Multi (2.2%). Risk of stillbirth: Dual 0.08 (0.04–0.2) and Multi 0.2 (0.1–0.3).
Botswana; 2012–2014[18]	11,932/10,592	• Multi-PI (398) • Multi-NNRTI (4,597)	• YES • Multi-PI: 1.36 (1.06–1.75) • Multi-NNRTI: 1.14 (1.01–1.29)	• SGA rates were significantly higher in Multi PI ART (27.7% and 20.4%) and NVP-based ART (24.9% and 28.2%) compared to EFV-based ART (16.9%). • Stillbirth rates were higher in NVP-based ART: 2.31 (1.64–3.26).

Table 5. Results of Studies Assessing the Association Between Antiretroviral Regimens and Preterm Delivery (page 7 of 8)

Study Location(s); Dates of Study	Total Number of Pregnancies/Total Number on ARV Drugs	Types of ARV Regimens Compared (Numbers)	Association Noted Between ARV Regimens and Preterm Delivery	Notes
19 Countries, 5 Continents; 2002–2013[35]	23,490 (meta-analysis of 10 studies)	• Mono, Dual, or Multi-no PI • Multi-PI	• YES • Multi-PI: 1.3 (1.04–1.6), I^2 = 47%	• 5 of 10 studies demonstrated increased risk of PTD with an aOR range of 1.2–4.14.
South Africa; 2011–2014[28]	1,461/1,159	• Dual (424) • Multi (735)	• YES • Multi: 1.65 (1.17-2.33) • ART before pregnancy: 1.72 (1.33-3.01)	• PTD rate was 25%. • Similar rates of PTD observed among women on ART before pregnancy and women starting ART during pregnancy.
Netherlands; 1997-2015[33]	2,184/1,392	• Multi (1,392) • PI-based and non-PI based ART	• NO • 1.39 (0.99–1.94); comparing women on ART before pregnancy to those who started ART during pregnancy	• PTD rate was 14.7%. • SGA rate was 23.8% overall; significantly higher in women taking ART before pregnancy (27.3%) vs. those starting ART during pregnancy (21.5%): aOR = 1.35 (1.0–1.9). • PI-based ART before pregnancy associated with SGA: 1.49 (1.1–2.1).
South Africa, SAPMTCTE; 2012–2013[20]	2,599/2,269	• Dual (873) • Multi (1,396)	• YES • 1.2 (1.0–1.5) compared to infants who were not exposed to HIV • 1.7 (1.1–2.5) in infants exposed to ART from conception	• PTD rate was 12.9%; women with HIV who were not on ARVs had higher rates of PTD than women without HIV. • LBW rate was 13.0%; HIV-exposed infants more likely to be LWB: 1.6 (1.3–1.9). • SGA rate was 16.9%; HIV-exposed infants more likely to have SGA: 1.3 (1.1–1.6).
Multiple Countries; 1993–2014[27]	37,877 (meta-analysis of 17 studies)	• Multi with TDF • Other ART without TDF	• NO • RR = 0.9 (0.81–0.99), I^2 = 59%; women on Multi with TDF had lower rates of PTD compared to women on other ART without TDF	• PTD rate over 4 studies was 20.3%. • Stillbirth rate over 3 studies was 4.4%; stillbirth rate was lower among TDF-exposed patients: 0.6 (0.43–0.84).

Table 5. Results of Studies Assessing the Association Between Antiretroviral Regimens and Preterm Delivery (page 8 of 8)

Study Location(s); Dates of Study	Total Number of Pregnancies/Total Number on ARV Drugs	Types of ARV Regimens Compared (Numbers)	Association Noted Between ARV Regimens and Preterm Delivery	Notes
United Kingdom/ Ireland; 2007–2015[55]	6,073/6,073	• Multi-PI (4,184) • Multi-NNRTI (1,889)	• YES • Multi-PI associated with PTD: 1.56 (1.19-2.04) • Multi-PI before conception with CD4 count <350 cells/mm^3, 1.99 (1.02–3.85) and 1.9 (1.01–3.57) and with CD4 count >350 cells/mm^3, 1.61 (1.07–2.43)	• PTD rate was 10.4%. • SGA rate was 20.4%.
South Africa; 2010–2015[29]	4,435/2,549	• Multi-NNRTI, EFV plus TDF plus FTC/3TC (1,481) • Multi-NNRTI, other EFV-based ART (187) • Multi-NNRTI, NVP-based ART (343) • ZDV (528)	• NO • NVP-based ART aOR = 0.66 (0.27–1.63) (NS) and other EFV-based ART (aOR 0.72; 95% CI, 0.24±2.12) vs. EFV plus TDF plus FTC/3TC.	• PTD rate was 10.4%. • SGA rate was 10.4%. • LBW rate was 9.6%.
North America; 2007–2013[19]	4,646/1,621	• Multi-PI, TDF plus FTC plus LPV/r, TDF plus FTC plus ATV/r, ZDV plus 3TC plus LPV/r (1,621)	• YES • TDF plus FTC plus ATV/r vs. ZDV plus 3TC plus LPV/r: aOR = 0.69 (0.51–0.94)	• PTD rate was 19%. • LBW rate was 19.6%.

Note: The data presented in the column Association Noted between ARV Regimens and Preterm Delivery represent the published results of the study in the corresponding row. Depending on the study designs, these are adjusted and unadjusted odds ratios and relative risks.

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; aOR = adjusted odds ratio; ART = antiretroviral therapy; ARV = antiretroviral; ATV/r = atazanavir/ritonavir; BMI = body mass index; CD4 = CD4 T lymphocyte; dual = 2 ARV drugs; EFV = efavirenz; FTC = emtricitabine; GA = gestational age; HCV = hepatitis C virus; LBW = low birth weight; mono = single ARV drug; multi = 3 or more ARV drugs; multi-PI = combination ART with PI; LPV/r = lopinavir/ritonavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NS = nonsignificant; NVP = nevirapine; OR = odds ratio; PI = protease inhibitor; PROMISE = Promoting Maternal and Infant Survival Everywhere; PTD = preterm delivery; RR = relative risk; RTV = ritonavir; SAPMTCTE = South African Prevention of Mother-to-Child Transmission Evaluation; SGA = small for gestational age; SMARTT = Surveillance Monitoring for ART Toxicities; TDF = tenofovir disoproxil fumarate; ZDV = zidovudine

References

1. European Collaborative Study, Swiss Mother Child HIV Cohort Study. Combination antiretroviral therapy and duration of pregnancy. *AIDS*. 2000;14(18):2913-2920. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11398741.

2. European Collaborative Study. Levels and patterns of neutrophil cell counts over the first 8 years of life in children of HIV-1-infected mothers. *AIDS*. 2004;18(15):2009-2017. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15577622.

3. Cotter AM, Garcia AG, Duthely ML, Luke B, O'Sullivan MJ. Is antiretroviral therapy during pregnancy associated with an increased risk of preterm delivery, low birth weight, or stillbirth? *J Infect Dis*. 2006;193(9):1195-1201. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16586354.

4. Kourtis AP, Schmid CH, Jamieson DJ, Lau J. Use of antiretroviral therapy in pregnant HIV-infected women and the risk of premature delivery: a meta-analysis. *AIDS*. 2007;21(5):607-615. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17314523.

5. Ravizza M, Martinelli P, Bucceri A, et al. Treatment with protease inhibitors and coinfection with hepatitis C virus are independent predictors of preterm delivery in HIV-infected pregnant women. *J Infect Dis*. 2007;195(6):913-914; author reply 916-917. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17299723.

6. Schulte J, Dominguez K, Sukalac T, Bohannon B, Fowler MG, Pediatric Spectrum of HIV Disease Consortium. Declines in low birth weight and preterm birth among infants who were born to HIV-infected women during an era of increased use of maternal antiretroviral drugs: Pediatric Spectrum of HIV Disease, 1989-2004. *Pediatrics*. 2007;119(4):e900-906. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17353299.

7. Townsend CL, Cortina-Borja M, Peckham CS, Tookey PA. Antiretroviral therapy and premature delivery in diagnosed HIV-infected women in the United Kingdom and Ireland. *AIDS*. 2007;21(8):1019-1026. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17457096.

8. Grosch-Woerner I, Puch K, Maier RF, et al. Increased rate of prematurity associated with antenatal antiretroviral therapy in a German/Austrian cohort of HIV-1-infected women. *HIV Med*. 2008;9(1):6-13. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18199167.

9. Rudin C, Spaenhauer A, Keiser O, et al. Antiretroviral therapy during pregnancy and premature birth: analysis of Swiss data. *HIV Med*. 2011;12(4):228-235. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20726902.

10. Powis KM, Kitch D, Ogwu A, et al. Increased risk of preterm delivery among HIV-infected women randomized to protease versus nucleoside reverse transcriptase inhibitor-based HAART during pregnancy. *J Infect Dis*. 2011;204(4):506-514. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21791651.

11. Chen JY, Ribaudo HJ, Souda S, et al. Highly active antiretroviral therapy and adverse birth outcomes among HIV-infected women in Botswana. *J Infect Dis*. 2012;206(11):1695-1705. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23066160.

12. Sibiude J, Warszawski J, Tubiana R, et al. Premature delivery in HIV-infected women starting protease inhibitor therapy during pregnancy: role of the ritonavir boost? *Clin Infect Dis*. 2012;54(9):1348-1360. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22460969.

13. Watts DH, Williams PL, Kacanek D, et al. Combination antiretroviral use and preterm birth. *J Infect Dis*. 2013;207(4):612-621. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23204173.

14. Kreitchmann R, Li SX, Melo VH, et al. Predictors of adverse pregnancy outcomes in women infected with HIV in Latin America and the Caribbean: a cohort study. *BJOG*. 2014;121(12):1501-1508. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24602102.

15. Kakkar F, Boucoiran I, Lamarre V, et al. Risk factors for pre-term birth in a Canadian cohort of HIV-positive women: role of ritonavir boosting? *J Int AIDS Soc*. 2015;18:19933. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26051165.

16. Li N, Sando MM, Spiegelman D, et al. Antiretroviral therapy in relation to birth outcomes among HIV-infected Women: a cohort study. *J Infect Dis*. 2015. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26265780.

17. Van Dyke RB, Chadwick EG, Hazra R, Williams PL, Seage GR 3rd. The PHACS SMARTT study: assessment of the safety of in utero exposure to antiretroviral drugs. *Front Immunol*. 2016;7:199. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27242802.

18. Zash R, Jacobsen DM, Mayondi G, et al. Dolutegravir/tenofovir/emtricitabine (DTG/TDF/FTC) started in pregnancy is as safe as efavirenz/tenofovir/emtricitabine (EFV/TDF/FTC) in nationwide birth outcomes surveillance in Botswana. Presented at: 9th International AIDS Society Conference. 2017. Paris, France.

19. Rough K, Seage GR, 3rd, Williams PL, et al. Birth outcomes for pregnant women with HIV using tenofovir-emtricitabine. *N Engl J Med*. 2018;378(17):1593-1603. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29694825.

20. Ramokolo V, Goga AE, Lombard C, Doherty T, Jackson DJ, Engebretsen IM. In utero ART exposure and birth and early growth outcomes among HIV-exposed uninfected infants attending immunization services: results from national PMTCT surveillance, South Africa. *Open Forum Infect Dis*. 2017;4(4):ofx187. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29062860.

21. Favarato G, Townsend CL, Bailey H, et al. Protease inhibitors and preterm delivery: another piece in the puzzle. *AIDS*. 2018;32(2):243-252. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29135577.

22. Machado ES, Hofer CB, Costa TT, et al. Pregnancy outcome in women infected with HIV-1 receiving combination antiretroviral therapy before versus after conception. *Sex Transm Infect*. 2009;85(2):82-87. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18987014.

23. van der Merwe K, Hoffman R, Black V, Chersich M, Coovadia A, Rees H. Birth outcomes in South African women receiving highly active antiretroviral therapy: a retrospective observational study. *J Int AIDS Soc*. 2011;14:42. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21843356.

24. Moodley T, Moodley D, Sebitloane M, Maharaj N, Sartorius B. Improved pregnancy outcomes with increasing antiretroviral coverage in South Africa. *BMC Pregnancy Childbirth*. 2016;16:35. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26867536.

25. Patel K, Shapiro DE, Brogly SB, et al. Prenatal protease inhibitor use and risk of preterm birth among HIV-infected women initiating antiretroviral drugs during pregnancy. *J Infect Dis*. 2010;201(7):1035-1044. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20196654.

26. Lopez M, Figueras F, Hernandez S, et al. Association of HIV infection with spontaneous and iatrogenic preterm delivery: effect of HAART. *AIDS*. 2012;26(1):37-43. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22008651.

27. Nachega JB, Uthman OA, Mofenson LM, et al. Safety of tenofovir disoproxil fumarate-based antiretroviral therapy regimens in pregnancy for HIV-infected women and their Infants: a systematic review and meta-analysis. *J Acquir Immune Defic Syndr*. 2017;76(1):1-12. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28291053.

28. Sebitloane HM, Moodley J. Maternal and obstetric complications among HIV-infected women treated with highly active antiretroviral treatment at a regional hospital in Durban, South Africa. *Niger J Clin Pract*. 2017;20(11):1360-1367. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29303121.

29. Chetty T, Thorne C, Coutsoudis A. Preterm delivery and small-for-gestation outcomes in HIV-infected pregnant women on antiretroviral therapy in rural South Africa: Results from a cohort study, 2010-2015. *PLoS One*. 2018;13(2):e0192805. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29470508.

30. Tuomala RE, Shapiro DE, Mofenson LM, et al. Antiretroviral therapy during pregnancy and the risk of an adverse outcome. *N Engl J Med*. 2002;346(24):1863-1870. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12063370.

31. Perry M, Taylor GP, Sabin CA, et al. Lopinavir and atazanavir in pregnancy: comparable infant outcomes, virological efficacies and preterm delivery rates. *HIV Med*. 2015. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26200570.

32. Duryea E, Nicholson F, Cooper S, et al. The use of protease inhibitors in pregnancy: maternal and fetal considerations. *Infect Dis Obstet Gynecol*. 2015;2015:563727. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26617456.

33. Snijdewind IJM, Smit C, Godfried MH, et al. Preconception use of cART by HIV-positive pregnant women increases the risk of infants being born small for gestational age. *PLoS One*. 2018;13(1):e0191389. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29351561.

34. 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.

35. Mesfin YM, Kibret KT, Taye A. Is protease inhibitors based antiretroviral therapy during pregnancy associated with an increased risk of preterm birth? Systematic review and a meta-analysis. *Reprod Health*. 2016;13:30. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27048501.

36. Papp E, Mohammadi H, Loutfy MR, et al. HIV protease inhibitor use during pregnancy is associated with decreased progesterone levels, suggesting a potential mechanism contributing to fetal growth restriction. *J Infect Dis*. 2015;211(1):10-18. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25030058.

37. Papp E, Balogun K, Banko N, et al. Low prolactin and high 20-alpha-hydroxysteroid dehydrogenase levels contribute to lower progesterone levels in HIV-infected pregnant women exposed to protease inhibitor-based combination antiretroviral therapy. *J Infect Dis*. 2016;213(10):1532-1540. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26740274.

38. Szyld EG, Warley EM, Freimanis L, et al. Maternal antiretroviral drugs during pregnancy and infant low birth weight and preterm birth. *AIDS*. 2006;20(18):2345-2353. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17117021.

39. Bisio F, Nicco E, Calzi A, et al. Pregnancy outcomes following exposure to efavirenz-based antiretroviral therapy in the Republic of Congo. *New Microbiol*. 2015;38(2):185-192. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25938743.

40. Vannappagari V, Koram N, Albano J, Tilson H, Gee C. Association between in utero zidovudine exposure and nondefect adverse birth outcomes: analysis of prospectively collected data from the Antiretroviral Pregnancy Registry. *BJOG*. 2016;123(6):910-916. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26269220.

41. Tuomala RE, Watts DH, Li D, et al. Improved obstetric outcomes and few maternal toxicities are associated with antiretroviral therapy, including highly active antiretroviral therapy during pregnancy. *J Acquir Immune Defic Syndr*. 2005;38(4):449-473. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15764963.

42. Watts DH, Brown ER, Maldonado Y, et al. HIV disease progression in the first year after delivery among African women followed in the HPTN 046 clinical trial. *J Acquir Immune Defic Syndr*. 2013. Available at: http://www.ncbi.nlm.

nih.gov/pubmed/23846568.

43. Aaron E, Bonacquisti A, Mathew L, Alleyne G, Bamford LP, Culhane JF. Small-for-gestational-age births in pregnant women with HIV, due to severity of HIV disease, not antiretroviral therapy. *Infect Dis Obstet Gynecol*. 2012;2012:135030. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22778533.

44. Parekh N, Ribaudo H, Souda S, et al. Risk factors for very preterm delivery and delivery of very-small-for-gestational-age infants among HIV-exposed and HIV-unexposed infants in Botswana. *Int J Gynaecol Obstet*. 2011;115(1):20-25. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21767835.

45. Calvert C, Ronsmans C. HIV and the risk of direct obstetric complications: a systematic review and meta-analysis. *PLoS One*. 2013;8(10):e74848. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24124458.

46. Browne JL, Schrier VJ, Grobbee DE, Peters SA, Klipstein-Grobusch K. HIV, antiretroviral therapy, and hypertensive Disorders in pregnancy: a systematic review and meta-analysis. *J Acquir Immune Defic Syndr*. 2015;70(1):91-98. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26322669.

47. Sansone M, Sarno L, Saccone G, et al. Risk of preeclampsia in human immunodeficiency virus-infected pregnant women. *Obstet Gynecol*. 2016;127(6):1027-1032. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27159742.

48. Machado ES, Krauss MR, Megazzini K, et al. Hypertension, preeclampsia and eclampsia among HIV-infected pregnant women from Latin America and Caribbean countries. *J Infect*. 2014;68(6):572-580. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24462561.

49. Suy A, Martinez E, Coll O, et al. Increased risk of pre-eclampsia and fetal death in HIV-infected pregnant women receiving highly active antiretroviral therapy. *AIDS*. 2006;20(1):59-66. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16327320.

50. Sebitloane HM, Moodley J, Sartorius B. Associations between HIV, highly active anti-retroviral therapy, and hypertensive disorders of pregnancy among maternal deaths in South Africa 2011-2013. *Int J Gynaecol Obstet*. 2017;136(2):195-199. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28099739.

51. The American College of Obstetricians Gynecologists Committee on Practice Bulletins-Obstetrics. Practice bulletin no. 130: prediction and prevention of preterm birth. *Obstet Gynecol*. 2012;120(4):964-973. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22996126.

52. Thorne C, Patel D, Newell ML. Increased risk of adverse pregnancy outcomes in HIV-infected women treated with highly active antiretroviral therapy in Europe. *AIDS*. 2004;18(17):2337-2339. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15577551.

53. Koss CA, Natureeba P, Plenty A, et al. Risk factors for preterm birth among HIV-infected pregnant Ugandan women randomized to lopinavir/ritonavir- or efavirenz-based antiretroviral therapy. *J Acquir Immune Defic Syndr*. 2014;67(2):128-135. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25072616.

54. d'Arminio Monforte A, Galli L, Lo Caputo S, et al. Pregnancy outcomes among ART-naive and ART-experienced HIV-positive women: data from the ICONA foundation study group, years 1997-2013. *J Acquir Immune Defic Syndr*. 2014;67(3):258-267. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25314248.

55. Favarato G, Bailey H, Burns F, Prieto L, Soriano-Arandes A, Thorne C. Migrant women living with HIV in Europe: are they facing inequalities in the prevention of mother-to-child-transmission of HIV?: the European pregnancy and paediatric HIV cohort collaboration (EPPICC) study group in EuroCoord. *Eur J Public Health*. 2017. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28449111.

Recommendations for Use of Antiretroviral Drugs during Pregnancy: Overview (Last updated December 12, 2019; last reviewed December 12, 2019)

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 6 and 7.
- 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 doses, more frequent dosing, boosting, or more frequent viral load monitoring **(AII)**.

Updated Panel Recommendations Regarding the Use of Dolutegravir in Pregnancy:

- Dolutegravir (DTG) exposure around the time of conception has been associated with a small but significant increase in the risk of infant neural tube defects (NTDs) in Botswana (0.3%). This risk was higher than the risk for NTDs in infants born to women who were receiving efavirenz (0.05%) and women without HIV (0.08%). There are not enough data to determine the risk of NTDs with preconception use of all *Preferred* and *Alternative* regimens, including DTG, in the United States. Based on the available evidence, the Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission (the Panel) recommends DTG as a ***Preferred* drug for pregnant women, irrespective of trimester (AII)**, and an ***Alternative* drug for women who are trying to conceive (AIII)**.
- 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 Living with HIV, Teratogenicity, Appendix D: Dolutegravir Counseling Guide for Health Care Providers, and Tables 6 and 7.
- When DTG use is continued after delivery, clinicians should discuss reproductive desires, the risks and benefits of conceiving on DTG, and contraceptive options **(AIII)**. See Preconception Counseling and Care and Postpartum Care for more information.
- Folic acid is known to prevent NTDs in the general population. All pregnant women and women who might conceive should take at least 400 mcg of folic acid daily **(AI)**. There is no established link between the use of DTG and impaired folate metabolism, nor is there evidence that folate supplementation prevents DTG-associated NTDs.

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 who have never received 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 are listed in the three sections that follow this overview. Table 6 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.

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 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.

Drugs of known benefit to women should not be withheld during pregnancy unless there are 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 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.**[1]

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 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 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 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.[2]

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 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 who are 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 who are 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 Living 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 women'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 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 [ddI], indinavir [IDV], nelfinavir [NFV], stavudine [d4T], and treatment-dose RTV) and drugs that should not be used in pregnant women because of PK or toxicity concerns (see Table 6).

For women who have achieved virologic suppression and who are receiving regimens that may increase the risk of virologic failure during pregnancy (e.g., darunavir/cobicistat [DRV/c], atazanavir/cobicistat [ATV/c], and elvitegravir/cobicistat [EVG/c]), consider changing the ARV 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 rapidly 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 the 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, 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 increasing the risk for virologic failure or drug toxicity.[3-5] During pregnancy, gastrointestinal transit time becomes prolonged; body water and fat increase throughout gestation, and these changes 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 [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.[6] 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).[7] Although some authors have suggested that ZDV plus 3TC should be used in place of TDF plus FTC,[8] this suggestion is based on data from a single study, the Promoting Maternal

and Infant Survival Everywhere (PROMISE) trial.[9] The generalizability of the PROMISE findings is limited by important 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.

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.

Safety and PK data for the use of **tenofovir alafenamide** (TAF) during pregnancy are insufficient to recommend initiating 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.[10,11]

Integrase Strand Transfer Inhibitors

Updated Guidance about the Use of Dolutegravir in Pregnancy: Dolutegravir (DTG) is now 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 August 2019 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 an ***Alternative* drug for women who are trying to conceive**; these designations reflect concerns about a possible increased risk of neural tube defects (NTDs). The decision to designate DTG as a *Preferred* ARV drug for therapy in pregnant women, irrespective of trimester, was based on several factors. First, DTG is associated with higher rates of virologic suppression, faster rates of viral load decline, and a higher genetic barrier to drug resistance than other *Preferred* and *Alternative* agents. Second, a recent study that evaluated a large number of pregnancies has shown that the risk of NTDs is lower than previously reported in preliminary data. This risk is also largely limited to a short period of time (before 6 weeks post-last menstrual period). A very small minority of women with HIV initiate their first ARV regimen during this period of time. Some Panel members would avoid using DTG in women who are initiating ART before 6 weeks gestation. After this time, any additional risk of NTDs due to DTG is minimal. Third, data are extremely limited on the risks that are 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 alternatives to DTG.

While this recommendation reflects Panel consensus, some Panel members favored recommending the use of DTG in the first trimester as an *Alternative* ARV drug, and the Panel discussed several possible recommendation ratings for the use of DTG in women who are trying to conceive, which ranged from not recommended to *Preferred*. The variety of proposed recommendations reflects how individual Panel members incorporate the available data into clinical decisions. Panel members weighed not only the updated data about DTG-associated NTD risk in specific settings (primarily Botswana), but also the important lack of comparable data about NTD risk with the use of DTG in other settings and about the risk of NTDs when using other *Preferred* and *Alternative* ARV drugs and drug combinations. All of these individual clinical decisions were made after reviewing the same available data, underscoring the importance of **counseling all patients on the risks and benefits of ARV drugs in order to promote informed, individual decision-making** (see Appendix D: Dolutegravir Counseling Guide for Healthcare Providers).[12]

It is important to weigh the available data about risks with DTG against what is known (or not known) about risks of NTDs with other *Preferred* and *Alternative* agents. These agents include atazanavir/ritonavir

(ATV/r), darunavir/ritonavir (DRV/r), and raltegravir (RAL) (Preferred), and lopinavir/ritonavir (LPV/r), efavirenz (EFV), rilpivirine (*Alternative*). Of these, systematic birth surveillance data are available only for EFV. Other adverse pregnancy outcomes are more common than NTDs and should also be considered. The use of PIs has been associated with an increased risk of preterm birth, which may lead to increases in infant morbidity and mortality. In the Botswana study, 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.[13] However, tolerability and long-term viral suppression may be enhanced with DTG-based regimens (see Combination Antiretroviral Regimens and Maternal and Neonatal Outcomes).[13,14]

For additional information and recommendations about the use of DTG before conception and during pregnancy, see Preconception Counseling and Care for Women of Childbearing Age Living with HIV, Teratogenicity, Pregnant Women Living with HIV Who Have Never Received Antiretroviral Drugs, and Pregnant Women Living with HIV Who are Currently Receiving Antiretroviral Therapy.

Data on use of Dolutegravir before Conception and During 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 DTG-based ART.[13] These data were updated during a planned analysis that included data through March of 2019. Five NTDs occurred among 1,683 infants born to women who received preconception DTG (0.30%; 95% confidence interval [CI], 0.13% to 0.69%). The risk of NTDs was higher among women who received DTG than the risks observed for women who received any ARV regimen that did not include DTG (0.10%; 95% CI, 0.06% to 0.17%), women who received EFV-based ART (0.04%; 95% CI, 0.01% to 0.11%), women who initiated DTG during pregnancy (0.03%; 95% CI, 0.00% to 0.15%), and women without HIV (0.08%; 95% CI, 0.06% to 0.10%).[15] Several other surveillance studies also contributed data in July 2019. The Botswana Ministry of Health used a comparable methodology to the Tsepamo study, including standardized outcome assessments for all available pregnancies, internal comparator groups, and ascertainment of outcomes among stillborn infants and for terminations. The Botswana Ministry of Health reported one NTD among 152 exposures at conception (0.66%; 95% CI, 0.02% to 3.69%).[16] The Brazil Ministry of Health used a slightly different methodology, collecting data on the number of stillbirths and terminations, but excluding assessment of birth defects among these outcomes. The Brazil Ministry of Health reported no NTDs among infants born to 382 women who were receiving DTG at the time of conception (0.0%; 95% CI, 0.0% to 0.3%).

The Tsepamo study in Botswana also reported outcomes among women who started DTG-based or EFV-based ART **during pregnancy**, and reported that no birth defects occurred among infants born to 280 women who initiated DTG during the first trimester (all women initiated at >4 weeks gestational age and most initiated at >6 weeks gestational age) and no birth defects occurred among infants born to 729 women who initiated DTG in the second or third trimesters.[13] These data were updated through March 2019. Seventeen major external structural malformations were observed among 3,840 women who initiated DTG at any time during pregnancy (0.44%; 95% CI, 0.28% to 0.71%).[15] A multicenter retrospective cohort study of infants born to 66 women in the United States (42% of whom initiated DTG-based ART preconception, 24% of whom initiated DTG-based ART during pregnancy, and 33% of whom switched to DTG-based ART during pregnancy) found two anomalies and no NTDs.[17] Published data that were reported to the Antiretroviral Pregnancy Registry through January 2019 include reports of anomalies in 11 of 307 infants (3.6%) who experienced first-trimester exposures to DTG and in six of 184 infants (3.3%) who experienced second-trimester or third-trimester exposures.[2]

Available data have not documented an increased risk of NTDs in infants born to women who received other INSTIs, but data are too limited to identify or calculate the specific risks that are associated with 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 three-fold increase in risk. Clinicians are encouraged to submit data for all patients who conceive while receiving ARV drugs or who receive ARV drugs during pregnancy to the Antiretroviral Pregnancy Registry.

If a causal association exists between the use of DTG and the occurrence of NTDs, it remains unknown what the mechanism of effect may be, whether folic acid deficiency 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. Although there is no established link between DTG use and impaired folate metabolism, nor is there evidence that folate prevents DTG-associated NTDs, folic acid is known to prevent NTDs in the general population.[18,19] All pregnant women and women who might conceive should take at least 400 mcg of folic acid daily.

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.[20] Although PK studies have found that DTG levels during the third trimester are lower than a pre-specified target level[21] and lower than levels assessed postpartum,[22] data regarding placental transfer and comparisons to levels in nonpregnant adults indicate that dose adjustments are not needed during pregnancy (see Dolutegravir).

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.[23-29] Clinical trial data from both pregnant women and nonpregnant adults, as well as case series from pregnant women, suggest a more rapid viral decay with the use of RAL than with EFV or LPV/r.[23,25,30-38] In an open-label, randomized clinical trial of late-presenting, ART-naive pregnant women, the median time to achieve a viral load of <200 copies/mL was 8 days for women who received RAL-based ART and 15 days for women who received EFV-based ART. The decline in viral load was greater at 2, 4, and 6 weeks after initiating therapy in the women who received RAL than in those who received EFV.[39] A case study reported a marked elevation of liver transaminases after RAL was initiated in late pregnancy. This elevation resolved rapidly after stopping the drug, suggesting that monitoring of transaminases may be indicated when RAL is initiated in late pregnancy.[40]

Although a once-daily formulation of RAL 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.[41]

There are currently limited data on the use of **elvitegravir/cobicistat** in pregnancy.[34,42] Data from the P1026 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). Viral breakthroughs did occur, with only 74% of women maintaining viral suppression at delivery.[43,44] 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%.[45] Providers should consider switching women who become pregnant while receiving EVG/c to more effective, recommended regimens. If an EVG/c 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 Monitoring of the Woman and Fetus During Pregnancy and Pregnant Women Living with HIV Who Are Currently Receiving Antiretroviral Treatment).

Bictegravir (BIC) is an INSTI that is recommended for initial use in nonpregnant adults. There are no published data on BIC PKs, and extremely limited data on clinical outcomes in pregnancy; in an abstract presented by the manufacturer of BIC, no NTDs were reported among 18 women with prospectively reported periconception exposures.[46]

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 (ATV) and the requirement for twice-daily dosing (DRV). Although the use of once-daily dosing of DRV/r is approved for nonpregnant adults, there are insufficient PK data to support its use in pregnancy.[47] 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; it has also been associated with an increased risk of preterm delivery (see Combination Antiretroviral Drug Regimens and Maternal and Neonatal Outcomes).

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.48 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.[49] ATV exposure was also associated with risk of late language emergence at 12 months that was no longer significant at 24 months.[50,51] The clinical significance of these findings associated with *in utero* ATV exposure is not known.

Darunavir/cobicistat and **atazanavir/cobicistat** **are not recommended** for use in pregnancy.[44,52,53] 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;[44] 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** in pregnancy. For women who become pregnant on DRV/c or ATV/c, providers should consider switching to more effective, recommended regimens. If a regimen that contains DRV/c or ATV/c 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 Monitoring of the Woman and Fetus During Pregnancy and Pregnant Women Living with HIV Who Are Currently Receiving Antiretroviral Treatment).

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).[54] 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.[54-62] 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 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 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.

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, vivid dreams and/or nightmares, and increased risk of suicidality.[13,63-67]

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.[13,63-65,68] 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[69] (see Teratogenicity and Pregnant Women Living with HIV Who Are Currently Receiving Antiretroviral Therapy). A recent observational study reported a two-fold increased risk of microcephaly among infants born to 141 women receiving EFV compared to women receiving other ARV drugs in the United States, although 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[70] (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^3. There are sufficient data from use in pregnancy to recommend RPV as an *Alternative* agent for ARV-naive pregnant women who meet these same CD4 count and viral load criteria.[71] 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; however, viral breakthroughs have been observed. Higher-than-standard doses of RPV have not been studied, so there are insufficient data to recommend a dosing change 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 there are 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.[22,72] 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; 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 EFV may increase the risk of depression and suicidality, this screening is particularly critical for women on EFV-containing regimens.[67,73]

Entry 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 is 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).[74] 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, because there are insufficient data to inform safety or dosing guidance for their use in pregnancy, these drugs should only be used after consulting HIV and obstetric specialists.

Ibalizumab is a humanized monoclonal antibody to the CD4 receptor. There are no data on the use of this drug 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 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.[44,53,75] However, the Panel recognizes that there may be situations where it is appropriate to continue using these drugs in women who become pregnant on a well-tolerated, fully suppressive regimen. See Pregnant Women Living 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. Minkoff H, Augenbraun M. Antiretroviral therapy for pregnant women. *Am J Obstet Gynecol*. 1997;176(2):478-489. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9065202.
2. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral Pregnancy Registry international interim report for 1 January 1989–31 January 2019. Wilmington, NC: Registry Coordinating Center. 2019. Available at: http://www.apregistry.com.
3. 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.
4. 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.
5. Bollen P, Colbers A, Schalkwijk S, et al. A comparison of the pharmacokinetics of dolutegravir during pregnancy and postpartum. Presented at: 18th International Workshop on Clinical Pharmacology of Antiviral Therapy. 2017. Chicago, IL.
6. 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.
7. 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.
8. 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.
9. 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.
10. 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.
11. 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.
12. 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.
13. 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.

14. 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.

15. 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.

16. Raesima MM, Ogbuabo CM, Thomas V, et al. Dolutegravir use at conception - additional surveillance data from Botswana. *N Engl J Med*. 2019;381(9):885-887. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31329378.

17. Grayhack C, Sheth A, Kirby O, et al. Evaluating outcomes of mother-infant pairs using dolutegravir for HIV treatment during pregnancy. *AIDS.* 2018;32(14):2017-2021. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29944472.

18. 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.

19. 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.

20. Kintu K, Malaba T, Nakibuka J, et al. Rct of dolutegravir vs efavirenz-based therapy initiated in late pregnancy: DolPHIN-2. Abstract 40. Presented at: Conference on Retroviruses and Opportunistic Infections. 2019. Seattle, Washington. Available at: http://www.croiconference.org/sessions/rct-dolutegravir-vs-efavirenz-based-therapy-initiated-late-pregnancy-dolphin-2.

21. 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.

22. 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.

23. Taylor N, Touzeau V, Geit M, et al. Raltegravir in pregnancy: a case series presentation. *Int J STD AIDS.* 2011;22(6):358-360. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21680678.

24. 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.

25. 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.

26. 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.

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

28. 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.

29. Gantner P, Sylla B, Morand-Joubert L, et al. "Real life" use of raltegravir during pregnancy in France: The Coferal-IMEA048 Cohort Study. *PLoS One.* 2019;14(4):e0216010. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31017957.

30. Westling K, Pettersson K, Kaldma A, Naver L. Rapid decline in HIV viral load when introducing raltegravir-containing antiretroviral treatment late in pregnancy. *AIDS Patient Care STDS.* 2012;26(12):714-717. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23101466.

31. Cha A, Shaikh R, Williams S, Berkowitz LL. Rapid reduction in HIV viral load in late pregnancy with raltegravir: a case report. *J Int Assoc Provid AIDS Care.* 2013;12(5):312-314. Available at: http://www.ncbi.nlm.nih.gov/

pubmed/23695227.

32. De Hoffer L, Di Biagio A, Bruzzone B, et al. Use of raltegravir in a late presenter HIV-1 woman in advanced gestational age: case report and literature review. *J Chemother.* 2013;25(3):181-183. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23783144.

33. Nobrega I, Travassos AG, Haguihara T, Amorim F, Brites C. Short communication: use of raltegravir in late-presenting HIV-infected pregnant women. *AIDS Res Hum Retroviruses.* 2013;29(11):1451-1454. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23731224.

34. 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.

35. Boucoiran I, Tulloch K, Pick N, et al. A case series of third-trimester raltegravir initiation: Impact on maternal HIV-1 viral load and obstetrical outcomes. *Can J Infect Dis Med Microbiol.* 2015;26(3):145-150. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26236356.

36. Maliakkal A, Walmsley S, Tseng A. Critical review: review of the efficacy, safety, and pharmacokinetics of raltegravir in pregnancy. *J Acquir Immune Defic Syndr.* 2016;72(2):153-161. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27183177.

37. Cecchini DM, Martinez M, Morganti L, Rodriguez C. Raltegravir containing antiretroviral therapy for prevention of mother to child transmission in a high risk population of HIV-infected pregnant women in Buenos Aires, Argentina: maternal and neonatal outcomes. Presented at: International AIDS Conference. 2016. Durban, South Africa.

38. 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.

39. Mirochnick M, Shapiro D, Morrison L, et al. Randomized trial of raltegravir-art vs efavirenz-art when initiated during pregnancy. Abstract 39. Presemted at: Conference on Retroviruses and Opportunistic Infections. 2019. Seattle, Washington. Available at: http://www.croiconference.org/sessions/randomized-trial-raltegravir-art-vs-efavirenz-art-when-initiated-during-pregnancy.

40. Renet S, Closon A, Brochet MS, Bussieres JF, Boucher M. Increase in transaminase levels following the use of raltegravir in a woman with a high HIV viral load at 35 weeks of pregnancy. *J Obstet Gynaecol Can.* 2013;35(1):68-72. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23343800.

41. 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. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29915921.

42. 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.

43. 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.

44. 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.

45. 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.

46. 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.

47. 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. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30715324.

48. 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.

49. 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.

50. 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.

51. 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.

52. 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.

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

54. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25599649.

55. Atazanavir [package insert]. Food and Drug Administration. 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021567s042,206352s007lbl.pdf.

56. 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.

57. 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.

58. 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.

59. 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.

60. 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.

61. 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.

62. 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.

63. 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.

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

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

66. 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.

67. 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.

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

69. British HIV Association. British HIV association guidelines for the management of HIV in pregnancy and postpartum 2018. *HIV Med.* 2019;20 Suppl 3:s2-s85. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30869192.

70. 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. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31740351.

71. 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.

72. 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.

73. 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.

74. 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.

75. Crauwels HM, Osiyemi O, Zorilla C, Bicer C, Brown K. Pharmacokinetics of total and unbound darunavir in HIV-1–infected pregnant women receiving a darunavir/cobicistat-based regimen. Presented at: 8th International Workshop on HIV & Women. 2018. Boston, Massachusetts. Available at: http://www.natap.org/2018/CROI/HIV&Women2018DRVcPKPregnancyPoster_JUV-63244_FINAL.PDF.

Pregnant Women Living with HIV Who Have Never Received Antiretroviral Drugs (Antiretroviral Naive) (Last updated December 12, 2019; last reviewed December 12, 2019)

Panel's Recommendations

- Antiretroviral therapy (ART) is recommended for all pregnant women living with HIV to reduce the risk of perinatal transmission of HIV and to optimize the health of the mother **(AI)**. Initiating ART as soon as possible in pregnant women who have never received antiretroviral (ARV) drugs is recommended, based on data demonstrating that earlier virologic suppression is associated with a lower risk of transmission **(AII)**.
- The results of HIV drug-resistance studies should guide the selection of antiretroviral (ARV) regimens in women whose HIV RNA levels are above the threshold for resistance testing (i.e., >500 copies/mL to 1,000 copies/mL), unless drug-resistance studies have already been performed (see Antiretroviral Drug Resistance and Resistance Testing in Pregnancy) **(AII)**. When ART is initiated before the results of the drug-resistance assays are available, the ARV regimen should be modified, if necessary, based on the resistance assay results **(BIII)**.
- ARV regimens that are *Preferred* for the treatment of pregnant women with HIV who are ARV-naive include: a dual-nucleoside reverse transcriptase inhibitor combination (abacavir plus lamivudine or tenofovir disoproxil fumarate plus either emtricitabine or lamivudine) and either a ritonavir-boosted protease inhibitor (atazanavir/ritonavir or darunavir/ritonavir) or an integrase strand transfer inhibitor (dolutegravir [irrespective of trimester] or raltegravir; see Table 6 and Updated Guidance about the Use of Dolutegravir in Pregnancy in Recommendations for the Use of Antiretroviral Drugs During Pregnancy) **(AIII)**.
- The Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission emphasizes the **importance of counseling and informed decision-making** with regard to all ARV regimens for people living with HIV **(AIII)**. See Appendix D: Dolutegravir Counseling Guide for Health Care Providers for more information.

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*

Pregnant women living with HIV should receive standard clinical, immunologic, and virologic evaluations. Consistent with the principles of HIV treatment for nonpregnant adults, clinicians should discuss treatment options with pregnant women and offer antiretroviral (ARV) regimens that contain at least three drugs. These regimens reduce the risk of perinatal HIV transmission and optimize the woman's health. Use of an ARV regimen that successfully reduces plasma HIV RNA to undetectable levels substantially lowers the risk of perinatal transmission of HIV, minimizes the need to consider elective cesarean delivery as an intervention to reduce the risk of transmission, and reduces the risk of ARV drug resistance in the mother.

Decisions about the timing and management of antiretroviral therapy (ART) in women who have not previously received ART should be guided by several key principles:

A suppressed viral load at the time of delivery markedly reduces perinatal transmission risk.

In an analysis of 12,486 infants delivered by women with HIV between 2000 and 2011 in the United Kingdom and Ireland, the overall perinatal transmission rate declined from 2.1% in 2000 and 2001 to 0.46% in 2010 and 2011. The transmission risk was significantly lower in women with viral loads <50 copies/mL (0.09%) than in women with viral loads of 50 copies/mL to 399 copies/mL (1.0%), regardless of the type of ARV regimen used or the mode of infant delivery.[1] The decline in perinatal transmission rates was attributed to the increasing number of women on ART at the time of conception and reductions in the proportion of women who either initiated ART late in pregnancy or who never received ART prior to delivery.

Initiating ART early increases the likelihood that a woman will achieve viral suppression by the time of delivery, further reducing transmission risk.

Although most perinatal transmission events occur late in pregnancy or during delivery, recent analyses suggest that early control of viral replication may be important in preventing transmission. In the prospective multicenter French Perinatal Cohort, both maternal viral load at delivery and the timing of ART initiation

were independently associated with perinatal transmission rate. For women who achieved viral loads <50 copies/mL at the time of delivery, transmission risks were 0.9% with third-trimester ART initiation, 0.5% with second-trimester initiation, 0.2% with first-trimester initiation, and 0% (of more than 2,500 infants) with preconception ART initiation. Regardless of when ART was initiated, the perinatal transmission rate was higher for women with viral loads of 50 copies/mL to 400 copies/mL near delivery than for those with <50 copies/mL, and higher still for women with viral loads >400 copies/mL at delivery (4.4% for women who initiated ART in the third trimester and who had viral loads >400 copies/mL at delivery).[2]

In an earlier publication that reported on the same cohort, lack of early and sustained control of maternal viral load appeared to be strongly associated with residual perinatal transmission of HIV.[3] Similar data from Canada in 1,707 pregnant women with HIV who were followed between 1997 and 2010 showed that the risk of perinatal transmission was 1% in all mothers who received ART and 0.4% if ART was taken for more than 4 weeks.[4]

These data suggest that ART should be initiated as early as possible in ARV-naive women, because early and sustained control of HIV viral replication is associated with a decreased risk of transmission. Other studies have demonstrated that baseline viral load is significantly associated with the likelihood of viral suppression by delivery; thus, prompt initiation of ART is particularly important in pregnant women who have high baseline viral loads.[5-7,8]

The benefits of initiating ART early in pregnancy generally outweigh the risks.

The susceptibility of fetuses to the potential adverse effects of drugs is dependent on multiple factors, including the gestational age of the fetus at the time of medication exposure (see Teratogenicity and Combination Antiretroviral Drug Regimens and Maternal and Neonatal Outcomes). The effects of taking ARV drugs during pregnancy are not fully known; however, in general, the data from observational studies on the incidence of birth defects among fetuses/infants of women who received ARV regimens during pregnancy have been reassuring. There have been no differences between the rates of birth defects among infants with first-trimester exposures to most ARV drugs and the rates among infants with later gestational exposures or the rates reported in the general population.[9-12] Please see Teratogenicity for a more detailed discussion of the adverse events that are associated with the use of specific ARV drugs, including dolutegravir (DTG). The decision about when to initiate ART should be discussed by health care providers and their patients. The discussion should include an assessment of a woman's health status and the risks and benefits to her health and the potential risks and benefits to the fetus.

ARV drugs further reduce transmission risk through infant pre-exposure and post-exposure prophylaxis.

Although rates of perinatal transmission are low in women with undetectable or low HIV RNA levels, there is no threshold below which lack of transmission can be ensured.[13-15] ARV drugs reduce the risk of perinatal transmission of HIV through a number of different mechanisms. Although lowering maternal antenatal viral load is an important component of preventing transmission in women with higher viral loads, maternal ART use reduces transmission even in women with low viral loads.[16-20] Additional mechanisms that reduce the risk of perinatal HIV transmission include pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP) for the infant.

With PrEP, the passage of an ARV drug across the placenta produces drug levels that inhibit viral replication in the fetus, particularly during the birth process when there is intensive viral exposure. Therefore, whenever possible, ARV regimens initiated during pregnancy should include a nucleoside reverse transcriptase inhibitor (NRTI) with high transplacental passage, such as lamivudine (3TC), emtricitabine (FTC), tenofovir disoproxil fumarate (TDF), or abacavir (ABC) (see Table 10).[21-24] With PEP, ARV drugs are administered to the infant after birth (see Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection).

Specific ARV regimens are *Preferred* for use in pregnancy.

Tables 6 and 7 outline the ARV regimens that are designated by the Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission as *Preferred* for treatment of pregnant women with HIV who have never received ARV drugs, as well as for women who are continuing or restarting ART

in pregnancy or women who are trying to conceive. 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 pregnancy-specific pharmacokinetic (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 who are trying to conceive. Therefore, it is important to read all the information on 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). *Preferred* regimens include a dual-NRTI combination (ABC plus 3TC or TDF plus FTC or 3TC) used with either a ritonavir-boosted protease inhibitor (PI; atazanavir/ritonavir or darunavir/ritonavir) or an integrase strand transfer inhibitor (INSTI; DTG or raltegravir [RAL]).

DTG is considered a *Preferred* INSTI for ART-naive women, irrespective of trimester. It is a recommended option for an initial ARV regimen in nonpregnant adults, and there are sufficient data about the efficacy and safety of DTG when this drug is initiated during pregnancy.[25-28] Maternal use of DTG at the time of conception or in early pregnancy has been associated with an increase in the risk of neural tube defects (NTDs) in infants. However, this risk is small, and **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 (infant)**. DTG is an *Alternative* medication for women who are trying to conceive, due to concerns about NTDs that were observed in infants born to women who conceived while receiving DTG (see Updated Guidance about the Use of Dolutegravir in Pregnancy in Recommendations for Use of Antiretroviral Drugs During Pregnancy).

RAL is also a *Preferred* INSTI for ARV-naive women, and the amount of efficacy and safety data for RAL in pregnant women is increasing. The selection of drugs for an ARV regimen should be based on individual patient characteristics and needs (see Table 6).

RAL or DTG have been suggested for use when ART is initiated late in pregnancy, particularly for women who have high viral loads, because of their ability to rapidly suppress viral load (a decrease of approximately 2 $\log_{10}$ copies/mL occurs by Week 2 of therapy with these drugs).[29-33] In two open-label, randomized clinical trials in women who presented for treatment late in pregnancy, viral decline was more rapid and a greater proportion of women reached viral suppression targets when using INSTI-based regimens with RAL (IMPAACT 1081) or DTG (DolPHIN-2 study) than efavirenz-based ART.[28,34] DTG is *Preferred* for treatment of acute infection during pregnancy irrespective of trimester because it has a higher barrier to resistance than RAL and can be administered once daily. Because RAL has a lower barrier to resistance than DTG, it **is not recommended** for use during acute infection, when viral loads are expected to be high (see Acute HIV Infection). For a discussion regarding the addition of DTG or RAL to current ARV regimens, see Lack of Viral Suppression.

Resistance tests should be performed, but ART initiation should not be delayed while waiting for results.

Standard ARV drug-resistance testing should be performed before starting an ARV regimen when plasma HIV RNA levels are above the threshold for resistance testing (i.e., >500 copies/mL to 1,000 copies/mL). INSTI-resistance testing is not routinely recommended, but it should be performed for women who are at risk for INSTI resistance (e.g., women with partners who were treated with INSTIs or women who had prior treatment that included INSTIs; see Antiretroviral Drug Resistance and Resistance Testing in Pregnancy). For details regarding genotypic and phenotypic resistance testing, see the Adult and Adolescent Antiretroviral Guidelines. Given the association between earlier viral suppression and lower risk of perinatal transmission, ART should be initiated as soon as possible in pregnant women who have never received ARV drugs, without waiting for the results of resistance testing. The regimen can be modified, if required, when test results return. Either a PI-based or an INSTI-based ARV regimen can be considered when the results of resistance testing are not available to inform the selection of ARV drugs, because clinically significant resistance to PIs and INSTIs is uncommon in ARV-naive individuals.

Regimens other than combination (three-drug) ART are not recommended.

The use of zidovudine (ZDV) monotherapy during pregnancy **is no longer recommended**, because ART provides clear health benefits to the mother and helps prevent perinatal HIV transmission. In the past, the use of ZDV monotherapy during pregnancy for prophylaxis of perinatal transmission was an option for women who had low viral loads (i.e., <1,000 copies/mL) on no ARV drugs. Although the Adult and Adolescent Antiretroviral Guidelines recommend some two-drug ARV regimens in certain clinical circumstances, two-drug ARV regimens **are not recommended** for use in pregnant women.

All pregnant women with HIV should be counseled that the use of ART is recommended, regardless of viral load, to optimally reduce the risk of perinatal transmission. If, after counseling, a woman chooses to forgo the use of ARV drugs during pregnancy, this decision should be re-addressed during subsequent medical appointments. The Perinatal HIV Hotline (1-800-439-4079) can provide information to assist with the discussion.

ARV regimens can be modified postpartum.

ARV regimens that were initiated during pregnancy can be modified after delivery. Women may be able to use some simplified regimens that could not be used during pregnancy because the pregnancy, safety, and/or PK data for those regimens were insufficient. Decisions regarding whether to continue an ARV regimen or which specific ARV agents to use postpartum should be made by women after they have discussed their options with their HIV care providers. These decisions should take several factors into consideration, including the current adult ART recommendations, a woman's plans for contraceptive use and future pregnancies, and individual adherence considerations and medication preferences (see General Principles Regarding Use of Antiretroviral Drugs during Pregnancy).

References

1. Townsend CL, Byrne L, Cortina-Borja M, et al. Earlier initiation of ART and further decline in mother-to-child HIV transmission rates, 2000-2011. *AIDS*. 2014;28(7):1049-1057. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24566097.
2. Mandelbrot L, Tubiana R, Le Chenadec J, et al. No perinatal HIV-1 transmission from women with effective antiretroviral therapy starting before conception. *Clin Infect Dis*. 2015. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26197844.
3. Tubiana R, Le Chenadec J, Rouzioux C, et al. Factors associated with mother-to-child transmission of HIV-1 despite a maternal viral load <500 copies/ml at delivery: a case-control study nested in the French perinatal cohort (EPF-ANRS CO1). *Clin Infect Dis*. 2010;50(4):585-596. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20070234.
4. Forbes JC, Alimenti AM, Singer J, et al. A national review of vertical HIV transmission. *AIDS*. 2012;26(6):757-763. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22210635.
5. Read PJ, Mandalia S, Khan P, et al. When should HAART be initiated in pregnancy to achieve an undetectable HIV viral load by delivery? *AIDS*. 2012;26(9):1095-1103. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22441248.
6. Katz IT, Shapiro R, Li D, et al. Risk factors for detectable HIV-1 RNA at delivery among women receiving highly active antiretroviral therapy in the women and infants transmission study. *J Acquir Immune Defic Syndr*. 2010;54(1):27-34. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20065861.
7. Aziz N, Sokoloff A, Kornak J, et al. Time to viral load suppression in antiretroviral-naive and -experienced HIV-infected pregnant women on highly active antiretroviral therapy: implications for pregnant women presenting late in gestation. *BJOG*. 2013. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23924192.
8. Myer L, Phillips TK, McIntyre JA, et al. HIV viraemia and mother-to-child transmission risk after antiretroviral therapy initiation in pregnancy in Cape Town, South Africa. *HIV Med*. 2017;18(2):80-88. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27353189.
9. da Costa TP, Machado ES, et al. Malformations among HIV vertically exposed newborns–results from a Brazilian cohort study. Presented at: 6th IAS Conference on HIV Pathogenesis and Treatment and Prevention. 2011. Rome, Italy.
10. Watts DH, Huang S, Culnane M, et al. Birth defects among a cohort of infants born to HIV-infected women on antiretroviral medication. *J Perinat Med*. 2011;39(2):163-170. Available at: http://www.ncbi.nlm.nih.gov/

pubmed/21142844.

11. Knapp KM, Brogly SB, Muenz DG, et al. Prevalence of congenital anomalies in infants with *in utero* exposure to antiretrovirals. *Pediatr Infect Dis J*. 2012;31(2):164-170. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21983213.

12. Floridia M, Mastroiacovo P, Tamburrini E, et al. Birth defects in a national cohort of pregnant women with HIV infection in Italy, 2001-2011. *BJOG*. 2013;120(12):1466-1475. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23721372.

13. Cooper ER, Charurat M, Mofenson L, et al. Combination antiretroviral strategies for the treatment of pregnant HIV-1-infected women and prevention of perinatal HIV-1 transmission. *J Acquir Immune Defic Syndr*. 2002;29(5):484-494. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11981365.

14. Mofenson LM, Lambert JS, Stiehm ER, et al. Risk factors for perinatal transmission of human immunodeficiency virus type 1 in women treated with zidovudine. Pediatric AIDS Clinical Trials Group Study 185 Team. *N Engl J Med*. 1999;341(6):385-393. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10432323.

15. Garcia PM, Kalish LA, Pitt J, et al. Maternal levels of plasma human immunodeficiency virus type 1 RNA and the risk of perinatal transmission. Women and Infants Transmission Study Group. *N Engl J Med*. 1999;341(6):394-402. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10432324.

16. Ioannidis JP, Abrams EJ, Ammann A, et al. Perinatal transmission of human immunodeficiency virus type 1 by pregnant women with RNA virus loads <1000 copies/ml. *J Infect Dis*. 2001;183(4):539-545. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11170978.

17. Wade NA, Birkhead GS, Warren BL, et al. Abbreviated regimens of zidovudine prophylaxis and perinatal transmission of the human immunodeficiency virus. *N Engl J Med*. 1998;339(20):1409-1414. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9811915.

18. Jackson JB, Musoke P, Fleming T, et al. Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: 18-month follow-up of the HIVNET 012 randomised trial. *Lancet.* 2003;362(9387):859-868. Available at: http://www.ncbi.nlm.nih.gov/pubmed/13678973.

19. Petra Study Team. Efficacy of three short-course regimens of zidovudine and lamivudine in preventing early and late transmission of HIV-1 from mother to child in Tanzania, South Africa, and Uganda (Petra study): a randomised, double-blind, placebo-controlled trial. *Lancet.* 2002;359(9313):1178-1186. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11955535.

20. Moodley D, Moodley J, Coovadia H, et al. A multicenter randomized controlled trial of nevirapine versus a combination of zidovudine and lamivudine to reduce intrapartum and early postpartum mother-to-child transmission of human immunodeficiency virus type 1. *J Infect Dis*. 2003;187(5):725-735. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12599045.

21. Hirt D, Urien S, Rey E, et al. Population pharmacokinetics of emtricitabine in human immunodeficiency virus type 1-infected pregnant women and their neonates. *Antimicrob Agents Chemother*. 2009;53(3):1067-1073. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19104016.

22. Hirt D, Urien S, Ekouevi DK, et al. Population pharmacokinetics of tenofovir in HIV-1-infected pregnant women and their neonates (ANRS 12109). *Clin Pharmacol Ther*. 2009;85(2):182-189. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18987623.

23. Moodley D, Pillay K, Naidoo K, et al. Pharmacokinetics of zidovudine and lamivudine in neonates following coadministration of oral doses every 12 hours. *J Clin Pharmacol*. 2001;41(7):732-741. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11452705.

24. Wade NA, Unadkat JD, Huang S, et al. Pharmacokinetics and safety of stavudine in HIV-infected pregnant women and their infants: pediatric AIDS clinical trials group protocol 332. *J Infect Dis*. 2004;190(12):2167-2174. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15551216.

25. 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.

26. Zash R, Holmes L, Makhema J, et al. Surveillance for neural tube defects following antiretroviral exposure from conception. Presented at: 22nd International AIDS Conference. 2018. Amsterdam, Netherlands. Available at: http://www.

natap.org/2018/IAC/IAC_52.htm.

27. 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.

28. Kintu K, Malaba T, Nakibuka J, et al. Rct of dolutegravir vs efavirenz-based therapy initiated in late pregnancy: DolPHIN-2. Abstract 40. Presented at:Conference on Retroviruses and Opportunistic Infections. 2019. Seattle, Washington. Available at: http://www.croiconference.org/sessions/rct-dolutegravir-vs-efavirenz-based-therapy-initiated-late-pregnancy-dolphin-2.

29. Grinsztejn B, Nguyen BY, Katlama C, et al. Safety and efficacy of the HIV-1 integrase inhibitor raltegravir (MK-0518) in treatment-experienced patients with multidrug-resistant virus: a Phase II randomised controlled trial. *Lancet.* 2007;369(9569):1261-1269. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17434401.

30. Papendorp SG, van den Berk GE. Preoperative use of raltegravir-containing regimen as induction therapy: very rapid decline of HIV-1 viral load. *AIDS*. 2009;23(6):739. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19279447.

31. 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.

32. 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.

33. Orrell C, Kintu JA, et al. DolPHIN-1: Randomised controlled trial of dolutegravir(DTG)-versus efavirenz(EFV)-based therapy in mothers initiating antiretroviral treatment in late pregnancy. Presented at: 22nd International AIDS Conference. 2018. Amsterdam, Netherlands. Available at: http://www.natap.org/2018/IAC/IAC_30.htm.

34. Mirochnick M, Shapiro D, Morrison L, et al. Randomized trial of raltegravir-art vs efavirenz-art when initiated during pregnancy. Abstract 39. Presented at: Conference on Retroviruses and Opportunistic Infections. 2019. Seattle, Washington. Available at: http://www.croiconference.org/sessions/randomized-trial-raltegravir-art-vs-efavirenz-art-when-initiated-during-pregnancy.

Table 6. What to Start: Initial Combination Regimens for Antiretroviral-Naive Pregnant Women (Last updated December 12, 2019; last reviewed: December 12. 2019) (page 1 of 4)

Recommendations for initial therapy are intended for pregnant women **who have never received ART or ARV drugs for prophylaxis** (i.e., women who are ARV-naive) and who have no evidence of significant resistance to regimen components (also see Pregnant Women Living with HIV Who Have Never Received Antiretroviral Drugs and Table 7).

In general, the Panel recommends that **women who are already on fully suppressive ART regimens when pregnancy occurs should continue to use those regimens**, unless they are receiving an ARV drug or ART regimen that is not recommended for use in adults or there are concerns about safety and inferior efficacy during pregnancy (see Table 7 and Pregnant Women Living with HIV Who Are Currently Receiving Antiretroviral Therapy). Clinicians may need to consider additional factors when initiating ART in women who previously received ART or ARV drugs for prophylaxis (see Pregnant Women Living with HIV Who Have Previously Received Antiretroviral Treatment or Prophylaxis but Are Not Currently Receiving Any Antiretroviral Medications and Table 7).

Regimens are listed alphabetically within each drug class and recommendation category, and the order does not indicate a ranking of preference. In addition, the Panel makes no recommendation of one agent or regimen over another within each category (*Preferred* or *Alternative*).

Note: For more information about the use of specific drugs and dosing in pregnancy, see Table 7, the individual drug sections in Appendix B, and Table 10.

Drug or Drug Combination	Comments
Preferred Initial Regimens in Pregnancy 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 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 who are trying to conceive. Therefore, it is important to read all the information on 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).	
Preferred Dual-NRTI Backbones	
ABC/3TC	Available as an FDC. Can be administered once daily. ABC **should not be used** in patients who test positive for HLA-B*5701 because of the risk of developing a hypersensitivity reaction. ABC/3TC administered with ATV/r or EFV is not recommended if pretreatment HIV RNA is >100,000 copies/mL.
TDF/FTC ***or*** **TDF/3TC**	TDF/FTC is available as an FDC. Either coformulated TDF/FTC or separate doses of TDF and 3TC can be administered once daily. TDF has potential renal toxicity; thus, TDF-based, dual-NRTI combinations should be used with caution in patients with renal insufficiency.
Preferred INSTI Regimens	
DTG/ABC/3TC (FDC) ***or*** **DTG plus a Preferred Dual-NRTI Backbone**[a]	Administered once daily. The use of DTG/ABC/3TC requires HLA-B*5701 testing, because this FDC contains ABC. INSTI-based regimens may be useful when drug interactions or the potential for preterm delivery with a PI-based regimen are a concern. In nonpregnant adults, DTG is associated with lower rates of INSTI resistance than RAL; like RAL, DTG has been shown to rapidly decrease viral load in ARV-naive pregnant women who present to care later in pregnancy. DTG is *Preferred* for the treatment of pregnant women with acute HIV infection and for women who present to care late in pregnancy. There are specific timing and/or fasting recommendations if DTG is taken with calcium or iron (e.g., in prenatal vitamins; see Table 10). The use of DTG at conception and in very early pregnancy has been associated with a small but statistically significant increase in the risk of NTDs; this information should be discussed with patients to ensure informed decision-making. For more information, see Updated Guidance About the Use of Dolutegravir in Pregnancy in Recommendations for Use of Antiretroviral Drugs During Pregnancy, Table 7, Teratogenicity, and Appendix D: Dolutegravir Counseling Guide for Health Care Providers.

Table 6. What to Start: Initial Combination Regimens for Antiretroviral-Naive Pregnant Women (page 2 of 4)

Drug or Drug Combination	Comments
RAL plus a Preferred Dual-NRTI Backbone	PK data are available for RAL use in pregnancy, and experience with use in pregnancy is increasing. RAL has been shown to produce rapid viral load decline to undetectable levels in women who present for initial therapy late in pregnancy. INSTI-based regimens may be useful when drug interactions or the potential for preterm delivery with PI-based regimens are a concern. Twice-daily dosing required. There are specific timing and/or fasting recommendations if RAL is taken with calcium or iron (e.g., in prenatal vitamins; see Table 10).
Preferred PI Regimens	
ATV/r plus a Preferred Dual-NRTI Backbone	Once-daily administration. Extensive experience with use in pregnancy. Maternal hyperbilirubinemia; no clinically significant neonatal hyperbilirubinemia or kernicterus reported, but neonatal bilirubin monitoring is recommended. Cannot be administered with PPIs. Specific timing recommended for dosing with H2 blockers (see Table 10).
DRV/r plus a Preferred Dual-NRTI Backbone	Better tolerated than LPV/r. Experience with use in pregnancy is increasing. Must be used twice daily in pregnancy.
Drug	**Comments**
Alternative Initial Regimens in Pregnancy 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 who are trying to conceive. Therefore, it is important to read all the information on 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 Dual-NRTI Backbones	
ZDV/3TC	Available as an FDC. Although not recommended for initial therapy in nonpregnant adults, ZDV/3TC is the NRTI combination with most experience for use in pregnancy. It has the disadvantages of requiring twice-daily administration and having an increased potential for hematologic toxicities and other toxicities.
Alternative PI Regimens	
LPV/r plus a Preferred Dual-NRTI Backbone	Abundant experience and established PKs in pregnancy. More nausea than with *Preferred* agents. Twice-daily administration. A dose increase is recommended during the third trimester (see Table 10). Once-daily LPV/r **is not recommended** for use in pregnant women.
Alternative NNRTI Regimens	
EFV/TDF/FTC (FDC) ***or*** **EFV/TDF/3TC (FDC)** ***or*** **EFV plus a Preferred Dual-NRTI Backbone**	Birth defects have been reported in primate studies of EFV, but there has been no evidence of an increased risk of birth defects in human studies and extensive experience in pregnancy; cautionary text remains in package insert (see Teratogenicity and Table 10). These regimens are useful for women who require treatment with drugs that have significant interactions with *Preferred* agents, or who need the convenience of a coformulated, single-tablet, once-daily regimen and are not eligible for DTG or RPV. Screening for antenatal and postpartum depression is recommended. Higher rate of adverse events than some *Preferred* drugs.
RPV/TDF/FTC (FDC) ***or*** **RPV plus a Preferred Dual-NRTI Backbone**	RPV **is not recommended** in patients with pretreatment HIV RNA >100,000 copies/mL or CD4 counts <200 cells/mm^3. Do not use with PPIs. PK data are available for pregnant individuals, but there is relatively little experience with use in pregnancy. PK data suggest lower drug levels and risk of viral rebound in second and third trimesters; if used, consider monitoring viral load more frequently. Should be taken with food. Available in a coformulated, single-tablet, once-daily regimen.
Drug	**Comments**
Insufficient Data in Pregnancy to Recommend for Initial Regimens in ART-Naive Women These drugs are approved for use in adults but lack adequate pregnancy-specific PK or safety data.	
BIC/TAF/FTC (FDC)	No data on the use of BIC in pregnancy. Limited data on the use of TAF in pregnancy.

Table 6. What to Start: Initial Combination Regimens for Antiretroviral-Naive Pregnant Women (page 3 of 4)

Drug	Comments
DOR	No data on the use of DOR in pregnancy.
IBA	No data on the use of IBA in pregnancy.
TAF/FTC (FDC) ***or*** **RPV/TAF/FTC (FDC)**	Plasma TAF exposures in pregnant adults are similar to those seen in nonpregnant adults, whether TAF is administered with a boosting agent or not. TAF has been studied in pregnant women, but data are not yet sufficient to recommend initiating TAF in pregnancy.
Drug	**Comments**
Not Recommended for Initial ART or Use in Pregnancy These drugs and drug combinations are recommended for use in adults but **are not recommended** for use during pregnancy because of concerns about maternal or fetal safety or inferior efficacy, including viral breakthroughs in the second and third trimester (see Table 7 and Table 10). **Note:** When a pregnant woman presents to care while virally suppressed on one of these drugs or drug combinations, providers should consider whether to continue her current regimen or switch to a recommended ART regimen (see Pregnant Women Living with HIV Who Are Currently Receiving Antiretroviral Therapy and Table 7).	
ATV/c	Limited data on the use of ATV with COBI in pregnancy. Substantial reductions in trough levels of ATV in the second and third trimesters have been reported when taken with COBI.
DRV/c (FDC) ***or*** **DRV/c/FTC/TAF (FDC)**	Limited data on use of DRV with COBI in pregnancy. Inadequate levels of both DRV and COBI in second and third trimester, as well as viral breakthroughs, have been reported. Insufficient data about the use of TAF in pregnancy (see above).
EVG/c/FTC/TAF (FDC)	Limited data on use of EVG with COBI and insufficient data on the use of TAF in pregnancy (see above). Inadequate levels of both EVG and COBI in second and third trimester, as well as viral breakthroughs, have been reported. Specific timing and/or fasting recommendations, especially if taken with calcium or iron (e.g., in prenatal vitamins; see Table 10).
EVG/c/FTC/TDF (FDC)	Limited data on use of EVG with COBI in pregnancy. Inadequate levels of both EVG and COBI in second and third trimester, as well as viral breakthroughs, have been reported. Specific timing and/or fasting recommendations, especially if taken with calcium or iron (e.g., in prenatal vitamins; see Table 10).
Drug	**Comments**
Not Recommended for Initial ART in Pregnancy and Not Recommended Except in Special Circumstances for Treatment-Experienced Women in Pregnancy These drugs **are not recommended** for use in pregnant women who have never received ART. With the exception of NVP, data about the PKs, safety, and efficacy of these drugs during pregnancy are limited. Some of these drugs are also categorized as not recommended except in special circumstances during pregnancy, because the Panel recognizes that there may be circumstances where pregnant women who are ART-experienced may need to initiate or continue these drugs to reach or maintain viral suppression (see Table 7).	
ETR	Not recommended for use in ART-naive populations. Available PK data suggest that using the standard adult dose is appropriate for pregnant patients, although data about use in pregnancy are limited.
MVC	Not recommended for use in ART-naive populations. MVC requires tropism testing before use. Available PK data suggest that using the standard adult dose is appropriate for pregnant patients, although data about use in pregnancy are limited.
NVP	Not recommended because of the potential for adverse events, complex lead-in dosing, and low barrier to resistance. NVP should be used with caution when initiating ART in women with CD4 counts >250 cells/mm^3. Use NVP and ABC together with caution; both can cause hypersensitivity reactions in the first few weeks after initiation.
T-20	Not recommended for use in ART-naive populations.

Table 6. What to Start: Initial Combination Regimens for Antiretroviral-Naive Pregnant Women (page 4 of 4)

[a] The decision to designate DTG as a *Preferred* ARV drug for therapy in pregnant women, irrespective of trimester, was based on several factors. First, DTG is associated with higher rates of virologic suppression, faster rates of viral load decline, and a higher genetic barrier to drug resistance than other *Preferred* and *Alternative* agents. Second, a recent study that evaluated a large number of pregnancies has shown that the risk of NTDs is lower than previously reported in preliminary data. This risk is also largely limited to a short period of time (before 6 weeks post-last menstrual period). A very small minority of women with HIV initiate their first ART regimen during this period of time. Some Panel members would avoid using DTG in women who are initiating ART before 6 weeks gestation. After this time, any additional risk of NTDs due to DTG is minimal. Third, data are extremely limited on the risks that are 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 alternatives to DTG. DTG is recommended as an *Alternative* agent for people who are trying to conceive, as these patients have more time to achieve virologic suppression on regimens that do not contain DTG. For additional information, see Teratogenicity, Updated Guidance About the Use of Dolutegravir in Pregnancy in Recommendations for Use of Antiretroviral Drugs in Pregnancy, and Appendix D: Dolutegravir Counseling Guide for Health Care Providers.

Note: The following drugs and drug combinations (that are not listed above) should not be used during pregnancy; if women become pregnant while taking these medications, they should switch to a recommended regimen: d4T, ddI, FPV, FPV/r, IDV, IDV/r, NFV, RTV (as the sole PI), SQV, SQV/r, TPV, TPV/r, two-drug ART regimens, or a three-NRTI ART regimen (e.g., ABC/ZDV/3TC). See Archived Drugs in the Perinatal Guidelines and What Not to Use in the Adult and Adolescent Antiretroviral Guidelines for individual ARV drugs, ARV combinations, and ART regimens that are not recommended or that should not be used in adults.

Key: 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; BIC = bictegravir; CD4 = CD4 T lymphocyte cell; COBI = cobicistat; d4T = stavudine; ddI = didanosine; DOR = doravirine; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FDC = fixed-dose combination; FPV = fosamprenavir; FPV/r = fosamprenavir/ritonavir; FTC = emtricitabine; IBA = ibalizumab; IDV = indinavir; IDV/r = indinavir/ritonavir; INSTI = integrase strand transfer inhibitor; LPV/r = lopinavir/ritonavir; MVC = maraviroc; NFV = nelfinavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NTD = neural tube defect; NVP = nevirapine; the Panel = the Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission; PI = protease inhibitor; PK = pharmacokinetic; PPI = proton pump inhibitor; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SQV = saquinavir; SQV/r = saquinavir/ritonavir; T-20 = enfuvirtide; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TPV = tipranavir; TPV/r = tipranavir/ritonavir; ZDV = zidovudine

Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs in Pregnant Women and Nonpregnant Women Who Are Trying to Conceive (Last updated December 12, 2019; last reviewed December 12, 2019) (page 1 of 4)

Women should be given information about the benefits and risks of initiating an ARV regimen or making changes to an existing regimen so they can make informed decisions about their care. Patient autonomy and informed choice should be considered in all aspects of medical care, including HIV and obstetric care. This is the primary guiding principle in all the Panel's recommendations.

ART Regimen Component	ART for Pregnant Women Who Have Never Received ARV Drugs and Who Are Initiating ART for the First Time	Continuing ART for Women Who Become Pregnant on a Fully Suppressive, Well-Tolerated Regimen	ART for Pregnant Women Who Have Received ARV Drugs in the Past and Who Are Restarting ART[a]	New ARV Regimen for Pregnant Women Whose Current Regimen is Not Well Tolerated and/or is Not Fully Suppressive[a]	ART for Nonpregnant Women Who Are Trying to Conceive[a,b]
INSTIs Used in combination with a dual-NRTI backbone[c]					
DTG[d]	Preferred	Continue	Preferred	Preferred	Alternative
RAL	Preferred	Continue	Preferred	Preferred	Preferred
BIC	Insufficient data	Insufficient data	Insufficient data	Insufficient data	Insufficient data
EVG/c[e]	Not recommended	Consider switching, or continuing the same regimen with frequent viral load monitoring	Not recommended	Not recommended	Not recommended
PIs Used in combination with a dual-NRTI backbone[c]					
ATV/r	Preferred	Continue	Preferred	Preferred	Preferred
DRV/r	Preferred	Continue	Preferred	Preferred	Preferred
LPV/r	Alternative	Continue	Alternative	Alternative	Alternative
ATV/c[e]	Not recommended	Consider altering the regimen, or continuing the same regimen with frequent viral load monitoring	Not recommended	Not recommended	Not recommended
DRV/c[e]	Not recommended	Consider altering the regimen, or continuing the same regimen with frequent viral load monitoring	Not recommended	Not recommended	Not recommended
NNRTIs Used in combination with a dual-NRTI backbone[c]					
EFV	Alternative	Continue	Alternative	Alternative	Alternative
RPV[f]	Alternative	Continue	Alternative	Alternative	Alternative
DOR	Insufficient data	Insufficient data	Insufficient data	Insufficient data	Insufficient data
ETR[g]	Not recommended	Continue	Not recommended, except in special circumstances	Not recommended, except in special circumstances	Not recommended, except in special circumstances

Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs in Pregnant Women and Nonpregnant Women Who Are Trying to Conceive (page 2 of 4)

ART Regimen Component	ART for Pregnant Women Who Have Never Received ARV Drugs and Who Are Initiating ART for the First Time	Continuing ART for Women Who Become Pregnant on a Fully Suppressive, Well-Tolerated Regimen	ART for Pregnant Women Who Have Received ARV Drugs in the Past and Who Are Restarting ART[a]	New ARV Regimen for Pregnant Women Whose Current Regimen is Not Well Tolerated and/or is Not Fully Suppressive[a]	ART for Nonpregnant Women Who Are Trying to Conceive[a,b]
NNRTIs Used in combination with a dual-NRTI backbone[c]					
NVP[g]	Not recommended	Continue	Not recommended, except in special circumstances	Not recommended, except in special circumstances	Not recommended, except in special circumstances
NRTIs[c,h]					
ABC[i]	Preferred	Continue	Preferred	Preferred	Preferred
FTC	Preferred	Continue	Preferred	Preferred	Preferred
3TC	Preferred	Continue	Preferred	Preferred	Preferred
TDF	Preferred	Continue	Preferred	Preferred	Preferred
ZDV	Alternative	Continue	Alternative	Alternative	Alternative
TAF[j]	Insufficient data	Continue	Insufficient data	Insufficient data	Insufficient data
Entry and Fusion Inhibitors					
IBA	Insufficient data	Insufficient data	Insufficient data	Insufficient data	Insufficient data
MVC[g]	Not recommended	Continue	Not recommended, except in special circumstances	Not recommended, except in special circumstances	Not recommended, except in special circumstances
T-20[g]	Not recommended	Continue	Not recommended, except in special circumstances	Not recommended, except in special circumstances	Not recommended, except in special circumstances
FDC Regimens[e,h] The individual drug component that is most responsible for the overall recommendation is indicated in parentheses.					
ABC/DTG/3TC[d,i]	Preferred	Continue	Preferred	Preferred	Alternative (DTG)
EFV/FTC/TDF	Alternative (EFV)	Continue	Alternative (EFV)	Alternative (EFV)	Alternative (EFV)
EFV/3TC/TDF	Alternative (EFV)	Continue	Alternative (EFV)	Alternative (EFV)	Alternative (EFV)
FTC/RPV/TDF[f]	Alternative (RPV)	Continue (RPV)	Alternative (RPV)	Alternative (RPV)	Alternative (RPV)
BIC/FTC/TAF	Insufficient data (BIC, TAF)	Insufficient data (BIC)	Insufficient data (BIC, TAF)	Insufficient data (BIC, TAF)	Insufficient data (BIC, TAF)
DOR/3TC/TDF	Insufficient data (DOR)	Insufficient data (DOR)	Insufficient data (DOR)	Insufficient data (DOR)	Insufficient data (DOR)

Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs in Pregnant Women and Nonpregnant Women Who Are Trying to Conceive (page 3 of 4)

ART Regimen Component	ART for Pregnant Women Who Have Never Received ARV Drugs and Who Are Initiating ART for the First Time	Continuing ART for Women Who Become Pregnant on a Fully Suppressive, Well-Tolerated Regimen	ART for Pregnant Women Who Have Received ARV Drugs in the Past and Who Are Restarting ART[a]	New ARV Regimen for Pregnant Women Whose Current Regimen is Not Well Tolerated and/or is Not Fully Suppressive[a]	ART for Nonpregnant Women Who Are Trying to Conceive[a,b]
FDC Regimens[e,h] The individual drug component that is most responsible for the overall recommendation is indicated in parentheses.					
FTC/RPV/TAF	Insufficient data (TAF[j])	Continue (RPV[f], TAF[j]) or consider switching to FTC/RPV/TDF	Insufficient data (TAF[j])	Insufficient data (TAF[j])	Insufficient data (TAF[j])
EVG/c/FTC/TDF[e]	Not recommended (EVG/c)	Consider switching, or continuing the same regimen with frequent viral load monitoring (EVG/c)	Not recommended (EVG/c)	Not recommended (EVG/c)	Not recommended (EVG/c)
EVG/c/FTC/TAF[e]	Not recommended (EVG/c)	Consider switching, or continuing the same regimen with frequent viral load monitoring (EVG/c)	Not recommended (EVG/c)	Not recommended (EVG/c)	Not recommended (EVG/c)
DRV/c/FTC/TAF[e]	Not recommended (DRV/c)	Consider switching, or continuing the same regimen with frequent viral load monitoring (DRV/c)	Not recommended (DRV/c)	Not recommended (DRV/c)	Not recommended (DRV/c)
DTG/3TC As a complete regimen[k]	Not recommended	Not recommended; switch, or add additional agents	Not recommended	Not recommended	Not recommended
DTG/RPV As a complete regimen[k]	Not recommended	Not recommended; switch, or add additional agents[f]	Not recommended	Not recommended	Not recommended

[a] **Do not initiate** ARV regimens with components that have documented resistance or suspected resistance based on prior ARV exposure.

[b] This guidance is intended for women who are trying to conceive. These recommendations are not intended for all women with HIV who might become pregnant.

[c] ABC plus 3TC, TDF plus FTC, and TDF plus 3TC are *Preferred* dual-NRTI backbones, and ZDV plus 3TC is an *Alternative* dual-NRTI backbone for ARV regimens.

[d] The decision to designate DTG as a *Preferred* ARV drug for therapy in pregnant women, irrespective of trimester, was based on several factors. First, DTG is associated with higher rates of virologic suppression, faster rates of viral load decline, and a higher genetic barrier to drug resistance than other *Preferred* and *Alternative* agents. Second, a recent study that evaluated a large number of pregnancies has shown that the risk of NTDs is lower than previously reported in preliminary data. This risk is also largely limited to a short period of time (before 6 weeks post-last menstrual period). A very small minority of women with HIV initiate their first ARV regimen during this period of time. Some Panel members would avoid using DTG in women who are initiating ART before 6 weeks of gestation. After this time, any additional risk of NTDs due to DTG is minimal. Third, data are extremely limited on the risks that are 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 alternatives to DTG. DTG is recommended as an Alternative agent for people trying to conceive, as these patients have more time to achieve virologic suppression on regimens that do not contain DTG. For additional information see Teratogenicity, Updated Guidance About the Use of Dolutegravir in Pregnancy in Recommendations for the Use of Antiretroviral Drugs in Pregnancy, and Appendix D: Dolutegravir Counseling Guide for Health Care Providers.

Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs in Pregnant Women and Nonpregnant Women Who Are Trying to Conceive (page 4 of 4)

[e] DRV/c, EVG/c, and ATV/c **are not recommended** for use in pregnancy due to PK changes that pose a risk for low drug levels and viral rebound in the second and third trimesters. However, in cases where virologically suppressed pregnant women present to care on regimens that include these drugs, clinicians can consider continuing the use of these drug combinations with frequent viral load monitoring. If there are concerns about switching, see Pregnant Women Living with HIV Who Are Currently Receiving Antiretroviral Therapy.

[f] Although PK data indicate that RPV plasma concentration is reduced during the second and third trimester, the reduction is less than the reductions seen with use of EVG/c or DRV/c. Higher-than-standard doses of RPV have not been studied, so there are insufficient data to recommend a dose change in pregnancy. With standard dosing, viral load should be monitored more frequently.

[g] Although these drugs are not recommended for initial treatment in ART-naive pregnant women, there may be special circumstances in which ART-experienced women may need to continue or initiate ETR, NVP, MVC, and T-20 in order to maintain or achieve viral suppression. There are limited safety and efficacy data about the use of ETR, MVC, and T-20 in pregnancy. NVP is not recommended for ART-naive women because it has a greater potential for adverse events than other NNRTIs, complex lead-in dosing, and a low barrier to resistance; however, if a pregnant woman presents to care on a well-tolerated, NVP-containing regimen, it is likely that NVP will be safe and effective during pregnancy. See Table 6 and Nevirapine for more information.

[h] When using FDC tablets, refer to Table 10 and the drug sections in Appendix B for information about the dosing and safety of individual components of the FDC tablet during pregnancy.

[i] Testing for HLA-B*5701 identifies patients who are at risk of developing hypersensitivity reactions while taking ABC; testing should be performed and a patient should be documented as negative before initiating ABC.

[j] Available data about the use of TAF in pregnancy support continuing it in pregnant women who are virally suppressed, although data are insufficient to recommend it when initiating ART in pregnancy.

[k] Two-drug ARV regimens **are not recommended** for use in pregnancy.

The following drugs and drug combinations (that are not listed above) should not be used during pregnancy; if a woman becomes pregnant while taking any of these medications, she should switch to a recommended regimen: d4T, ddI, FPV, FPV/r, IDV, IDV/r, NFV, RTV (as the sole PI), SQV, SQV/r, TPV, TPV/r, or a three-NRTI ARV regimen (e.g., ABC/ZDV/3TC). See Archived Drugs in the Perinatal Guidelines and What Not to Use in the Adult and Adolescent Antiretroviral Guidelines for individual ARV drugs, ARV combinations, and ARV regimens that are not recommended or that should not be used in adults. Refer to the table above and Table 6 for ARV regimens that are recommended for use in pregnancy.

Key: 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; ARV = antiretroviral; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; BIC = bictegravir; d4T = stavudine; ddI = didanosine; DOR = doravirine; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG/c = elvitegravir/cobicistat; FDC = fixed-dose combination; FPV = fosamprenavir; FPV/r = fosamprenavir/ritonavir; FTC = emtricitabine; IBA =ibalizumab; IDV = indinavir; IDV/r = indinavir/ritonavir; INSTI = integrase strand transfer inhibitor; LPV/r = lopinavir/ritonavir; MVC = maraviroc; NFV = nelfinavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; PK = pharmacokinetic; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SQV = saquinavir; SQV/r = saquinavir/ritonavir; T-20 = enfuvirtide; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TPV = tipranavir; TPV/r = tipranavir/ritonavir; ZDV = zidovudine

Pregnant Women Living with HIV Who Are Currently Receiving Antiretroviral Therapy (Last updated December 12, 2019; last reviewed December 12, 2019)

Panel's Recommendations

- Women living with HIV who are receiving antiretroviral therapy (ART) and who present for pregnancy care should continue their ART during pregnancy, provided that the regimen is tolerated, safe, and effective in suppressing viral replication (defined as a regimen that maintains an HIV viral load less than lower limits of detection of the assay) **(AII)**.
- Women who present during pregnancy on drugs that are not recommended for use because of toxicity (e.g., stavudine, didanosine) should stop taking these drugs and be switched to other antiretroviral (ARV) drugs that are recommended for use in pregnancy **(AIII)**. See Table 7 for more information.
- For pregnant women who are receiving dolutegravir (DTG) and present to care during pregnancy, providers should counsel these women about the risks and benefits of continuing DTG or switching to another ARV regimen **(AIII)**. In most cases, the Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission recommends **continuation** of DTG **(AIII)**.
- There are no data on the use of two-drug regimens during pregnancy (e.g., DTG plus lamivudine, DTG plus rilpivirine); women who present to care on one of these regimens should switch regimens or add additional ARV agents to these regimens.
- Regimens that contain atazanavir/cobicistat, darunavir/cobicistat, or elvitegravir/cobicistat are associated with pharmacokinetic changes and an increased risk of virologic failure in the second and third trimesters of pregnancy (see Table 6 and Table 7); when a pregnant woman presents to care on one of these regimens, providers should consider switching her to a more effective regimen that is recommended for use in pregnant women **(BIII)**. If one of these regimens is continued, absorption should be optimized, and viral load should be monitored frequently (i.e., every 1–2 months).
- If an ARV regimen is altered during pregnancy, drugs in the new regimen should include ARV drugs that are recommended for use in pregnancy (see Table 6 and Table 7 **(BIII)**, and more frequent virologic monitoring is warranted **(CIII)**.
- ARV drug-resistance testing should be performed to assist the selection of active drugs when changing ARV regimens in pregnant women who are experiencing virologic failure on ART and who have HIV RNA levels >500 copies/mL to 1,000 copies/mL **(AII)**. In individuals who have HIV RNA levels >500 copies/mL but <1,000 copies/mL, testing may be unsuccessful but should still be considered **(BII)**. See Lack of Viral Suppression for more information.
- Clinicians should discuss future reproductive plans and timing as well as the risks and benefits of conceiving on specific ARV medications and use of appropriate contraceptive options to prevent unintended pregnancy **(AIII)**.

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*

Women who are taking antiretroviral therapy (ART) for HIV infection should continue their ART regimen during pregnancy, provided it is well tolerated, safe, and effective in suppressing viral replication. Discontinuing or altering therapy could cause an increase in viral load, leading to disease progression, a decline in immune status, and an increased risk of perinatal HIV transmission.[1] Maintenance of viral suppression is paramount for both maternal health and the prevention of perinatal transmission. However, a change in ART may be indicated or considered in specific circumstances.

Women who present during pregnancy on drugs that are not recommended for use because of toxicity (e.g., stavudine, didanosine) should stop taking these drugs and switch to other antiretroviral (ARV) drugs that are recommended for use in pregnancy (see Table 6 and Table 7).

Dolutegravir (DTG) exposure at the time of conception has been associated with a small increase in the risk of neural tube defects (NTDs) in infants.[2,3] Pregnant women who present to care on DTG-based regimens should receive counseling about the benefits and risks of continuing to use DTG or switching regimens. 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 Tsepamo study in Botswana reported five NTDs among infants born to women who were receiving DTG at the time of conception. One of the observed NTDs may have been a defect that can occur during the first trimester, but after the neural tube has closed (a post-neurulation event). However, in cases where a woman conceives while taking DTG, the clinician and patient

must discuss whether the patient should continue using DTG or switch to another ARV regimen.

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

- Most NTDs occur before the neural tube closes at 4 weeks post-conception, approximately 6 weeks post-last menstrual period. After 6 weeks gestation, the additional risk of NTDs developing is thought to be much less likely;
- There is a background risk of NTDs regardless of ART regimen or HIV status (in the United States, the background risk of NTDs in the general population is 0.07%);[4] *and*
- Changes in ARV regimens can lead to viral rebound, which may increase the risk of perinatal HIV transmission and may reduce future ARV drug options due to the development of resistance.

A careful consideration of these risks and benefits will allow patients and providers to reach individualized decisions about whether a patient should continue using DTG or switch to a different ARV regimen during the pregnancy. In most cases, the Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission (the Panel) recommends **continuation** of DTG. There are no data on the use of two-drug regimens in pregnancy (e.g., DTG plus lamivudine, DTG plus rilpivirine [RPV]); women who present to care on one of these regimens should switch regimens or add additional ARV agents to these regimens.

It is important to weigh the available data about the risks of using DTG against what is known (or not known) about the risks of NTDs when using other *Preferred* and *Alternative* agents. These agents include atazanavir/ritonavir, darunavir/ritonavir, and raltegravir (*Preferred*), and lopinavir/ritonavir, EFV, RPV (*Alternative*). Of these, systematic birth surveillance data are available only for EFV. In addition, other adverse pregnancy outcomes are more common than NTDs and should also be considered. The use of protease inhibitors has been associated with an increased risk of preterm birth, which may lead to increases in infant morbidity and mortality (see Combination Antiretroviral Drug Regimens and Maternal and Neonatal Outcomes). While DTG carries a higher risk of NTDs than EFV, the two drugs have similar rates of other adverse pregnancy outcomes. However, tolerability and long-term viral suppression may be enhanced with DTG-based regimens.[5,6]

When a pregnant woman presents to care on a regimen that contains atazanavir/cobicistat, darunavir/cobicistat, or elvitegravir/cobicistat (EVG/c), providers should consider switching her to a more effective regimen that is recommended for use in pregnant women. The use of these regimens is associated with pharmacokinetic changes and an increased risk of virologic failure in the second and third trimesters of pregnancy (see Table 6 and Table 7).[7-9] A recent multicenter, retrospective study of 134 pregnant women with HIV who received elvitegravir (EVG)-containing ART at any time during pregnancy reported that 81.3% of study participants had viral suppression at delivery (HIV RNA <40 copies/mL); among 68 women who initiated EVG before pregnancy and continued receiving EVG through delivery, the rate of viral suppression at delivery was 88.2%. The perinatal HIV transmission rate was 0.8% in this study.[10] If one of these regimens is continued, absorption should be optimized by taking the drugs with food. Women who are taking regimens that include EVG/c should take ARV drugs and prenatal vitamins ≥2 hours apart. In addition, viral load should be monitored more frequently in patients taking cobicistat boosted regimens (e.g., every 1–2 months) (see Monitoring of the Woman and Fetus During Pregnancy).[11] Lack of virologic suppression on subsequent testing indicates a need for a regimen change, and a woman may need a scheduled cesarean delivery if the lack of suppression is detected late in pregnancy.

Although PK data indicate that RPV plasma concentration is reduced during the second and third trimesters of pregnancy, the reduction is less than the reductions seen with the cobicistat-containing regimens described above, and most women will have adequate exposure. Standard RPV dosing is recommended, and viral load should be monitored frequently (e.g., every 1–2 months; see Recommendations for Use of Antiretroviral Drugs During Pregnancy).

As newer, highly effective ARV drugs are approved by the Food and Drug Administration, women with

HIV may present for prenatal care on ART regimens that include ARV drugs for which there is a lack of significant experience in pregnancy and limited PK and safety data. If questions arise about specific drugs in an ART regimen, providers are encouraged to consult with an HIV perinatal specialist before discontinuing or altering a fully suppressive regimen that is well tolerated. In addition, more frequent virologic monitoring is warranted when an ARV regimen is altered during pregnancy. Because little is known about the use of newly approved drugs in pregnancy, providers should make every effort to report all ART exposures in pregnant women to the Antiretroviral Pregnancy Registry.

Women with HIV who are on ART and who present for care during the first trimester should be counseled regarding the benefits and potential risks of receiving ARV drugs during this period. Providers should emphasize that continuing an effective ARV regimen is recommended. Nonhuman primate data and retrospective case reports have raised concerns about an association between EFV use during the first trimester and an increased risk of NTDs in infants (for more details, see Efavirenz). However, a meta-analysis that included data on 2,026 women with first-trimester EFV exposure from 21 prospective studies did not find an increased relative risk (RR) of overall birth defects in infants born to women who received EFV-based regimens compared to women who received regimens that did not include EFV (RR 0.78; 95% confidence interval, 0.56–1.08).[12] A recent multicohort analysis of seven observational studies across 13 European countries and Thailand included 24,963 live births to women with HIV. This study evaluated the incidence of birth defects among infants who had been exposed to either EFV-based ART (n = 1,200) or ART that did not contain EFV (n = 7,537) at the time of conception or during the first trimester; the study also evaluated infants who were not exposed to ART (n = 16,226) at the time of conception or during the first trimester. There was no difference in the prevalence of birth defects among infants in these three groups.[13] The Panel recommends continuing to use EFV in pregnant women who are receiving EFV-based ART, provided that the ARV regimen is well tolerated and results in virologic suppression.

Resistance testing should be performed when considering altering an ARV regimen in a pregnant woman who is experiencing virologic failure and who has HIV RNA levels >1,000 copies/mL. In individuals who have HIV RNA levels >500 copies/mL but <1,000 copies/mL, testing may be unsuccessful, but it still should be considered. The results can be used to select a new regimen with a greater likelihood of suppressing viral replication to undetectable levels.

During and after pregnancy, clinicians should discuss future reproductive plans and timing as well as the risks and benefits of conceiving on specific ARV medications and contraceptive options to prevent unintended pregnancy (see Preconception Counseling and Care for Women of Childbearing Age Living with HIV).

References

1. Floridia M, Ravizza M, Pinnetti C, et al. Treatment change in pregnancy is a significant risk factor for detectable HIV-1 RNA in plasma at end of pregnancy. *HIV Clin Trials*. 2010;11(6):303-311. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21239358.

2. 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.

3. 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.

4. Williams J, Mai CT, Mulinare J, et al. Updated estimates of neural tube defects prevented by mandatory folic acid fortification-United States, 1995-2011. *MMWR Morb Mortal Wkly Rep*. 2015;64(1):1-5. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25590678.

5. 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.

6. 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.

7. 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.

8. 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.

9. 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. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29915921.

10. 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.

11. Best B, Caparelli E, Stek A, et al. Elvitegravir/cobicistat pharmacokinetics in pregnancy and postpartum. Presented at: Conference on Retroviruses and Opportunistic Infections. 2017. Seattle, WA.

12. Ford N, Mofenson L, Shubber Z, et al. Safety of efavirenz in the first trimester of pregnancy: an updated systematic review and meta-analysis. *AIDS*. 2014;28 Suppl 2:S123-131. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24849471.

13. 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.

Pregnant Women Living with HIV Who Have Previously Received Antiretroviral Treatment or Prophylaxis but Are Not Currently Receiving Any Antiretroviral Medications (Last updated December 7, 2018; last reviewed December 7, 2018)

Panel's Recommendations
• Obtain an accurate history of all prior antiretroviral (ARV) regimens used for treatment of HIV disease or prevention of transmission, including virologic efficacy, the patient's tolerance of the medications, results of prior resistance testing, and problems with adherence **(AIII)**.
• Choose and initiate a combination antiretroviral therapy (ART) regimen based on results of prior resistance testing, prior ARV use, concurrent medical conditions, and current recommendations for ART in pregnancy, avoiding drugs with potential known adverse effects for the mother or fetus/infant (see Table 7) **(AII)**.
• If HIV RNA is above the threshold for resistance testing (i.e., >500 to 1,000 copies/mL), ARV resistance testing should be performed prior to starting an ARV drug regimen (see Antiretroviral Drug Resistance and Resistance Testing in Pregnancy) **(AIII)**.
• In general, ART should be initiated prior to receiving results of current ARV resistance studies, because longer use of ART during pregnancy has been associated with reduced transmission rates to the infant compared to shorter treatment periods. ART should be modified based on the results of the resistance assay, if necessary **(BIII)**.
• If the ART regimen results in insufficient viral suppression, repeat resistance testing and assess other considerations, including adherence, food requirements, and drug interactions **(AII)**.
• Consider consulting with an HIV treatment specialist about the choice of ART regimen to initiate in women who previously received ARV drugs or to modify ART in those who are not fully suppressed **(BIII)**.
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*

Pregnant women living with HIV who are currently not receiving antiretroviral therapy (ART) may have received ART in the past for their own health and/or prevention of perinatal transmission in a prior pregnancy. A small number of clinical trials and observational studies have generated information about effectiveness of combination ART in individuals who previously received ART for prevention of perinatal transmission of HIV.[1-4]

There has been concern that prior, time-limited use of ART during pregnancy for prevention of perinatal transmission may lead to resistance and, thus, reduced efficacy if these antiretroviral (ARV) drugs are used as a part of subsequent ART regimens. Rates of resistance appear to be low, based on standard genotyping, after time-limited use of ART consisting of zidovudine, lamivudine, and nevirapine during pregnancy.[5,6] However, minority populations of virus with resistance to nevirapine or lamivudine have been detected using sensitive allele-specific polymerase chain reaction techniques, particularly in women whose virus was inadequately suppressed.[6-11] Both standard and sensitive genotyping techniques appear to show a low rate of resistance to protease inhibitors (PIs) after pregnancy-limited use of PI-based ART, but these results reflect assessments in a limited number of women.[8,12]

Increased risk of treatment failure has not been demonstrated with re-initiation of ART following time-limited use for prevention of perinatal transmission. However, only a limited number of sufficiently large, prospective, observational studies and/or clinical trials have been done to assess the effect of pregnancy-limited ART on the outcome of subsequent treatment. In ACTG 5227, 52 women who had previously received pregnancy-limited ART and who had no evidence of resistance were started on a fixed-dose combination of efavirenz/tenofovir disoproxil fumarate/emtricitabine once daily. After 6 months of therapy, 81% of these women achieved plasma viral loads that were below the limit of detection; the virologic suppression rate was not affected by the classes of previously used ARV drugs or whether women had received similar ART during one or more previous pregnancies.[1] Data from the French Perinatal Cohort

was used to assess virologic suppression with PI-based ART administered to women who had received ART during a previous pregnancy for prevention of perinatal transmission. ARV-naive women and women who received ART during previous pregnancies had similar rates of undetectable viral load at delivery. The type of ART previously received did not affect the rate of undetectable viral load at delivery.[13] In addition, the National Study of HIV in Pregnancy and Childhood in the United Kingdom and Ireland found no increased risk of perinatal transmission in sequential pregnancies compared with a single pregnancy when most women received ART for prevention of perinatal HIV transmission.[14] However, in a comparison between 5,372 ARV-naive pregnant women and 605 women who had previously received ART (but who were not being treated immediately prior to the current pregnancy), ARV-experienced women had a small but significant increase in the risk of detectable viral load at delivery (adjusted odds ratio [aOR] 1.27; 95% CI, 1.01–1.60). This risk was confined to those ARV-experienced women who received non-nucleoside reverse transcriptase inhibitor (NNRTI)-based therapy, as opposed to those who received PI-based therapy.[15]

ART is now recommended worldwide for women living with HIV during pregnancy and throughout their lives.[16] Data have been reported regarding the benefits of ART for women with higher CD4 T lymphocyte (CD4) cell counts (>350 cells/mm^3) and the potential harm of stopping ARV after pregnancy in such women. Data from the HAART Standard version of the PROMISE study showed that women with CD4 cell counts ≥400 cells/mm^3 who were randomized to continue ART postpartum had half the rate of WHO Stage 2 and 3 events as those who discontinued ART.[17] Further, poor adherence was a common problem for women during the postpartum period in this study. Among women randomized to continue ART, 189 of 827 women (23%) had virologic failure. Of the 156 women with virologic failure who had resistance testing, 12% had resistance to their current ART (which was more common in women experiencing failure on NNRTI-based regimens), but 66% did not have resistance to their current regimen, suggesting nonadherence.[17] When counselling women about the benefits of taking ART during pregnancy and continuing for life, health care providers should emphasize the health benefits of maintaining ART and the importance of adherence during the postpartum period (see Postpartum Follow-Up of Women Living with HIV Infection).

Women may choose to discontinue ART for a variety of reasons, and the length of time off treatment prior to pregnancy may vary. Choice of ART in pregnant women who have been previously treated should be made based on treatment history and all prior drug resistance test results, even when the results of drug resistance testing performed during the current pregnancy are not yet available. Interpretation of resistance testing can be complex because it is most accurate when performed while an individual is still taking ART or within 4 weeks of treatment discontinuation. In the absence of selective drug pressure, resistant virus may revert to wild-type and, although detection of drug resistance mutations is informative for choosing a regimen, a negative finding does not rule out the presence of archived resistant virus that could re-emerge once ART is restarted. Therefore, when selecting a new ART regimen, all information, including regimens received, viral response, laboratory testing (including HLA-B*5701 results), any tolerance or adherence problems, food requirements, concomitant medications, prior medical conditions, and the results of resistance testing should be taken into consideration. In general, ART should be initiated prior to receiving the results of ARV drug-resistance studies, especially because longer duration of ART has been associated with reduced transmission rates compared to shorter treatment periods.[18,19] ART should be modified, when necessary, based on subsequent resistance assay results. Careful monitoring of virologic response is essential.

A woman may restart a previous ARV regimen that successfully suppressed her viral load, if the regimen was well tolerated, there is no evidence of resistance to that regimen, and (preferably) the regimen is currently recommended as first-line or an alternative regimen for initial ART in pregnancy (see Table 6: What to Start). Drugs that are not recommended for initial use because of toxicity (stavudine, didanosine, treatment-dose ritonavir) should not be used; drugs that are not recommended for initial use because of concerns about viral breakthrough during pregnancy should also be avoided. Even experienced health care providers may have difficulty with the selection of appropriate ART for women who have advanced HIV disease, a history of extensive prior ART, or previous significant toxicity or nonadherence. In addition to obtaining genotypic resistance testing, it is strongly recommended that specialists in the treatment of HIV be consulted early in

the pregnancy about the choice of a suitable ART regimen for such women.

If ART produces an insufficient viral response (e.g., <1 log drop over 2–4 weeks),[20] repeat resistance testing and assess medication adherence, food requirements, and potential drug interactions (including, if available, relevant pharmacokinetic studies) to inform potential regimen changes. Consultation with an HIV treatment specialist is recommended (see Lack of Viral Suppression).

References

1. Vogler MA, Smeaton LM, Wright RL, et al. Combination antiretroviral treatment for women previously treated only in pregnancy: week 24 results of AIDS clinical trials group protocol a5227. *J Acquir Immune Defic Syndr*. 2014;65(5):542-550. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24759064.

2. Aziz N, Sokoloff A, Kornak J, et al. Time to viral load suppression in antiretroviral-naive and -experienced HIV-infected pregnant women on highly active antiretroviral therapy: implications for pregnant women presenting late in gestation. *BJOG*. 2013;120(12):1534-1547. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23924192.

3. Huntington S, Thorne C, Anderson J, et al. Response to antiretroviral therapy (ART): comparing women with previous use of zidovudine monotherapy (ZDVm) in pregnancy with ART naive women. *BMC Infect Dis*. 2014;14:127. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24593018.

4. Geretti AM, Fox Z, Johnson JA, et al. Sensitive assessment of the virologic outcomes of stopping and restarting non-nucleoside reverse transcriptase inhibitor-based antiretroviral therapy. *PLoS One*. 2013;8(7):e69266. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23874928.

5. Perez H, Vignoles M, Laufer N, et al. Low rate of emergence of nevirapine and lamivudine resistance after post-partum interruption of a triple-drug regimen. *Antivir Ther*. 2008;13(1):135-139. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18389908.

6. Lehman DA, Chung MH, Mabuka JM, et al. Lower risk of resistance after short-course HAART compared with zidovudine/single-dose nevirapine used for prevention of HIV-1 mother-to-child transmission. *J Acquir Immune Defic Syndr*. 2009;51(5):522-529. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19502990.

7. Rowley CF, Boutwell CL, Lee EJ, et al. Ultrasensitive detection of minor drug-resistant variants for HIV after nevirapine exposure using allele-specific PCR: clinical significance. *AIDS Res Hum Retroviruses*. 2010;26(3):293-300. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20334564.

8. Paredes R, Cheng I, Kuritzkes DR, Tuomala RE, Women, Infants Transmission Study Group. Postpartum antiretroviral drug resistance in HIV-1-infected women receiving pregnancy-limited antiretroviral therapy. *AIDS*. 2010;24(1):45-53. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19915448.

9. Olson SC, Ngo-Giang-Huong N, Beck I, et al. Resistance detected by pyrosequencing following zidovudine monotherapy for prevention of HIV-1 mother-to-child-transmission. *AIDS*. 2015;29(12):1467-1471. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26244386.

10. Palombi L, Galluzzo CM, Andreotti M, et al. Drug resistance mutations 18 months after discontinuation of nevirapine-based ART for prevention of mother-to-child transmission of HIV in Malawi. *J Antimicrob Chemother*. 2015;70(10):2881-2884. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26111981.

11. Samuel R, Julian MN, Paredes R, et al. HIV-1 drug resistance by ultra-deep sequencing following short course zidovudine, single-dose nevirapine, and single-dose tenofovir with emtricitabine for prevention of mother-to-child transmission. *J Acquir Immune Defic Syndr*. 2016;73(4):384-389. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27327263.

12. Gingelmaier A, Eberle J, Kost BP, et al. Protease inhibitor-based antiretroviral prophylaxis during pregnancy and the development of drug resistance. *Clin Infect Dis*. 2010;50(6):890-894. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20166821.

13. Briand N, Mandelbrot L, Blanche S, et al. Previous antiretroviral therapy for prevention of mother-to-child transmission of HIV does not hamper the initial response to PI-based multitherapy during subsequent pregnancy. *J Acquir Immune Defic Syndr*. 2011;57(2):126-135. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21436712.

14. French CE, Thorne C, Tariq S, Cortina-Borja M, Tookey PA. Immunologic status and virologic outcomes in repeat pregnancies to HIV-positive women not on antiretroviral therapy at conception: a case for lifelong antiretroviral therapy? *AIDS*. 2014;28(9):1369-1372. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24685820.

15. French CE, Tookey PA, Cortina-Borja M, de Ruiter A, Townsend CL, Thorne C. Influence of short-course antenatal antiretroviral therapy on viral load and mother-to-child transmission in subsequent pregnancies among HIV-infected women. *Antivir Ther*. 2013;18(2):183-192. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23475123.

16. World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventin HIV infecition—recommendations for a public health approach; second edition. 2016. Available at: http://www.who.int/hiv/pub/arv/arv-2016/en/.

17. Currier JS, Britto P, Hoffman RM, et al. Randomized trial of stopping or continuing ART among postpartum women with pre-ART CD4 ≥400 cells/mm^3. *PLoS One*. 2017;12(5):e0176009. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28489856.

18. Mandelbrot L, Tubiana R, Le Chenadec J, et al. No perinatal HIV-1 transmission from women with effective antiretroviral therapy starting before conception. *Clin Infect Dis*. 2015. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26197844.

19. Townsend CL, Byrne L, Cortina-Borja M, et al. Earlier initiation of ART and further decline in mother-to-child HIV transmission rates, 2000–2011. *AIDS*. 2014;28(7):1049-1057. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24566097.

20. 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.

Monitoring of the Woman and Fetus During Pregnancy (Last updated December 7, 2018; last reviewed December 7, 2018)

Panel's Recommendations

- Plasma HIV RNA levels of pregnant women with HIV should be monitored at the initial antenatal visit **(AI)**; 2 to 4 weeks after initiating (or changing) antiretroviral (ARV) drug regimens **(BI)**; monthly until RNA levels are undetectable **(BIII)**; and then at least every 3 months during pregnancy **(BIII)**. HIV RNA levels also should be assessed at approximately 34 to 36 weeks' gestation to inform decisions about mode of delivery (see Transmission and Mode of Delivery) and to inform decisions about optimal treatment for the newborn (see Antiretroviral Management of Newborns) **(AIII)**.
- CD4 T lymphocyte (CD4) cell count should be monitored at the initial antenatal visit **(AI)**. For patients who have been on antiretroviral therapy (ART) for ≥2 years and who have had consistent viral suppression and CD4 cell counts that are consistently >300 cells/mm^3, CD4 cell count should be monitored at the initial antenatal visit; CD4 cell counts do not have to be repeated for these patients during this pregnancy, per the Adult and Adolescent Antiretroviral Guidelines **(CIII)**. Women who have been on ART for <2 years, women with CD4 cell counts <300 cells/mm^3, and women with inconsistent adherence and/or detectable viral loads should have CD4 cell counts monitored every 3 to 6 months during pregnancy **(CIII)**.
- HIV drug-resistance testing should be performed in women whose HIV RNA levels are above the threshold for resistance testing (i.e., >500 copies/mL to 1,000 copies/mL) before:
  - Initiating ART in ARV-naive pregnant women who have not been previously tested for ARV resistance **(AII)**;
  - Initiating ART in ARV-experienced pregnant women **(AIII)**; *or*
  - Modifying ART regimens for women entering pregnancy while receiving ARV drugs or women who have suboptimal virologic response to ARV drugs started during pregnancy **(AII)**.
- ART should be initiated in pregnant women prior to receiving results of ARV-resistance tests. ART should be modified, if necessary, based on the results of the resistance assay **(BIII)**.
- Monitoring for complications of ARV drugs during pregnancy should be based on what is known about the adverse effects of the drugs a woman is receiving **(AIII)**.
- Women taking ART during pregnancy should undergo standard glucose screening at 24 to 28 weeks' gestation **(AIII)**. Some experts suggest glucose screening early in pregnancy for women who are receiving protease inhibitor (PI)-based regimens initiated before pregnancy, in accordance with recommendations for women who are at risk for glucose intolerance **(BIII)**. For more information on PIs, see Combination Antiretroviral Drug Regimens and Maternal and Neonatal Outcomes.
- An ultrasound, performed as soon as possible, is recommended to confirm gestational age and, if scheduled cesarean delivery is necessary, to guide the timing of the procedure (see Transmission and Mode of Delivery) **(AII)**.
- Amniocentesis, if clinically indicated, should be performed on women with HIV only after initiation of an effective ART regimen and, ideally, when HIV RNA levels are undetectable **(BIII)**. In women with detectable HIV RNA levels in whom amniocentesis is deemed necessary, consultation with an expert in the management of HIV in pregnancy should be considered **(BIII)**.

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*

Viral loads should be monitored more frequently in pregnant individuals than in nonpregnant individuals because of the importance of rapid and sustained viral suppression in preventing perinatal HIV transmission. Individuals who are adherent to their antiretroviral (ARV) regimen and who do not harbor resistance mutations to the prescribed drugs should achieve viral suppression within 12 to 24 weeks. Individuals with higher viral loads and lower CD4 T lymphocyte (CD4) cell counts are more likely to take more time to achieve viral suppression during this time period,[1,2] whereas those with lower viral loads and higher CD4 counts and those using integrase strand transfer inhibitors (INSTIs) are more likely to achieve suppression in much shorter time frames. Most patients with adequate viral response at 24 weeks of treatment have had at least a 1 log viral load decrease within 1 to 4 weeks after starting therapy.[3,4] Viral load should be monitored in pregnant women who are living with HIV at the initial clinic visit, 2 to 4 weeks after initiating or changing ARV regimens, monthly until undetectable, and at least every 3 months thereafter. If adherence is a concern, especially during early pregnancy, more frequent monitoring is recommended because of the potential increased risk of perinatal HIV transmission associated with detectable HIV viremia during pregnancy.[5-7]

Similarly, pregnancy may affect the drug exposure levels or efficacy of some drugs; women who are taking these drugs may require a change in therapy or more frequent viral load monitoring (see Table 6 and Table 7).

Viral load also should be assessed at approximately 34 to 36 weeks' gestation to inform decisions about mode of infant delivery and optimal treatment for newborns (see Transmission and Mode of Delivery).

In pregnant women with HIV, CD4 cell count should be monitored at the initial clinic visit. For patients who have been on antiretroviral therapy (ART) for ≥2 years, who have had consistent viral suppression and CD4 cell counts that are consistently >300 cells/mm^3, and who are tolerating ART in pregnancy, CD4 cell count should be monitored only at the initial antenatal visit; CD4 cell counts do not need to be repeated for these patients during this pregnancy, as per the Adult and Adolescent Antiretroviral Guidelines.[3,8,9] Women who have been on ART for <2 years, women with CD4 cell counts of <300 cells/mm^3, or women with inconsistent adherence and/or detectable viral loads should have CD4 cell counts monitored every 3 to 6 months during pregnancy. The safety of this approach is supported by research that demonstrates that patients who are stable on ART (defined as viral load levels <50 copies/mL and CD4 cell counts >500 cells/mm^3 for 1 year) are highly unlikely to experience a CD4 cell count <350 cells/mm^3 in the span of a year.[10]

HIV drug-resistance testing should be performed in women with HIV before starting or modifying ARV regimens if HIV RNA levels are above the threshold for resistance testing (i.e., >500 to 1,000 copies/mL). See Antiretroviral Drug Resistance and Resistance Testing in Pregnancy for more information on resistance testing, including considerations regarding INSTI genotypic resistance testing. ART should not be delayed while waiting for resistance test results. If the results demonstrate resistance, then the regimen can be subsequently adjusted. ARV drug resistance testing should also be performed on women who are taking an ARV regimen but who have suboptimal viral suppression (i.e., failure to achieve undetectable levels of virus during an appropriate time frame, as noted above) or who have sustained viral rebound to detectable levels after prior viral suppression on an ARV regimen (see Lack of Viral Suppression and Antiretroviral Drug Resistance and Resistance Testing in Pregnancy). Drug-resistance testing in the setting of virologic failure is most useful when it is performed while patients are receiving ARV drugs or within 4 weeks after discontinuation of drugs. Even if more than 4 weeks have elapsed since the ARV drugs were discontinued, resistance testing can still provide useful information to guide therapy, though it may not detect all resistance mutations that were selected by previous ART regimens.

Laboratory monitoring for potential complications of ARV drugs during pregnancy should be based on what is known about the adverse effects of the drugs a woman is receiving. For example, routine hematologic monitoring is recommended for women who are receiving zidovudine-containing regimens, and routine renal monitoring is recommended for women on tenofovir disoproxil fumarate. Liver function should be monitored in all women who are receiving ARV drugs. Hepatic dysfunction has been observed in pregnant women on protease inhibitors (PIs), and hepatic steatosis and lactic acidosis in pregnancy have been related to the use of nucleoside reverse transcriptase inhibitors. Pregnant women in general are more likely to have elevated liver enzymes than their nonpregnant counterparts.[11,12]

Pregnancy increases the risk of glucose intolerance. PIs have been associated with increased risk of hyperglycemia, new-onset diabetes mellitus, exacerbation of existing diabetes mellitus, and diabetic ketoacidosis.[13-16] However, the majority of studies in pregnant women with HIV have not shown an increased risk of glucose intolerance with the use of PI-based regimens during pregnancy.[17] A prospective study reported that pregnant women with HIV who received PI-containing regimens did not have more glucose intolerance or insulin resistance than did women who received regimens that did not contain a PI.[18] In both groups, the rate of impaired glucose tolerance was high (38%), but that may be related to specific characteristics of the study participants, including high body mass index and race/ethnicity. Women with HIV who are on ART during pregnancy should receive the standard glucose screening at 24 to 28 weeks' gestation that is recommended for all pregnant women. Some experts would perform glucose screening early in pregnancy for women receiving PI-based ART that was initiated before pregnancy, similar to recommendations for women with risk factors for glucose intolerance.[19]

Accurate estimation of date of delivery is critical when planning scheduled cesarean deliveries at 38 weeks' gestation to prevent perinatal transmission in women with HIV who have elevated HIV RNA viral loads (or when scheduling cesarean delivery or induction for an obstetric indication). Therefore, a first-trimester ultrasound is recommended to confirm gestational age and to provide the most accurate estimation of gestational age at delivery (see Transmission and Mode of Delivery).[20-22] In patients who are not seen until later in gestation, a second-trimester ultrasound can be used for both an anatomical survey and for determining gestational age.

Noninvasive methods of aneuploidy screening should be offered, using tests with high sensitivity and low false-positive rates as recommended by American College of Obstetricians and Gynecologists. Screening can be accomplished using serum analyte screening alone or combined with nuchal translucency, cell-free DNA screening, or ultrasonographic screening alone.[33,34] Women with HIV who have indications for invasive testing during pregnancy (e.g., abnormal ultrasound or aneuploidy screening) should be counseled about the potential risk of HIV transmission along with other risks of the procedure so that they can make an informed decision about testing. Although data are still somewhat limited, the risk of HIV transmission does not appear to increase with the use of amniocentesis or other invasive diagnostic procedures in women who have virologic suppression on ART.[23,24] This is in contrast to the era before effective ART, during which invasive procedures such as amniocentesis and chorionic villus sampling (CVS) were associated with a two- to four-fold increase in risk of perinatal transmission of HIV.[25-28] Although no transmissions occurred among 159 reported cases of amniocentesis or other invasive diagnostic procedures performed in women who were on effective ART, a small increase in the risk of transmission cannot be ruled out.[29-32] Some experts consider CVS and cordocentesis too risky to offer to women with HIV, and they recommend limiting invasive procedures to amniocentesis. At a minimum, pregnant women with HIV should receive effective ART before undergoing any invasive prenatal testing. In addition, they should ideally have undetectable HIV RNA levels at the time of the procedure, and every effort should be made to avoid inserting the needle through, or very close to, the placenta. In women with detectable HIV RNA levels for whom amniocentesis is deemed necessary, consultation with an expert in the management of HIV in pregnancy should be considered, see Other Intrapartum Management Considerations.

References

1. Aziz N, Sokoloff A, Kornak J, et al. Time to viral load suppression in antiretroviral-naive and -experienced HIV-infected pregnant women on highly active antiretroviral therapy: implications for pregnant women presenting late in gestation. *BJOG*. 2013;120(12):1534-1547. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23924192.
2. Snippenburg W, Nellen F, Smit C, Wensing A, Godfried MH, Mudrikova T. Factors associated with time to achieve an undetectable HIV RNA viral load after start of antiretroviral treatment in HIV-1-infected pregnant women. *J Virus Erad*. 2017;3(1):34-39. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28275456.
3. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV. 2018. Available at: http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf.
4. Read PJ, Mandalia S, Khan P, et al. When should HAART be initiated in pregnancy to achieve an undetectable HIV viral load by delivery? *AIDS*. 2012;26(9):1095-1103. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22441248.
5. Garcia PM, Kalish LA, Pitt J, et al. Maternal levels of plasma human immunodeficiency virus type 1 RNA and the risk of perinatal transmission. Women and infants transmission study group. *N Engl J Med*. 1999;341(6):394-402. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10432324.
6. Townsend CL, Byrne L, Cortina-Borja M, et al. Earlier initiation of ART and further decline in mother-to-child HIV transmission rates, 2000–2011. *AIDS*. 2014;28(7):1049-1057. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24566097.
7. Mandelbrot L, Tubiana R, Le Chenadec J, et al. No perinatal HIV-1 transmission from women with effective antiretroviral therapy starting before conception. *Clin Infect Dis*. 2015. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26197844.
8. Gale HB, Gitterman SR, Hoffman HJ, et al. Is frequent CD4+ T-lymphocyte count monitoring necessary for persons

with counts >=300 cells/muL and HIV-1 suppression? *Clin Infect Dis*. 2013;56(9):1340-1343. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23315315.

9. Girard PM, Nelson M, Mohammed P, Hill A, van Delft Y, Moecklinghoff C. Can we stop CD4+ testing in patients with HIV-1 RNA suppression on antiretroviral treatment? *AIDS*. 2013;27(17):2759-2763. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23842127.

10. Di Biagio A, Ameri M, Sirello D, et al. Is it still worthwhile to perform quarterly CD4+ t lymphocyte cell counts on HIV-1 infected stable patients? *BMC Infect Dis*. 2017;17(1):127. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28166729.

11. Huntington S, Thorne C, Anderson J, et al. Does pregnancy increase the risk of ART-induced hepatotoxicity among HIV-positive women? *J Int AIDS Soc*. 2014;17(4 Suppl 3):19486. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25393995.

12. Huntington S, Thorne C, Newell ML, et al. Pregnancy is associated with elevation of liver enzymes in HIV-positive women on antiretroviral therapy. *AIDS*. 2015;29(7):801-809. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25710412.

13. Food and Drug Administration. FDA Public Health Advisory: reports of diabetes and hyperglycemia in patients receiving protease inhibitors for treatment of human immunodeficiency virus (HIV). 1997. Available at: http://www.fda.gov/cder/news/proteaseletter.htm.

14. Eastone JA, Decker CF. New-onset diabetes mellitus associated with use of protease inhibitor [letter]. *Ann Intern Med*. 1997;127(10):948. Available at: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9382376&dopt=Abstract.

15. Visnegarwala F, Krause KL, Musher DM. Severe diabetes associated with protease inhibitor therapy. *Ann Intern Med*. 1997;127(10):947. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9382374.

16. Dube MP, Sattler FR. Metabolic complications of antiretroviral therapies. *AIDS Clin Care*. 1998;10(6):41-44. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11365497.

17. Soepnel LM, Norris SA, Schrier VJ, et al. The association between HIV, antiretroviral therapy, and gestational diabetes mellitus. *AIDS*. 2017;31(1):113-125. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27677165.

18. Hitti J, Andersen J, McComsey G, et al. Protease inhibitor-based antiretroviral therapy and glucose tolerance in pregnancy: AIDS Clinical Trials Group A5084. *Am J Obstet Gynecol*. 2007;196(4):331 e331-337. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17403409.

19. American College of Obstetricians and Gynecologists. ACOG practice bulletin No. 190 summary: gestational diabetes mellitus. *Obstet Gynecol*. 2018;131(2):406-408. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29370044.

20. American College of Obstetricians and Gynecologists. ACOG practice bulletin No. 58. ultrasonography in pregnancy. *Obstet Gynecol*. 2004;104(6):1449-1458. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15572512.

21. Bennett KA, Crane JM, O'Shea P, Lacelle J, Hutchens D, Copel JA. First trimester ultrasound screening is effective in reducing postterm labor induction rates: a randomized controlled trial. *Am J Obstet Gynecol*. 2004;190(4):1077-1081. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15118645.

22. American College of Obstetricians and Gynecologists. Method for estimating due date. Ostet Gynecol. 2014;124(5):863-866. Available at: https://www.acog.org/Clinical-Guidance-and-Publications/Committee-Opinions/Committee-on-Obstetric-Practice/Methods-for-Estimating-the-Due-Date.

23. Floridia M, Masuelli G, Meloni A, et al. Amniocentesis and chorionic villus sampling in HIV-infected pregnant women: a multicentre case series. *BJOG*. 2017;124(8):1218-1223. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27319948.

24. Peters H, Francis K, Harding K, Tookey PA, Thorne C. Operative vaginal delivery and invasive procedures in pregnancy among women living with HIV. *Eur J Obstet Gynecol Reprod Biol*. 2017;210:295-299. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28092853.

25. Mandelbrot L, Mayaux MJ, Bongain A, et al. Obstetric factors and mother-to-child transmission of human immunodeficiency virus type 1: the French perinatal cohorts. SEROGEST French Pediatric HIV Infection Study Group. *Am J Obstet Gynecol*. 1996;175(3 Pt 1):661-667. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8828431.

26. Tess BH, Rodrigues LC, Newell ML, Dunn DT, Lago TD. Breastfeeding, genetic, obstetric and other risk factors associated with mother-to-child transmission of HIV-1 in Sao Paulo State, Brazil. Sao Paulo collaborative study for vertical transmission of HIV-1. *AIDS*. 1998;12(5):513-520. Available at: http://www.ncbi.nlm.nih.gov/

pubmed/9543450.

27. Shapiro DE, Sperling RS, Mandelbrot L, Britto P, Cunningham BE. Risk factors for perinatal human immunodeficiency virus transmission in patients receiving zidovudine prophylaxis. Pediatric AIDS Clinical Trials Group protocol 076 Study Group. *Obstet Gynecol*. 1999;94(6):897-908. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10576173.

28. Maiques V, Garcia-Tejedor A, Perales A, Cordoba J, Esteban RJ. HIV detection in amniotic fluid samples. Amniocentesis can be performed in HIV pregnant women? *Eur J Obstet Gynecol Reprod Biol*. 2003;108(2):137-141. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12781400.

29. Somigliana E, Bucceri AM, Tibaldi C, et al. Early invasive diagnostic techniques in pregnant women who are infected with the HIV: a multicenter case series. *Am J Obstet Gynecol*. 2005;193(2):437-442. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16098867.

30. Coll O, Suy A, Hernandez S, et al. Prenatal diagnosis in human immunodeficiency virus-infected women: a new screening program for chromosomal anomalies. *Am J Obstet Gynecol*. 2006;194(1):192-198. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16389031.

31. Ekoukou D, Khuong-Josses MA, Ghibaudo N, Mechali D, Rotten D. Amniocentesis in pregnant HIV-infected patients. Absence of mother-to-child viral transmission in a series of selected patients. *Eur J Obstet Gynecol Reprod Biol*. 2008;140(2):212-217. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18584937.

32. Mandelbrot L, Jasseron C, Ekoukou D, et al. Amniocentesis and mother-to-child human immunodeficiency virus transmission in the Agence Nationale de Recherches sur le SIDA et les Hepatites Virales French Perinatal Cohort. *Am J Obstet Gynecol*. 2009;200(2):160 e161-169. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18986640.

33. American College of Obstetricians and Gynecologists. Committee Opinion No. 545. Non-invasive prenatal testing for fetal aneuploidy. *Obstet Gynecol*. 2012 Dec;120(6):1532-4. Available at: http://www.acog.org/Resources_And_Publications/Committee_Opinions/Committee_on_Genetics/Noninvasive_Prenatal_Testing_for_Fetal_Aneuploidy.

34. Gagnon A, Davies G, Wilson RD, et al. Prenatal invasive procedures in women with hepatitis B, hepatitis C, and/or human immunodeficiency virus infections. *JOGC*. 2014;36(7):648-655. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25184985.

Antiretroviral Drug Resistance and Resistance Testing in Pregnancy (Last updated December 7, 2018; last reviewed December 7, 2018)

Panel's Recommendations

- HIV drug-resistance genotype studies should be performed in women living with HIV whose HIV RNA levels are above the threshold for resistance testing (i.e., >500 to 1,000 copies/mL) before:
  - Initiating antiretroviral therapy (ART) in antiretroviral (ARV)-naive pregnant women who have not been previously tested for ARV resistance **(AII)**,
  - Initiating ART in ARV-experienced pregnant women **(AIII)**, *or*
  - Modifying ART regimens for women who are entering pregnancy while receiving ARV drugs or who have suboptimal virologic response to ARV drugs started during pregnancy **(AII)**.
- ART should be initiated in pregnant women prior to receiving results of ARV-resistance studies; ART should be modified, if necessary, based on the results of the resistance assay **(BIII)**.
- If an integrase strand transfer inhibitor (INSTI) is being considered for an ART-naive patient and INSTI resistance is a concern, providers should supplement standard resistance testing with a specific INSTI genotypic resistance assay **(BIII)**. INSTI resistance may be a concern because:
  - A patient received prior treatment that included an INSTI,
  - A patient has a history with a sexual partner on INSTI therapy, *or*
  - A patient is starting or changing ART regimen late in pregnancy, in which case an INSTI might be selected because of its ability to rapidly decrease viral load.
- Documented zidovudine resistance does not affect the indications for use of intrapartum zidovudine **(BIII)**.
- Choice of ARV regimen for an infant born to a woman with known or suspected drug resistance should be determined in consultation with a pediatric HIV specialist, preferably before delivery (see Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV) **(AIII)**.
- Pregnant women living with HIV should be given ART to maximally suppress viral replication, which is the most effective strategy for preventing development of resistance and minimizing risk of perinatal transmission **(AII)**.
- All pregnant and postpartum women should be counseled about the importance of adherence to prescribed ARV medications to reduce the potential for development of resistance **(AII)**.

Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*

Rating of Evidence: *I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

Indications for Antiretroviral Drug-Resistance Testing in Pregnant Women Living with HIV

Identification of baseline resistance mutations allows for the selection of more effective and durable antiretroviral (ARV) regimens. Genotypic resistance testing (in addition to a comprehensive history of ARV drug use) is recommended for women living with HIV who have HIV RNA levels above the threshold for resistance testing (i.e., >500 to 1,000 copies/mL) before:

- Initiating antiretroviral therapy (ART) in ARV-naive pregnant women who have not been previously tested for ARV resistance,
- Initiating ART in ARV-experienced pregnant women, *or*
- Modifying ART regimens for women who are entering pregnancy while receiving ARV drugs or who have suboptimal virologic response to ARV drugs started during pregnancy.

In most settings, the results of resistance testing guide the selection of the initial ART regimen. However, given the association between earlier viral suppression and lower risk of perinatal transmission, in ARV-naive pregnant women or ARV-experienced women not presently on ART, ART should be initiated without waiting for the results of resistance testing. The regimen can be modified, if required, when test results return.

Use of integrase strand transfer inhibitors (INSTIs) as part of the ART regimen for pregnant women is becoming increasingly common.[1] Resistance to INSTIs is generally uncommon among ARV-naive individuals in the United States.[2] INSTI resistance was detected in 2.4% of ART-naive persons and 9.6% of ART-experienced persons with HIV in North Carolina.[3] The prevalence of INSTI resistance increased slightly from 0.0% in 2004 to 1.4% in 2013 in Washington, DC.[4] A polymorphism or a substitution associated with INSTI resistance was found in 1.4% of INSTI-naive persons in 16 clinical trials.[5]

Among people who receive INSTI-based ART, the development of INSTI resistance is infrequent (1.48% to 3.80%). A modelling study of INSTI-resistance testing at ART initiation found increased costs without improved clinical outcomes.[6] Routine INSTI-resistance testing is generally not indicated in pregnant women. However, such testing can be considered in the following circumstances:

- A patient received prior treatment that included an INSTI,
- A patient has a history with a sexual partner on INSTI therapy, *or*
- A patient is starting or changing her ART regimen late in pregnancy, in which case an INSTI might be selected because of its ability to rapidly decrease viral load.

HIV drug resistance genotype testing detects mutations that confer resistance to protease inhibitors (PIs), nucleoside reverse transcriptase inhibitors (NRTIs), and non-nucleoside reverse transcriptase inhibitors (NNRTIs). Phenotypic resistance testing is generally reserved for cases of complex NRTI-resistance patterns in patients with limited treatment options (see Drug-Resistance Testing in the Adult and Adolescent Guidelines). At some institutions, testing for INSTI resistance may require a separate order.

Incidence and Significance of Antiretroviral Drug Resistance in Pregnancy

The development of ARV drug resistance is one of the major factors leading to therapeutic failure in individuals living with HIV. In addition, pre-existing resistance to a drug in an ART regimen may diminish the regimen's efficacy in preventing perinatal transmission. Infant treatment options also may be limited if maternal drug resistance is present (or develops) and resistant virus is transmitted to the fetus. Resistance to ARV drugs appears to be more common in women who acquired HIV perinatally than in other women with HIV.[7] The complexities of managing pregnant women with perinatally acquired HIV warrant consultation with an expert in HIV.

Several factors that are unique to pregnancy may increase the risk of developing resistance. Problems such as nausea and vomiting in early pregnancy may compromise adherence and increase the risk of developing resistance in women receiving ARV drugs. Pharmacokinetic changes during pregnancy, such as increased plasma volume and renal clearance, may lead to sub-therapeutic drug levels, increasing the risk that resistance will develop.

Impact of Resistance on the Risk of Perinatal Transmission of HIV and Maternal Response to Subsequent Therapy

Perinatal Transmission

There is little evidence that the presence of resistance mutations increases the risk of transmission when current recommendations for ARV management in pregnancy are followed. A sub-study of the Women and Infants Transmission Study followed pregnant women receiving zidovudine alone for treatment of HIV in the early 1990s. In this study, detection of zidovudine resistance conferred an increased risk of transmission when analysis was adjusted for duration of membrane rupture and total lymphocyte count;[8] however, women in this cohort had characteristics that would indicate a need for ART under current recommendations from the Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission (the Panel). When transmitting mothers had mixed viral populations of wild-type virus and virus with low-level zidovudine resistance, only wild-type virus was detected in their infants with HIV.[9] Other studies have suggested that drug-resistance mutations may diminish viral fitness,[10] possibly leading to a decrease in transmissibility.

Neither resistance to NNRTI drugs that develops as a result of exposure to single-dose nevirapine nor exposure to single-dose nevirapine in a prior pregnancy has been shown to affect perinatal transmission rates.[11]

Although perinatal exposure to ARVs has not been found to be associated with a significant risk for the presence of resistance, the prevalence of ARV drug resistance among newborns diagnosed with HIV in New York State was 11 of 91 infants (12.1%) born between 1989 and 1999 and 8 of 42 (19%) infants born between 2001 and 2002.[12,13] Thus, for infants with HIV, there is a high risk of ARV drug resistance.

Maternal Response to Subsequent Treatment Regimens

The French Perinatal Cohort evaluated the association between exposure to ARV drugs to prevent perinatal transmission during a previous pregnancy and presence of a detectable viral load with exposure to ARV drugs during the current pregnancy in women followed between 2005 and 2009.[14] Among 1,166 women who were not receiving ARV drugs at the time of conception, 869 were ARV-naive and 247 had received ARV drugs to prevent perinatal transmission during a previous pregnancy. Previous ARV prophylaxis was PI-based in 48% of these women, non-PI-based in 4%, NRTI dual ARV drugs in 19%, and zidovudine as a single ARV drug in 29%. A PI-based ART regimen was initiated in 90% of the women during the current pregnancy; in multivariate analysis, ARV exposure during a prior pregnancy was not associated with detectable viral load in the current pregnancy. A separate study (ACTG A5227) evaluated viral suppression in 52 women with prior combination ARV exposure to prevent perinatal transmission who had stopped ARV drugs at least 24 weeks before study entry and were now initiating ART (efavirenz, tenofovir disoproxil fumarate, and emtricitabine) for treatment.[15] None of the women had prior or recent resistance detected on standard bulk genotyping. Viral suppression was observed in 81% of women after 24 weeks of follow-up, with no difference in response by number of prior ARV drug exposures to prevent perinatal transmission or the drug class of prior exposure. Recent clinical series have confirmed this observation.[16,17]

Management of Antiretroviral Drug Resistance during Pregnancy

For women who have documented zidovudine resistance and whose antepartum regimen does not include zidovudine, intravenous (IV) zidovudine still should be given during labor when indicated (for HIV RNA >1,000 copies/mL near delivery; see Intrapartum Antiretroviral Therapy/Prophylaxis). Other ARVs should be continued orally during labor to the extent possible. The rationale for including zidovudine intrapartum when a woman is known to harbor virus with zidovudine resistance is based on several factors. Only wild-type virus appears to be transmitted to infants by mothers who have mixed populations of wild-type virus and virus with low-level zidovudine resistance.[9] Other studies have suggested that drug-resistance mutations may diminish viral fitness and possibly decrease transmissibility.[10] The efficacy of the zidovudine prophylaxis appears to be based not only on a reduction in maternal HIV viral load but also on the use of pre- and post-exposure prophylaxis in the infant.[18-20] Zidovudine crosses the placenta readily and has a high cord-to-maternal-blood ratio. In addition, zidovudine is metabolized to the active triphosphate within the placenta,[21,22] which may provide additional protection against transmission. Zidovudine penetrates the central nervous system (CNS) better than other nucleoside analogues except stavudine, which has similar CNS penetration; this may help eliminate a potential reservoir for transmitted HIV in the infant.[23,24] Thus, intrapartum IV administration of zidovudine, when indicated, is recommended even in the presence of known zidovudine resistance, due to the drug's unique characteristics and its proven record in reducing perinatal transmission.

The optimal prophylactic regimen for newborns of women with ARV drug-resistant virus is unknown. Therefore, ARV prophylaxis for infants born to women with known or suspected drug-resistant virus should be determined with the help of a pediatric HIV specialist, preferably before delivery (see Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV). There is no evidence that neonatal prophylaxis regimens that have been customized based on the presence of maternal drug resistance are more effective than standard neonatal prophylaxis regimens.

Prevention of Antiretroviral Drug Resistance

The most effective way to prevent development of ARV drug resistance in pregnancy is to adhere to an effective ARV regimen that achieves maximal viral suppression.

Several studies have demonstrated that women's adherence to ART may worsen during the postpartum period.[25-30]

Previous versions of the Perinatal Guidelines have provided guidance for clinicians in cases where women stop their ART regimen postpartum. However, the Panel strongly recommends that ART, once initiated, not be discontinued. If a woman desires to discontinue ART after delivery, a consultation with an HIV specialist is strongly recommended (see Discontinuation or Interruption of Antiretroviral Therapy in the Adult and Adolescent Guidelines).

References

1. PHACS/SMARTT. Annual Administrative Report. 2017. Available at: https://phacsstudy.org/cms_uploads/Latest%20Documents/SMARTT_Annual_Administrative_Report_Apr2017_web.pdf.
2. Stekler JD, McKernan J, Milne R, et al. Lack of resistance to integrase inhibitors among antiretroviral-naive subjects with primary HIV-1 infection, 2007–2013. *Antivir Ther*. 2015;20(1):77-80. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24831260.
3. Menza TW, Billock R, Samoff E, Eron JJ, Dennis AM. Pretreatment integrase strand transfer inhibitor resistance in North Carolina from 2010–2016. *AIDS*. 2017;31(16):2235-2244. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28991024.
4. Aldous AM, Castel AD, Parenti DM, D. C. Cohort Executive Committee. Prevalence and trends in transmitted and acquired antiretroviral drug resistance, Washington, DC, 1999–2014. *BMC Res Notes*. 2017;10(1):474. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28893321.
5. Abram ME, Ram RR, Margot NA, et al. Lack of impact of pre-existing T97A HIV-1 integrase mutation on integrase strand transfer inhibitor resistance and treatment outcome. *PLoS One*. 2017;12(2):e0172206. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28212411.
6. Koullias Y, Sax PE, Fields NF, Walensky RP, Hyle EP. Should we be testing for baseline integrase resistance in patients newly diagnosed with human immunodeficiency virus? *Clin Infect Dis*. 2017;65(8):1274-1281. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28605418.
7. Lazenby GB, Mmeje O, Fisher BM, et al. Antiretroviral resistance and pregnancy characteristics of women with perinatal and nonperinatal HIV infection. *Infect Dis Obstet Gynecol*. 2016;2016:4897501. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27413359.
8. Welles SL, Pitt J, Colgrove R, et al. HIV-1 genotypic zidovudine drug resistance and the risk of maternal--infant transmission in the women and infants transmission study. The women and infants transmission study group. *AIDS*. 2000;14(3):263-271. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10716502.
9. Colgrove RC, Pitt J, Chung PH, Welles SL, Japour AJ. Selective vertical transmission of HIV-1 antiretroviral resistance mutations. *AIDS*. 1998;12(17):2281-2288. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9863870.
10. Sheth PM, Kovacs C, Kemal KS, et al. Persistent HIV RNA shedding in semen despite effective antiretroviral therapy. *AIDS*. 2009;23(15):2050-2054. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19710596.
11. Martinson NA, Ekouevi DK, Dabis F, et al. Transmission rates in consecutive pregnancies exposed to single-dose nevirapine in Soweto, South Africa and Abidjan, Cote d'Ivoire. *J Acquir Immune Defic Syndr*. 2007;45(2):206-209. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17438480.
12. Parker MM, Wade N, Lloyd RM, Jr., et al. Prevalence of genotypic drug resistance among a cohort of HIV-infected newborns. *J Acquir Immune Defic Syndr*. 2003;32(3):292-297. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12626889.
13. Karchava M, Pulver W, Smith L, et al. Prevalence of drug-resistance mutations and non-subtype B strains among HIV-infected infants from New York State. *J Acquir Immune Defic Syndr*. 2006;42(5):614-619. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16868498.

14. Briand N, Mandelbrot L, Blanche S, et al. Previous antiretroviral therapy for prevention of mother-to-child transmission of HIV does not hamper the initial response to PI-based multitherapy during subsequent pregnancy. *J Acquir Immune Defic Syndr*. 2011;57(2):126-135. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21436712.

15. Vogler MA, Smeaton LM, Wright RL, et al. Combination antiretroviral treatment for women previously treated only in pregnancy: week 24 results of AIDS clinical trials group protocol a5227. *J Acquir Immune Defic Syndr*. 2014;65(5):542-550. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24759064.

16. Aziz N, Sokoloff A, Kornak J, et al. Time to viral load suppression in antiretroviral-naive and -experienced HIV-infected pregnant women on highly active antiretroviral therapy: implications for pregnant women presenting late in gestation. *BJOG*. 2013. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23924192.

17. Boltz VF, Bao Y, Lockman S, et al. Low-frequency nevirapine (NVP)-resistant HIV-1 variants are not associated with failure of antiretroviral therapy in women without prior exposure to single-dose NVP. *J Infect Dis*. 2014. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24443547.

18. Sperling RS, Shapiro DE, Coombs RW, et al. Maternal viral load, zidovudine treatment, and the risk of transmission of human immunodeficiency virus type 1 from mother to infant. Pediatric AIDS clinical trials group protocol 076 study group. *N Engl J Med*. 1996;335(22):1621-1629. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8965861.

19. Wade NA, Birkhead GS, Warren BL, et al. Abbreviated regimens of zidovudine prophylaxis and perinatal transmission of the human immunodeficiency virus. *N Engl J Med*. 1998;339(20):1409-1414. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9811915.

20. Melvin AJ, Burchett SK, Watts DH, et al. Effect of pregnancy and zidovudine therapy on viral load in HIV-1-infected women. *J Acquir Immune Defic Syndr Hum Retrovirol*. 1997;14(3):232-236. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9117455.

21. Qian M, Bui T, Ho RJ, Unadkat JD. Metabolism of 3'-azido-3'-deoxythymidine (AZT) in human placental trophoblasts and Hofbauer cells. *Biochem Pharmacol*. 1994;48(2):383-389. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8053935.

22. Sandberg JA, Binienda Z, Lipe G, et al. Placental transfer and fetal disposition of 2',3'-dideoxycytidine and 2',3'-dideoxyinosine in the rhesus monkey. *Drug Metabolism Dispos*. 1995;23(8):881-884. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7493557.

23. Peters PJ, Stringer J, McConnell MS, et al. Nevirapine-associated hepatotoxicity was not predicted by CD4 count ≥250 cells/μL among women in Zambia, Thailand and Kenya. *HIV Med*. 2010;11(10):650-660. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20659176.

24. Thomas SA. Anti-HIV drug distribution to the central nervous system. *Curr Pharm Des*. 2004;10(12):1313-1324. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15134483.

25. Cohn SE, Umbleja T, Mrus J, Bardeguez AD, Andersen JW, Chesney MA. Prior illicit drug use and missed prenatal vitamins predict nonadherence to antiretroviral therapy in pregnancy: adherence analysis A5084. *AIDS Patient Care STDS*. 2008;22(1):29-40. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18442305.

26. Bardeguez AD, Lindsey JC, Shannon M, et al. Adherence to antiretrovirals among US women during and after pregnancy. *J Acquir Immune Defic Syndr*. 2008;48(4):408-417. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18614923.

27. Mellins CA, Chu C, Malee K, et al. Adherence to antiretroviral treatment among pregnant and postpartum HIV-infected women. *AIDS Care*. 2008;20(8):958-968. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18608073.

28. Rana AI, Gillani FS, Flanigan TP, Nash BT, Beckwith CG. Follow-up care among HIV-infected pregnant women in Mississippi. *J Womens Health (Larchmt)*. 2010;19(10):1863-1867. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20831428.

29. Anderson J. Women and HIV: motherhood and more. *Curr Opin Infect Dis*. 2012;25(1):58-65. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22156896.

30. Nachega JB, Uthman OA, Anderson J, et al. Adherence to antiretroviral therapy during and after pregnancy in low-income, middle-income, and high-income countries: a systematic review and meta-analysis. *AIDS*. 2012;26(16):2039-2052. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22951634.

Lack of Viral Suppression (Last updated December 7, 2018; last reviewed December 7, 2018)

Panel's Recommendations

• Because maternal antenatal viral load correlates with the risk of perinatal transmission of HIV, suppression of HIV RNA to undetectable levels should be achieved as rapidly as possible **(AII)**.
• If an ultrasensitive HIV RNA assay indicates failure of viral suppression (after an adequate period of treatment):
  • If HIV RNA level is >500 copies/mL, assess medication adherence, adherence to food requirements, and possible drug interactions and perform tests for resistance **(AII)**.
  • Consult an HIV treatment expert and consider possible antiretroviral regimen modification **(AIII)**.
• Scheduled cesarean delivery at 38 weeks' gestation is recommended for pregnant women living with HIV who have HIV RNA levels >1,000 copies/mL near the time of delivery **(AII)**.

Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*
Rating of Evidence: *I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

Virologic suppression is defined as a confirmed HIV RNA level that is below the lower limits of detection of an ultrasensitive assay, and virologic failure is the inability to achieve or maintain an HIV RNA level <200 copies/mL. Baseline HIV RNA levels have been shown to affect the time to response in both pregnant and nonpregnant individuals, with no difference in time to response between pregnant and nonpregnant women.[1,2] In women living with HIV who participated in three prospective studies from seven African countries and became pregnant after antiretroviral therapy (ART) initiation, incident pregnancy did not affect time to viral suppression or time to virologic failure.[3] HIV RNA levels should be assessed 2 to 4 weeks after an antiretroviral (ARV) drug regimen is initiated or changed to provide an initial assessment of effectiveness.[4] Most patients with an adequate viral response at 24 weeks of treatment have had at least a 1 log decrease in HIV RNA within 1 to 4 weeks after starting therapy.[4] Suppression of HIV RNA to undetectable levels should be achieved as rapidly as possible, because maternal antenatal HIV RNA level correlates with the risk of perinatal transmission of HIV. In addition, an analysis from the Women's Interagency HIV Study cohort found that higher viral loads were associated with an increased risk of pregnancy loss (miscarriage or stillbirth).[5]

Poor adherence is frequently associated with lack of virologic suppression, and this issue should be addressed when viral load does not decline as expected. A systematic review and meta-analysis of adherence to ART) during and after pregnancy in low-, middle-, and high-income countries (27% of studies were from the United States) found that only 73.5% of pregnant women achieved adequate (>80%) ART adherence.[6] Evaluation of and support for adherence during pregnancy is critical to achieving and maintaining maximal viral suppression.

The lack of virologic suppression by late pregnancy may indicate virologic failure, but it may also represent inadequate time on ART. In a retrospective multicenter cohort of 378 pregnant women, 77.2% achieved HIV RNA <50 copies/mL by delivery, with success of viral suppression varying by baseline HIV RNA level. For women with baseline HIV RNA levels <10,000 copies/mL, the gestational age of their infants at ART initiation did not affect success of viral suppression up to 26.3 weeks. In women with baseline >10,000 copies/mL, however, delaying initiation past 20.4 weeks significantly reduced the ability to achieve maximal suppression at delivery.[1] Among 1,070 treatment-naive pregnant women with HIV who participated in IMPAACT P1025, a prospective cohort study, initiation of ART at >32 weeks' gestation was also associated with a significantly higher risk of having viral load >400 copies/mL at delivery.[7] A report from the French Perinatal Cohort found no perinatal transmission among 2,651 infants born to women who were receiving ART before conception, continued ART throughout pregnancy, and delivered with a plasma HIV RNA <50 copies/mL (upper limits of CI, 0.1%). In the entire cohort of 8,075 mother/infant pairs followed from 2000 through 2011, HIV RNA level and timing of ART initiation were independently associated with perinatal transmission in a logistic regression analysis.[8]

The response to ART may also be affected by other factors. A prospective study recorded serial measures of plasma HIV RNA and CD4 T lymphocyte (CD4) counts after non-nucleoside reverse transcriptase inhibitor-based ART was initiated in 25 women with acute HIV infection and 30 women with chronic HIV infection in Kenya. The mean baseline HIV viral load was similar among women with acute HIV and women with chronic infection after adjustment for baseline CD4 count, but the rate of viral decline following ART initiation was significantly slower among women with acute HIV infection.[9] Strategies to accelerate viral decline may be considered in this situation, though these strategies should be discussed with HIV treatment experts (see Acute HIV Infection). In a population-based surveillance study in the United Kingdom and Ireland that compared 70 pregnancies in 45 women with perinatally acquired HIV and 184 pregnancies in 118 women with horizontally-acquired HIV, perinatal HIV in the mother was a risk factor for detectable viral load near delivery, reflecting complex clinical, psychosocial, adherence, and resistance issues.[10] If needed, ART regimens should be optimized in consultation with HIV treatment experts and attention should be given to other possible contributing factors (see The Management of Prenatal Care and General Principles of Antiretroviral Therapy and HIV Management in Women with Perinatal HIV Infection).

A three-pronged approach is indicated for managing women on ART regimens who have suboptimal suppression of HIV RNA, taking time on treatment into account. The three steps are:

- Assessment of adherence, tolerability, correct dosing, or potential problems with absorption (e.g., nausea/vomiting, gastroesophageal reflux disease [GERD], lack of attention to food requirements);
- ARV drug resistance studies if plasma HIV RNA is above the threshold for resistance testing, generally >500 copies/mL; and
- Consideration of ART regimen modification (see Pregnant Women Living with HIV Who Are Currently Receiving Antiretroviral Therapy and Table 7).

The role of therapeutic drug monitoring (TDM) in reducing the risk of virologic failure is still undefined.[11] In a cohort of pregnant women with HIV, 66 (39%) had TDM.[12] Comparing women who did and did not have TDM, multivariate analysis found that TDM was associated with medication alterations during pregnancy but was not associated with any difference in viral breakthrough during pregnancy or detectable viral load at birth; there were no transmissions in either group.

Experts with experience in caring for ARV-experienced adults should be consulted, particularly if a change in drug regimen is necessary due to resistance or adverse effects. Regimen simplification may be considered to promote better adherence. Other possible interventions include adherence education, treatment of problems that may interfere with drug absorption such as vomiting, taking ART in accordance with food requirements, and directly-observed drug administration in the home or hospital setting (See Table 10).[13]

Among 662 pregnancies that were followed in Italy between 2001 and 2008, treatment modification during pregnancy was independently associated with an HIV-1 RNA level >400 copies/mL in late pregnancy (adjusted odds ratio, 1.66; 95% CI, 1.07–2.57; $P = 0.024$), highlighting the importance of using potent and well-tolerated regimens during pregnancy to maximize effectiveness and minimize the need to modify treatment.[14] These findings also highlight the importance of avoiding changing effective ARV regimens whenever possible in women who become pregnant on ART (see Pregnant Women Currently Receiving ART).

The integrase strand transfer inhibitor (INSTI) class of drugs has been associated with rapid viral load reduction. Raltegravir has been shown to reduce viral load by approximately 2 log copies/mL by week 2 of therapy in ART-naive patients.[15,16] Because of these data, the addition of raltegravir or another INSTI in late pregnancy has been suggested for women who have high viral loads and/or in whom multiple drug-resistant mutations have resulted in incomplete suppression of viremia.[17-19] However, the efficacy and safety of this approach during pregnancy have not been evaluated in clinical trials, and only case series and two retrospective cohorts are available, primarily involving raltegravir.[20-22] In a recent retrospective study from Argentina, 13 women had raltegravir added to a standard PI-based ART regimen after their initial regimen failed to achieve viral suppression. The mean gestational age at raltegravir initiation was 33 weeks

(range: 29–37 weeks) and median exposure was 25.5 days (range: 7–43 days); 70% of women achieved viral suppression (<50 copies/mL) prior to delivery, with a median viral decay of 1.48 log. In the same study, 15 women had raltegravir added to a standard PI-based regimen due to late presentation; the mean gestational age at raltegravir initiation was 34 weeks (range: 33–36 weeks), baseline viral load was 12,217 copies/mL (range: 3,881–40,310 copies/mL) and median exposure was 30 days (range: 7–30 days). Prior to delivery, 45.5% of women achieved viral suppression with a median viral decay of 2.15 log.[22]

Including raltegravir or dolutegravir as part of an ART regimen for women who have never been on ART and present late in pregnancy with high viral loads may be considered to more rapidly reduce viral load and decrease risk of perinatal transmission. (See Pregnant Women Living with HIV Who Have Never Received ARV Drugs, Table 6, and Table 7.) However, in the setting of a failing regimen related to nonadherence and/or resistance, there are concerns that the addition of a single agent may further increase risk of resistance and potential loss of future effectiveness. In addition, when poor adherence is the reason for viremia, it is unclear that adding a new drug to the existing regimen will improve adherence. Currently, there are insufficient data to recommend adding an INSTI to a failing ART regimen for women in late pregnancy.

There have been two reports of marked elevations in transaminase levels following introduction of a raltegravir-containing regimen in late pregnancy, with these levels returning to normal after discontinuation.[20,23] Furthermore, data in 19 mother-infant pairs enrolled in a multicenter trial to determine washout pharmacokinetics and safety of *in utero*/intrapartum exposure to raltegravir found that, while raltegravir readily crossed the placenta, elimination was highly variable and extremely prolonged in some infants, raising potential infant safety concerns.[24]

A recent retrospective study of 318 pregnant women addressed the risk of viral rebound in pregnancy among women who received ART for ≥4 weeks and who had had ≥1 prior undetectable viral load. Nineteen women (6%) had viral rebound (HIV RNA >50 copies/mL) within 1 month before delivery; six of these 19 women had viral loads above 1,000 copies/mL. Significant predictors of viral rebound included cocaine use and positive hepatitis C virus (HCV) RNA.[25] Viral load testing is currently recommended at 34 to 36 weeks gestation for delivery planning; providers may consider repeat testing subsequently in selected women who are at increased risk for viral rebound.

Scheduled cesarean delivery at 38 weeks' gestation is recommended for pregnant women living with HIV who have HIV RNA levels >1,000 copies/mL near the time of delivery (see Transmission and Mode of Delivery).[26,27]

References

1. Read PJ, Mandalia S, Khan P, et al. When should HAART be initiated in pregnancy to achieve an undetectable HIV viral load by delivery? *AIDS*. 2012;26(9):1095-1103. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22441248.
2. Rachas A, Warszawski J, Le Chenadec J, et al. Does pregnancy affect the early response to cART? *AIDS*. 2013;27(3):357-367. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23079802.
3. Kourtis AP, Wiener J, King CC, et al. Effect of pregnancy on response to antiretroviral therapy in HIV-infected African women. *J Acquir Immune Defic Syndr*. 2017;74(1):38-43. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27787340.
4. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV. 2018. Available at: http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf.
5. Cates JE, Westreich D, Edmonds A, et al. The effects of viral load burden on pregnancy loss among HIV-infected women in the United States. *Infect Dis Obstet Gynecol*. 2015;2015:362357. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26582966.
6. Nachega JB, Uthman OA, Anderson J, et al. Adherence to antiretroviral therapy during and after pregnancy in low-income, middle-income, and high-income countries: a systematic review and meta-analysis. *AIDS*. 2012;26(16):2039-2052. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22951634.
7. Katz IT, Leister E, Kacanek D, et al. Factors associated with lack of viral suppression at delivery among highly active antiretroviral therapy-naive women with HIV: a cohort study. *Ann Intern Med*. 2015;162(2):90-99. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25599347.
8. Mandelbrot L, Tubiana R, Le Chenadec J, et al. No perinatal HIV-1 transmission from women with effective antiretroviral

therapy starting before conception. *Clin Infect Dis*. 2015. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26197844.

9. Drake AL, Kinuthia J, Matemo D, et al. ART response among pregnant and postpartum women with acute versus chronic HIV-1. Presented at: 22nd Conference on Retroviruses and Opportunistic Infections. 2015. Seattle, WA.

10. Byrne L, Sconza R, Foster C, Tookey PA, Cortina-Borja M, Thorne C. Pregnancy incidence and outcomes in women with perinatal HIV infection. *AIDS*. 2017;31(12):1745-1754. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28590327.

11. Matsui DM. Therapeutic drug monitoring in pregnancy. *Ther Drug Monit*. 2012;34(5):507-511. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22846897.

12. Whitfield T, Dessain A, Taylor K, McQuillan O, Kingston M, Ajdukiewicz K. Retrospective analysis of the associations and effectiveness of performing therapeutic drug monitoring in pregnant HIV-positive women in two large centres in Manchester. *Int J STD AIDS*. 2017;28(5):499-504. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27335118.

13. McCabe CJ, Goldie SJ, Fisman DN. The cost-effectiveness of directly observed highly-active antiretroviral therapy in the third trimester in HIV-infected pregnant women. *PLoS One*. 2010;5(4):e10154. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20405011.

14. Floridia M, Ravizza M, Pinnetti C, et al. Treatment change in pregnancy is a significant risk factor for detectable HIV-1 RNA in plasma at end of pregnancy. *HIV Clin Trials*. 2010;11(6):303-311. Available at: http://www.ncbi.nlm.nih.gov/pubmed/212393588.

15. Markowitz M, Morales-Ramirez JO, Nguyen BY, et al. Antiretroviral activity, pharmacokinetics, and tolerability of MK-0518, a novel inhibitor of HIV-1 integrase, dosed as monotherapy for 10 days in treatment-naive HIV-1-infected individuals. *J Acquir Immune Defic Syndr*. 2006;43(5):509-515. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17133211.

16. Lennox JL, DeJesus E, Lazzarin A, et al. Safety and efficacy of raltegravir-based versus efavirenz-based combination therapy in treatment-naive patients with HIV-1 infection: a multicentre, double-blind randomised controlled trial. *Lancet*. 2009;374(9692):796-806. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19647866.

17. Grinsztejn B, Nguyen BY, Katlama C, et al. Safety and efficacy of the HIV-1 integrase inhibitor raltegravir (MK-0518) in treatment-experienced patients with multidrug-resistant virus: a Phase II randomised controlled trial. *Lancet*. 2007;369(9569):1261-1269. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17434401.

18. Papendorp SG, van den Berk GE. Preoperative use of raltegravir-containing regimen as induction therapy: very rapid decline of HIV-1 viral load. *AIDS*. 2009;23(6):739. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19279447.

19. 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.

20. Boucoiran I, Tulloch K, Pick N, et al. A case series of third-trimester raltegravir initiation: Impact on maternal HIV-1 viral load and obstetrical outcomes. *Can J Infect Dis Med Microbiol*. 2015;26(3):145-150. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26236356.

21. 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.

22. Cecchini DM, Martinez MG, Morganti LM, Rodriguez CG. Antiretroviral therapy containing raltegravir to prevent mother-to-child transmission of HIV in infected pregnant women. *Infect Dis Rep*. 2017;9(2):7017. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28663779.

23. Renet S, Closon A, Brochet MS, Bussieres JF, Boucher M. Increase in transaminase levels following the use of raltegravir in a woman with a high HIV viral load at 35 weeks of pregnancy. *J Obstet and Gynaecol Can*. 2013;35(1):68-72. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23343800.

24. Clarke DF, Acosta EP, Rizk ML, et al. Raltegravir pharmacokinetics in neonates following maternal dosing. *J Acquir Immune Defic Syndr*. 2014;67(3):310-315. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25162819.

25. Boucoiran I, Albert AYK, Tulloch K, et al. Human immunodeficiency virus viral load rebound near delivery in previously suppressed, combination antiretroviral therapy-treated pregnant women. *Obstet Gynecol*. 2017;130(3):497-501. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28796673.

26. International Perinatal HIV Group, Andiman W, Bryson Y, et al. The mode of delivery and the risk of vertical transmission of human immunodeficiency virus type 1--a meta-analysis of 15 prospective cohort studies. *N Engl J Med*. 1999;340(13):977-987. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10099139.

27. European Mode of Delivery Collaboration. Elective caesarean-section versus vaginal delivery in prevention of vertical HIV-1 transmission: a randomised clinical trial. *Lancet*. 1999;353(9158):1035-1039. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10199349.

Stopping Antiretroviral Drugs during Pregnancy (Last updated December 7, 2018; last reviewed December 7, 2018)

Panel's Recommendations
• If an antiretroviral (ARV) drug regimen must be stopped during pregnancy (e.g., for severe toxicity), all ARV drugs should be stopped simultaneously, and antiretroviral therapy should be reinitiated as soon as possible **(AIII)**.
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*

Discontinuation of antiretroviral (ARV) drug regimens during pregnancy may be indicated in some situations, including serious drug-related toxicity, pregnancy-induced hyperemesis that is unresponsive to antiemetics, or acute illnesses or planned surgeries that preclude oral intake. Other reasons for discontinuation of ARV drug regimens during pregnancy include lack of available medication or patient request. If an ARV drug regimen must be stopped for any reason, all ARV drugs should be stopped simultaneously and antiretroviral therapy (ART) should be reinitiated as soon as possible, whether restarting the same regimen or a new regimen.

Discontinuation of therapy could lead to an increase in viral load, with possible disease progression and decline in immune status. There may also be adverse consequences for the fetus, including increased risk of *in utero* transmission of HIV. An analysis from a prospective cohort of 937 mother-child pairs found that interruption of ART during pregnancy, including interruption in the first and third trimesters, was independently associated with perinatal transmission of HIV. In the first trimester, the median time at interruption was 6 weeks' gestation and length of time without therapy was 8 weeks (interquartile range [IQR], 7–11 weeks); in the third trimester, the median time at interruption was 32 weeks and length of time without therapy was 6 weeks (IQR, 2–9 weeks). Although the perinatal transmission rate for the entire cohort was only 1.3%, transmission occurred in 4.9% of mother-child pairs (95% CI, 1.9% to 13.2%; adjusted odds ratio [aOR] 10.33; $P = 0.005$) with first-trimester interruption and 18.2% (95% CI, 4.5% to 72.7%; aOR 46.96; $P = 0.002$) with third-trimester interruption.[1]

Continuation of all drugs during the intrapartum period generally is recommended. Women who are having elective cesarean delivery can take oral medications before the procedure and restart drugs following surgery. Because most drugs are given once or twice daily, it is likely that no doses would be missed or that the postpartum dose would be given a few hours late at most.

Efavirenz can be detected in blood for longer than 3 weeks after discontinuation.[2,3] If an efavirenz-containing regimen must be stopped for more than a few days due to toxicity, clinicians should consider assessing the patient for rebound viremia and potential drug resistance.[4]

In the rare case in which a woman has limited oral intake that does not meet food requirements for certain ARV agents, decisions about the ART administered during the antepartum or intrapartum period should be made on an individual basis and in consultation with an HIV treatment expert and a clinical pharmacologist who is experienced with ARV medications.

References

1. Galli L, Puliti D, Chiappini E, et al. Is the interruption of antiretroviral treatment during pregnancy an additional major risk factor for mother-to-child transmission of HIV type 1? *Clin Infect Dis*. 2009;48(9):1310-1317. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19309307.

2. Sadiq ST, Fredericks S, Khoo SH, Rice P, Holt DW. Efavirenz detectable in plasma 8 weeks after stopping therapy and subsequent development of non-nucleoside reverse transcriptase inhibitor-associated resistance. *AIDS*. 2005;19(15):1716-1717. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16184054.

3. Ribaudo HJ, Haas DW, Tierney C, et al. Pharmacogenetics of plasma efavirenz exposure after treatment discontinuation: an Adult AIDS Clinical Trials Group Study. *Clin Infect Dis*. 2006;42(3):401-407. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16392089.

4. Geretti AM, Fox Z, Johnson JA, et al. Sensitive assessment of the virologic outcomes of stopping and restarting non-nucleoside reverse transcriptase inhibitor-based antiretroviral therapy. *PLoS One*. 2013;8(7):e69266. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23874928.

Special Populations: Hepatitis B Virus/HIV Coinfection (Last updated December 7, 2018; last reviewed December 7, 2018)

Panel's Recommendations

- All pregnant women living with HIV should be screened during the current pregnancy for
  1. Hepatitis B virus (HBV) infection, unless they are known to have HBV/HIV coinfection or serologic documentation of HBV immunity coinfection, *and*
  2. Hepatitis C virus (HCV) infection, unless they are already known to have HCV/HIV coinfection (see Hepatitis C Virus/HIV Coinfection) **(AIII)**.
- All pregnant women living with HIV who screen negative for HBV (i.e., HBV surface antigen negative, HBV core antibody negative, and HBV surface antibody negative) should receive the HBV vaccine series **(AII)**.
- Women with chronic HBV infection who have not already received the hepatitis A virus (HAV) vaccine series should be screened for immunity to HAV. If they screen negative for HAV immunoglobulin G antibody, they should receive the HAV vaccine series **(AIII)**.
- All pregnant and postpartum women with HBV/HIV coinfection should receive antiretroviral therapy (ART). Antepartum ART in pregnant women with HBV/HIV coinfection should include tenofovir disoproxil fumarate (TDF) plus lamivudine or emtricitabine **(AI)**. If a woman with HBV/HIV coinfection becomes pregnant while virally suppressed on an antiretroviral (ARV) regimen that includes tenofovir alafenamide (TAF) plus lamivudine or emtricitabine, she can be offered the choice of continuing that ART regimen or switching TAF to TDF in her ART regimen **(BIII)**.
- Pregnant women with HBV/HIV coinfection who are receiving ARV drugs should be counseled about signs and symptoms of liver toxicity, and liver transaminases should be assessed 1 month following initiation of ART and at least every 3 months thereafter during pregnancy **(BIII)**.
- Women with chronic HBV should be counseled on the importance of continuing anti-HBV medications indefinitely, both during and after pregnancy. If ARV drugs that include anti-HBV activity are discontinued in women with HBV/HIV coinfection, frequent monitoring of liver function tests for potential exacerbation of HBV infection is recommended, with prompt re-initiation of treatment for HBV when a flare is suspected (**BIII**).
- Decisions concerning mode of delivery of the infant in a pregnant woman with HBV/HIV coinfection should be based on standard obstetric and HIV-related indications alone; HBV/HIV coinfection does not necessitate a cesarean delivery if not otherwise indicated (see Transmission and Mode of Delivery) **(AIII)**.
- Within 12 hours of birth, infants born to women with HBV infection should receive hepatitis B immune globulin and the first dose of the HBV vaccine series **(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*

For additional information on hepatitis B virus (HBV) and HIV, see Hepatitis B Virus/HIV Coinfection in the Adult and Adolescent Guidelines[1] and Hepatitis B Virus Infection in the Adult and Adolescent Opportunistic Infections Guidelines.[2] The management of HBV/HIV coinfection in pregnancy is complex, and consultation with an expert in HIV and HBV infection is strongly recommended.

Screening and Vaccination

All women living with HIV should be screened for HBV and hepatitis C virus (HCV) at entry into general HIV care. All pregnant women living with HIV should be screened during each pregnancy for HBV, unless they are known to have HBV/HIV coinfection or serologic documentation of HBV immunity, and for HCV, unless they are known to have HCV/HIV coinfection. Screening for HBV should include hepatitis B surface antigen (HBsAg), hepatitis B core antibody (anti-HBc), and hepatitis B surface antibody (anti-HBs). Women who test positive for HBsAg should have follow-up testing to evaluate liver function, prothrombin time, and levels of HBV DNA, HB e antigen, and HB e antibody.[1]

To prevent horizontal transmission of HIV and HBV from women with HBV/HIV coinfection to their male partners, their sexual contacts should be counseled and tested for HIV and HBV. All HBV-susceptible contacts should receive the HBV vaccine series, and all partners who do not have HIV infection should be

counseled about condom use and the potential benefits and risks of starting pre-exposure prophylaxis.[2,3]

Pregnant women living with HIV who screen negative for HBV (i.e., HBsAg negative, anti-HBc negative, and anti-HBs negative) should receive the HBV vaccine series. Women living with HIV who have remote HBV infection and current isolated anti-HBc antibody (they test negative for HBV DNA, HBsAg, and anti-HBs) may have lost immunity to HBV and should be vaccinated.[2] Women with HIV infection whose anti-HBs titers are below 10 IU/mL despite having received the HBV vaccine series should receive a second HBV vaccine series; some experts advise using a double dose of HBV vaccine (i.e., a 40-mg dose) and delaying revaccination until after a sustained increase in CD4 T lymphocyte (CD4) cell count >350 cells/mm^3 is achieved on antiretroviral therapy (ART).[2] There is no evidence that the hepatitis B vaccine causes adverse effects in developing fetuses or newborns, and current vaccines contain noninfectious HBsAg.[4] Anti-HBs titers should be obtained 1 month after completion of the vaccine series in patients with HIV infection; if anti-HBs titers are below 10 IU/mL, a second vaccine series is recommended (some specialists delay revaccination until after a sustained increase in CD4 cell count >350 cells/mm^3 is achieved on ART). There is no consensus on how to manage patients whose anti-HBs titers remain below 10 IU/mL following a second HBV vaccine series.[2]

A positive test for anti-HBc alone can be a false positive; alternatively, it may signify remote infection with subsequent loss of anti-HBs antibody or longstanding chronic HBV infection with loss of surface antigen ("occult" HBV infection, which can be confirmed by detection of HBV DNA).[5,6] Incidence of HBV viremia with the isolated anti-HBc pattern ranges from 1% to 36% in patients with HIV. The clinical significance of isolated anti-HBc is unknown.[7,8] Some experts recommend that individuals with HIV infection and anti-HBc alone be tested for HBV DNA to inform decisions about vaccination for HBV and treatment with antiretroviral (ARV) drugs. It may also be important to test for HIV DNA levels in women with isolated anti-HBc, since those with detectable HBV DNA levels are at risk for developing a paradoxical exacerbation of HBV and the occurrence of immune reconstitution inflammatory syndrome (IRIS). Pregnant women with HIV infection with isolated anti-HBc and occult HBV infection typically have very low levels of HBV DNA and are thought to be at extremely low risk of transmitting HBV to their infants.[2,9]

Women who have HBV infection and who have not already received the hepatitis A virus (HAV) vaccine series should also be screened for HAV using antibody testing for immunoglobulin G (IgG), because there is an added risk of hepatic decompensation from acute infection with HAV in individuals with chronic HBV (note that some labs only provide a combined IgG and immunoglobulin M [IgM] HAV titer, which is acceptable). Women with chronic HBV infection who have not already received the HAV vaccine series and are HAV IgG antibody negative should receive the HAV vaccine series, which is safe in pregnancy. Responses to the HAV vaccine are reduced in patients living with HIV who have CD4 cell counts <200 cells/mm^3. Antibody response should be assessed in such patients 1 month after HAV vaccine series is complete. If HAV antibody immunoglobulin (HAV Ab IgG) is negative, patients should be revaccinated when the CD4 cell count is >200 cells/mm^3.[2] Women who have already received the HAV vaccine series when their CD4 cell count was ≥200 cells/mm^3 do not need to be revaccinated for HAV, because they are likely protected (even if their HAV IgG levels are undetectable using commercially available assays). Although the safety of HAV vaccination during pregnancy has not been directly evaluated, HAV vaccine is produced from inactivated HAV and the theoretical risk to the developing fetus is expected to be low.[4]

Outcomes of HIV/Hepatitis B Virus Coinfection in Pregnancy

A study of 4,236 pregnant women with HIV-1 in France who were followed between 2005 and 2013 found the prevalence of HBV (HBsAg positive) to be 6.2%; HBV/HIV coinfection was six times more frequent in pregnant women who were born in sub-Saharan Africa than in those who were born in France.[10] HBV/HIV coinfection was not associated with preterm delivery, lower CD4 cell counts, or HIV viral load in this cohort.[10] In a retrospective analysis of response to ART among 1,462 pregnant women with HIV, 12% of women had contracted both HBV/HIV.[11] In a multivariable analysis, women with HIV had better CD4 cell responses on ART during pregnancy than women with both HBV/HIV coinfection. However, no differences in maternal and infant outcomes were observed between women with HBV/HIV and women with HIV alone.

Therapy for HIV and Hepatitis B Virus in Pregnancy

An ART regimen that includes drugs that are active against both HIV and HBV is recommended for all individuals with HBV/HIV coinfection, including all pregnant women. Initiation of ART may be associated with reactivation of HBV and development of IRIS, particularly in patients with high HBV DNA levels and severe liver disease.[2,12] Risk of miscarriage[13] and preterm labor and delivery may increase[14] in people with acute HBV infection (see Hepatitis B Virus Infection in the Adult and Adolescent Opportunistic Infections Guidelines).

In addition, the use of ARV drugs with anti-HBV activity during pregnancy lowers HBV viremia and lowers the risk of HBV transmission to the infant. Lowering HBV viremia may reduce the risk of HBV transmission to an even greater extent than neonatal prophylaxis with hepatitis B immune globulin (HBIG) and hepatitis B vaccine.[15] High maternal HBV DNA levels are strongly correlated with perinatal HBV transmission and with failures of HBV passive-active immunoprophylaxis.[16-19] Several studies and a meta-analysis suggest that lamivudine or telbivudine may reduce the risk of perinatal transmission of HBV if given during the third trimester to HIV-seronegative women with HBV infection and high HBV DNA levels.[20-28] In addition to HBV viral load, the presence of certain HBV variants is also a risk factor for failure of HBV prophylaxis.[9,29] In a study of 2,048 pregnant women living with HIV in Malawi, 103 women (5%) were HBsAg positive, and 70 of those women also had HBV viremia. Nearly 10% of infants born to mothers with HBV/HIV coinfection had HBV DNA that was detected by age 48 weeks, despite being immunized according to national recommendations at ages 6, 10, and 14 weeks.[30]

Lamivudine, tenofovir disoproxil fumarate (TDF), tenofovir alafenamide (TAF, a prodrug of TDF), and emtricitabine have activity against both HIV and HBV. TDF or TAF with emtricitabine or lamivudine is the preferred dual nucleoside reverse transcriptase inhibitor backbone in women with HBV/HIV coinfection. However, only lamivudine, TDF, and emtricitabine are recommended for use in pregnancy (see Table 6). There is no pharmacokinetic information for TAF use in pregnancy, and there are few reports of TAF being used during pregnancy. In animal studies, however, there were no developmental effects when TAF was administered during the period of organogenesis at exposures that were either equal to or 51 times the usual therapeutic dosage (in rats and rabbits, respectively).[31,32] Cases of exposure during pregnancy to any of the ARV drugs and HBV drugs listed should be reported to the Antiretroviral Pregnancy Registry (online or by telephone at 1-800-258-4263).

Some pregnant women may already be receiving TAF-containing ART prior to pregnancy. TAF is effective against HBV in nonpregnant adults,[33-35] but has not been studied in pregnancy. In this case, the woman can be offered a choice of continuing that ART regimen or switching TAF to TDF in their ART regimen. Please see individual drug sections for TDF, TAF, emtricitabine, and lamivudine for detailed reviews of safety, pharmacologic, and other clinical data for use in pregnancy.

Consultation with an expert in HIV and HBV is strongly recommended for a pregnant woman with HBV/HIV coinfection who continues to have detectable HBV DNA viremia despite receiving an ART regimen that includes two anti-HBV nucleos(t)ides.

Several other antivirals with activity against HBV, including entecavir, adefovir, and telbivudine, have not been well evaluated in pregnancy. Entecavir is associated with skeletal anomalies in rats and rabbits but only at doses high enough to cause toxicity to the mother. Seventy-nine cases of exposure to entecavir, 77 during the first trimester and two during the second trimester, have been reported to the Antiretroviral Pregnancy Registry with no birth defects noted, but this number of exposures is too low to assess overall risk.[31] Seventy-nine cases of exposure to telbivudine have been reported to the Antiretroviral Pregnancy Registry, with 68 cases occurring during the first trimester, seven during the second trimester, and four during the third trimester. Telbivudine was given during the third trimester to 135 women with HBV infection and without HIV infection; it was well tolerated, and the incidence of perinatal transmission of HBV was lower in telbivudine-treated mothers than in the comparison group that did not receive telbivudine (0% vs. 8%; $P = 0.002$).[23,36] In a recent systematic review and meta-analysis of single-drug anti-HBV therapy during pregnancy in cases of

chronic HBV monoinfection, antiviral therapy reduced perinatal transmission with no significant differences in congenital malformation rate, prematurity rate, and Apgar scores. TDF, lamivudine, or telbivudine all improved maternal HBV viral suppression at delivery with no significant differences in postpartum hemorrhage, cesarean section or creatinine kinases levels.[37] For pregnant women with HBV/HIV coinfection, both entecavir and telbivudine should be administered only in addition to a fully suppressive ART regimen for HIV. Because these anti-HBV drugs also have weak activity against HIV, their use in the absence of a fully suppressive ART regimen may lead to development of cross-resistance to other ARV drugs (e.g., entecavir can select for the M184V mutation, which confers HIV resistance to lamivudine and emtricitabine). The Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents does not currently recommend the use of adefovir or telbivudine for patients with HBV/HIV coinfection, because these agents have lower potency than the preferred agents and are associated with certain adverse events—renal disease with adefovir-containing regimens, and myopathy and neuropathy with telbivudine-containing regimens.[2]

Interferon alfa and pegylated interferon alfa are not recommended for use during pregnancy and should be used only if the potential benefits outweigh the potential risks. Although interferons are not teratogenic, they are abortifacient at high doses in monkeys and should not be used in pregnant women because of their direct antigrowth and antiproliferative effects.[38]

Monitoring Women With HIV/Hepatitis B Virus Coinfection During Pregnancy

Prior to initiating ARV drugs that are active against HBV, a baseline HBV DNA level should be measured. After initiation of therapy, HBV DNA should be monitored every 12 weeks to ensure adequate response to therapy (see Hepatitis B Virus Infection in the Adult and Adolescent Opportunistic Infections Guidelines).

Following initiation of ART, an elevation in hepatic enzymes can occur in women with HBV/HIV coinfection—particularly those with low CD4 cell counts at the time of treatment initiation—as a result of an immune-mediated flare in HBV disease triggered by immune reconstitution with effective HIV therapy. HBV infection also can increase hepatotoxic risk of certain ARV drugs, specifically protease inhibitors and nevirapine. Pregnant women with HBV/HIV coinfection should be counseled about signs and symptoms of liver toxicity, and transaminases should be assessed 1 month following initiation of ARV drugs and at least every 3 months thereafter. If hepatic toxicity occurs, it may be necessary to consider substituting a less hepatotoxic regimen or, if clinical symptoms or significant elevations of transaminases occur, drugs may need to be temporarily discontinued. Differentiating between the effects of drug toxicity and a flare in HBV disease caused by immune reconstitution often can be difficult, and consultation with an expert in HIV and HBV coinfection is strongly recommended. Because TDF can potentially cause renal toxicity, kidney function also should be monitored regularly in pregnant women as in nonpregnant adults.

Once HBV therapy with anti-HBV nucleos(t)ide analogs is initiated, lifelong treatment is recommended.[1,2] Discontinuing anti-HBV agents may lead to reactivation of HBV, resulting in hepatocellular damage. If anti-HBV-active drugs are discontinued, serum transaminase levels should be monitored every 6 weeks for 3 months, then every 3 to 6 months thereafter, with prompt re-initiation of HBV treatment if a flare is suspected.[2]

Mode of Delivery

Decisions concerning mode of delivery in pregnant women with HBV/HIV coinfection should be based on standard obstetric and HIV-related indications alone (see Transmission and Mode of Delivery). There are no data on the role of cesarean delivery in reducing the risk of perinatal transmission of HBV in women with HBV/HIV coinfection. Current guidelines for women with HBV monoinfection advise that cesarean delivery is not indicated to prevent perinatal transmission of HBV.[39-41]

Evaluating and Managing Infants Exposed to Hepatitis B Virus

Within 12 hours of birth, all infants born to mothers with chronic HBV infection, including those with HIV, should receive HBIG and the first dose of the HBV vaccination series to prevent perinatal transmission

of HBV. For infants weighing ≥2,000 g at birth, the second and final doses of the vaccine series should be administered at ages 1 month and 6 months, respectively. For infants with birth weights <2,000 g, do not count the birth dose as part of the vaccine series and administer three additional doses at ages 1, 2 to 3, and 6 months.[42,43] This regimen is >95% effective in preventing HBV infection in these infants. ART that includes nucleos(t)ides with anti-HBV activity will result in low or suppressed HBV viral loads near delivery, which should further reduce the risk of HBV perinatal transmission in women with HBV/HIV coinfection.

Infant postvaccination testing for anti-HBs and HBsAg should be performed after completion of the vaccine series, at ages 9 months to 18 months. Testing should not be performed before age 9 months to avoid detection of anti-HBs from HBIG administered during infancy and to maximize the likelihood of detecting late HBV infection. Anti-HBc testing of infants is not recommended, because passively acquired maternal anti-HBc might be detected in infants born to mothers with HBV infection up to age 24 months. HBsAg-negative infants with anti-HBs levels >10 mIU/mL are protected and need no further medical management. HBsAg-negative infants with anti-HBs levels <10 mIU/mL should be revaccinated with a second three-dose series and retested 1 to 2 months after the final dose of vaccine.

References

1. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV. 2018. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf.

2. Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. 2018. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf.

3. Centers for Disease Control and Prevention. Preexposure prophylaxis for the prevention of HIV infection in the United States. 2017. Available at: https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2017.pdf.

4. Centers for Disease Control and Prevention. Guidelines for vaccinating pregnant women. 2017. Available at: https://www.cdc.gov/vaccines/pregnancy/hcp/guidelines.html.

5. Grob P, Jilg W, Bornhak H, et al. Serological pattern "anti-HBc alone": report on a workshop. *J Med Virol*. 2000;62(4):450-455. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11074473.

6. Hofer M, Joller-Jemelka HI, Grob PJ, Luthy R, Opravil M. Frequent chronic hepatitis B virus infection in HIV-infected patients positive for antibody to hepatitis B core antigen only Swiss HIV Cohort Study. *Eur J Clin Microbiol Infect Dis*. 1998;17(1):6-13. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9512175.

7. Silva AE, McMahon BJ, Parkinson AJ, Sjogren MH, Hoofnagle JH, Di Bisceglie AM. Hepatitis B virus DNA in persons with isolated antibody to hepatitis B core antigen who subsequently received hepatitis B vaccine. *Clin Infect Dis*. 1998;26(4):895-897. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9564471.

8. Lok AS, Lai CL, Wu PC. Prevalence of isolated antibody to hepatitis B core antigen in an area endemic for hepatitis B virus infection: implications in hepatitis B vaccination programs. *Hepatology*. 1988;8(4):766-770. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2968945.

9. Khamduang W, Gaudy-Graffin C, Ngo-Giang-Huong N, et al. Analysis of residual perinatal transmission of hepatitis B virus (HBV) and of genetic variants in human immunodeficiency virus and HBV co-infected women and their offspring. *J Clin Virol*. 2013;58(2):415-421. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23916828.

10. Benhammou V, Tubiana R, Matheron S, et al. HBV or HCV coinfection in HIV-1-infected pregnant women in France: prevalence and pregnancy outcomes. *J Acquir Immune Defic Syndr*. 2018;77(5):439-450. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29287028.

11. Floridia M, Masuelli G, Tamburrini E, et al. HBV coinfection is associated with reduced CD4 response to antiretroviral treatment in pregnancy. *HIV Clin Trials*. 2017;18(2):54-59. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28067163.

12. Crane M, Oliver B, Matthews G, et al. Immunopathogenesis of hepatic flare in HIV/hepatitis B virus (HBV)-coinfected individuals after the initiation of HBV-active antiretroviral therapy. *J Infect Dis*. 2009;199(7):974-981. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19231993.

13. Cui AM, Cheng XY, Shao JG, et al. Maternal hepatitis B virus carrier status and pregnancy outcomes: a prospective cohort study. *BMC Pregnancy and Childbirth*. 2016;16:87. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27113723.

14. Huang QT, Wei SS, Zhong M, et al. Chronic hepatitis B infection and risk of preterm labor: a meta-analysis of observational studies. *J Clin Virol*. 2014;61(1):3-8. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24973811.

15. Kubo A, Shlager L, Marks AR, et al. Prevention of vertical transmission of hepatitis B: an observational study. *Ann Intern Med*. 2014;160(12):828-835. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24862434.

16. del Canho R, Grosheide PM, Schalm SW, de Vries RR, Heijtink RA. Failure of neonatal hepatitis B vaccination: the role of HBV-DNA levels in hepatitis B carrier mothers and HLA antigens in neonates. *J Hepatol*. 1994;20(4):483-486. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8051386.

17. Ngui SL, Andrews NJ, Underhill GS, Heptonstall J, Teo CG. Failed postnatal immunoprophylaxis for hepatitis B: characteristics of maternal hepatitis B virus as risk factors. *Clin Infect Dis*. 1998;27(1):100-106. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9675462.

18. Wiseman E, Fraser MA, Holden S, et al. Perinatal transmission of hepatitis B virus: an Australian experience. *Med J Aust*. 2009;190(9):489-492. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19413519.

19. Jourdain G, Ngo-Giang-Huong N, Harrison L, et al. Tenofovir versus placebo to prevent perinatal transmission of hepatitis B. *N Engl J Med*. 2018;378(10):911-923. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29514030.

20. van Nunen AB, de Man RA, Heijtink RA, Niesters HG, Schalm SW. Lamivudine in the last 4 weeks of pregnancy to prevent perinatal transmission in highly viremic chronic hepatitis B patients. *J Hepatol*. 2000;32(6):1040-1041. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10898328.

21. van Zonneveld M, van Nunen AB, Niesters HG, de Man RA, Schalm SW, Janssen HL. Lamivudine treatment during pregnancy to prevent perinatal transmission of hepatitis B virus infection. *J Viral Hepat*. 2003;10(4):294-297. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12823596.

22. Shi Z, Yang Y, Ma L, Li X, Schreiber A. Lamivudine in late pregnancy to interrupt in utero transmission of hepatitis B virus: a systematic review and meta-analysis. *Obstet Gynecol*. 2010;116(1):147-159. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20567182.

23. Pan CQ, Han GR, Jiang HX, et al. Telbivudine prevents vertical transmission from HBeAg-positive women with chronic hepatitis B. *Clin Gastroenterol Hepatol*. 2012;10(5):520-526. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22343511.

24. Deng M, Zhou X, Gao S, et al. The effects of telbivudine in late pregnancy to prevent intrauterine transmission of the hepatitis B virus: a systematic review and meta-analysis. *Virology Journal*. 2012;9:185. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22947333.

25. Liu M, Cai H, Yi W. Safety of telbivudine treatment for chronic hepatitis B for the entire pregnancy. *J Viral Hepat*. 2013;20 Suppl 1:65-70. Available at: *http://www.ncbi.nlm.nih.gov/pubmed/23458527*.

26. Cheung KW, Seto MT, Wong SF. Towards complete eradication of hepatitis B infection from perinatal transmission: review of the mechanisms of in utero infection and the use of antiviral treatment during pregnancy. *Eur J Obstet Gynecol Reprod Biol*. 2013;169(1):17-23. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23465469.

27. Zhang H, Pan CQ, Pang Q, Tian R, Yan M, Liu X. Telbivudine or lamivudine use in late pregnancy safely reduces perinatal transmission of hepatitis B virus in real-life practice. *Hepatology*. 2014. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25227594.

28. Chen HL, Lee CN, Chang CH, et al. Efficacy of maternal tenofovir disoproxil fumarate in interrupting mother-to-infant transmission of hepatitis B virus. *Hepatology*. 2015;62(2):375-386. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25851052.

29. Kazim SN, Wakil SM, Khan LA, Hasnain SE, Sarin SK. Vertical transmission of hepatitis B virus despite maternal lamivudine therapy. *Lancet*. 2002;359(9316):1488-1489. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11988251.

30. Chasela CS, Kourtis AP, Wall P, et al. Hepatitis B virus infection among HIV-infected pregnant women in Malawi and transmission to infants. *J Hepatol*. 2014;60(3):508-514. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24211737.

31. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral pregnancy registry international interim report for 1 January–31 January 2018.Wilmington, NC: Registry Coordinating Center. 2018. Available at: http://www.apregistry.com/.

32. Tenofovir alafenamide [package insert]. Food and Drug Administration. 2016. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208464s001lbl.pdf.

33. Agarwal K, Fung SK, Nguyen TT, et al. Twenty-eight day safety, antiviral activity, and pharmacokinetics of tenofovir alafenamide for treatment of chronic hepatitis B infection. *J Hepatol*. 2015;62(3):533-540. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25450717.

34. Gallant J, Brunetta J, Crofoot G, et al. Brief report: efficacy and safety of switching to a single-tablet regimen of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide in HIV-1/hepatitis B-coinfected adults. *J Acquir Immune Defic Syndr*. 2016;73(3):294-298. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27171740.

35. Abdul Basit S, Dawood A, Ryan J, Gish R. Tenofovir alafenamide for the treatment of chronic hepatitis B virus infection. *Expert Rev Clin Pharmacol*. 2017;10(7):707-716. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28460547.

36. Han GR, Cao MK, Zhao W, et al. A prospective and open-label study for the efficacy and safety of telbivudine in pregnancy for the prevention of perinatal transmission of hepatitis B virus infection. *J Hepatol*. 2011;55(6):1215-1221. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21703206.

37. Brown RS, Jr., McMahon BJ, Lok AS, et al. Antiviral therapy in chronic hepatitis B viral infection during pregnancy: A systematic review and meta-analysis. *Hepatology*. 2016;63(1):319-333. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26565396.

38. Boskovic R, Wide R, Wolpin J, Bauer DJ, Koren G. The reproductive effects of beta interferon therapy in pregnancy: a longitudinal cohort. *Neurology*. 2005;65(6):807-811. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16186517.

39. Keeffe EB, Dieterich DT, Han SH, et al. A treatment algorithm for the management of chronic hepatitis B virus infection in the United States: 2008 update. *Clin Gastroenterol Hepatol*. 2008;6(12):1315-1341; quiz 1286. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18845489.

40. Asian Pacific Association for the Study of the Liver. Asian-Pacific consensus statement on the management of chronic hepatitis B: a 2012 update. *Hepatol Int*. 2012(6):531-561. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26201469.

41. European Association for the Study of the Liver. EASL 2017 clinical practice guidelines on the management of hepatitis B virus infection. *J Hepatol*. 2017;67(2):370-398. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28427875.

42. Mast EE, Margolis HS, Fiore AE, et al. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the advisory committee on immunization practices (ACIP) part 1: immunization of infants, children, and adolescents. *MMWR Recomm Rep*. 2005;54(RR-16):1-31. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16371945.

43. Centers for Disease Control and Prevention. Errata: Vol. 54,No. RR-16, p1267 which corrects the Tables published in Recommendations of the Advisory Committee on Immunization Practices (ACIP)–Part 1: Immunization of infants, children, and adolescents in Trends in childhood cancer mortality—United States, 1990–2004. *MMWR Morb Mortal Wkly Rep*. 2007;56(48):1257-1261. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18059256.

Special Populations: Hepatitis C Virus/HIV Coinfection (Last updated December 7, 2018; last reviewed December 7, 2018)

Panel's Recommendations
• All pregnant women with HIV should be screened during the current pregnancy for 1. Hepatitis B virus (HBV) infection, unless they are known to have HBV/HIV coinfection or serologic documentation of HBV immunity coinfection (see Hepatitis B Virus/HIV Coinfection), *and* 2. Hepatitis C virus (HCV) infection unless they are known to have HCV/HIV coinfection **(AIII)**. • Women with HCV infection who have not already received the hepatitis A virus (HAV) vaccine series should be screened for immunity to HAV, because they are at increased risk of complications from coinfection with other viral hepatitis infections **(AIII)**. If they screen negative for HAV antibodies (IgG or IgG plus IgM), they should receive the HAV vaccine series **(AIII)**. • All pregnant women with HIV and/or HCV who screen negative for HBV infection (i.e., HBV surface antigen negative and HBV core antibody negative) and lack HBV immunity (i.e., HBV surface antibody negative) should receive the HBV vaccine series **(AII)**. • When considering HCV treatment in a pregnant woman with HIV coinfection, consultation with an expert in HIV and HCV is strongly recommended **(AIII)**. • Recommendations for antiretroviral therapy (ART) during pregnancy are the same for all women living with HIV, whether they have HCV or not **(AIII)**. • Pregnant women with HCV/HIV coinfection who are receiving ART should be counseled about signs and symptoms of liver toxicity, and hepatic transaminases should be assessed 1 month following initiation of ART and at least every 3 months thereafter during pregnancy **(BIII)**. • Decisions concerning the mode of infant delivery in pregnant women with HCV/HIV coinfection should be based on standard obstetric and HIV-related indications alone; HCV coinfection does not necessitate cesarean delivery when it is not otherwise indicated (see Transmission and Mode of Delivery) **(AIII)**. • Infants born to women with HCV/HIV coinfection should be evaluated for HCV infection **(AIII)**. Decisions regarding the specific type of assays to use for HCV screening in children and the timing of those assays should be made after consultation with an expert in pediatric HCV infection **(AIII)**.
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*

For additional information on hepatitis C virus (HCV) and HIV, see Hepatitis C Virus in the Pediatric Opportunistic Infection Guidelines, Hepatitis C Virus/HIV Coinfection in the Adult and Adolescent Guidelines, and Hepatitis C Virus Infection in the Adult and Adolescent Opportunistic Infection Guidelines. The American Association for the Study of Liver Diseases, the Infectious Diseases Society of America, and the International Antiviral Society-USA maintain updated information about treating patients with HCV/HIV coinfection. The guidelines are available online at HCVguidelines.org. The management of HCV/HIV coinfection in pregnancy is complex, and none of the approved HCV direct-acting antivirals (DAAs) have yet been fully evaluated in pregnant women; thus, consultation with an expert in HIV and HCV infection is strongly recommended, particularly when HCV treatment during pregnancy is being considered.

Screening and Vaccination

All pregnant women living with HIV should be screened at entry into general HIV care and during each pregnancy for

1. Hepatitis B virus (HBV), unless they are known to have HBV/HIV coinfection or serologic documentation of HBV immunity, *and*
2. HCV infection, unless they are known to have HCV/HIV coinfection.

Among women with HIV, the observed risks for HCV infection were 2% to 12% in European cohorts of pregnant women with HIV[1] and 3.8% among women with HIV in New York State.[2] Although data about secular trends in HCV risk among women living with HIV are limited in the United States, the prevalence of HCV among women of childbearing age and children aged <2 years in the general population has increased substantially in recent years.[3-6] The male partners of all patients with HCV/HIV coinfection should be referred for both HIV and hepatitis counseling and testing to prevent the sexual transmission of HIV and HCV from women to their male partners; however, people who do not share injection equipment have a very low risk of horizontal transmission of HCV. Partners who do not have HIV infection should be counseled about the potential benefits and risks of starting oral pre-exposure prophylaxis to prevent HIV acquisition (see Preconception Counseling).

Newly available DAAs have dramatically improved HCV therapy; it is now possible to cure HCV infection in most patients.[7] Current HCV treatment guidelines recommend therapy for nearly all patients with HCV infection.[7] The management of HCV/HIV coinfection during pregnancy is complex, however. Although a single Phase 1 study is now evaluating the safety and pharmacokinetics (PKs) of HCV treatment in pregnancy, with data expected in late 2018,[8] none of the approved DAAs have been fully evaluated in pregnant women. The use of ribavirin, although rarely needed now with DAAs, is also **contraindicated** in pregnancy.[9] When considering HCV treatment in a pregnant person, consultation with an expert in HIV and HCV is strongly recommended. In addition, the risks of perinatal HCV transmission are much lower than those of perinatal HIV transmission, and some children will clear HCV infection spontaneously,[5,10,11] making the balance of risks and benefits for treating HCV in pregnancy different from that for treating HIV.

The primary reasons for HCV testing during pregnancy are:

- To identify women with HCV/HIV coinfection at a time when they are engaged with the health system, so that HCV treatment can be offered after delivery (ideally before a subsequent pregnancy);
- To monitor for the increased risk of HCV-related hepatotoxicity related to antiretroviral (ARV) use[12] and the potential increased risk of preterm birth with HCV infection[13,14] in women with HCV/HIV coinfection;
- To ensure vaccination against other viral hepatitis infections (hepatitis A virus [HAV] and HBV) if needed; *and*
- To ensure appropriate follow-up and evaluation of infants exposed to HCV.

Screening for chronic HCV infection using a sensitive immunoassay for HCV antibodies is recommended for all individuals with HIV, including those who are pregnant. False-negative anti-HCV immunoassay results can occur in individuals with HIV, but it is uncommon with the more sensitive immunoassays. If HCV infection is suspected despite a negative HCV antibody screen, a quantitative HCV RNA assay can be performed.[15,16] Individuals who have a positive HCV antibody test should undergo confirmatory testing for plasma HCV RNA using a commercially available quantitative diagnostic assay. Many laboratories now perform reflex RNA testing for individuals who test positive for HCV antibodies. Testing for HCV RNA also should be performed during pregnancy on individuals whose serologic test results are indeterminate or negative but in whom HCV infection is suspected because of elevated aminotransaminase levels or risk factors such as a history of injection drug use.[17]

Because of the added risk of hepatic decompensation from acute infection with any viral hepatitis, women with HCV infection should also be screened for both HAV and HBV. Women with chronic HCV infection who have not already received the HAV vaccine series should be screened for immunity to HAV (either IgG alone or IgG and IgM together). If they screen negative for HAV antibodies, they should receive the HAV vaccine series. In women with CD4 T lymphocyte (CD4) cell counts <200 cells/mm^3, antibody responses to HAV vaccine should be assessed 1 month after completion of vaccination series; those who are HAV Ab IgG negative should be revaccinated when the CD4 count is >200 cells/mm^3.[18] Women with HCV/

HIV coinfection who screen negative for HBV (i.e., they are hepatitis B surface antigen [HBsAg] negative, hepatitis B core antibody negative, and hepatitis B surface antibody negative [HBsAb]) should receive the HBV vaccine series. Women with HCV/HIV coinfection who are HBsAb negative despite having received the HBV vaccine series may benefit from revaccination (see Hepatitis B Virus/HIV Coinfection).[19] The hepatitis B vaccination poses no apparent risk to developing fetuses, as current vaccines contain noninfectious HBsAg.[20]

Impact of HCV/HIV Coinfection on Progression and Perinatal Transmission of Both Viruses

Although the HCV viral load appears to peak in the third trimester, pregnancy does not appear to influence the course of HCV infection clinically. Women with chronic HCV generally do well during pregnancy, provided that they have not progressed to decompensated cirrhosis.[21,22]

HCV Transmission

Approximately six of every 100 infants born to women with HCV acquire HCV infection.[16] In most studies of women with HCV/HIV coinfection who are not receiving treatment for either infection, the incidence of perinatal HCV transmission is approximately two-fold higher among women with HCV/HIV coinfection (10% to 20% transmission risk) than among women with HCV monoinfection.[23-26] These higher transmission rates are likely related to an increase in HCV viremia and/or other HIV-related impacts on HCV disease activity.[14,27] However, early and sustained control of HIV viremia with antiretroviral therapy (ART) may reduce the risk of HCV transmission to infants.[22,28,29] A European study of perinatal transmission of HCV found that use of effective ART for HIV was associated with a strong trend toward reduced rates of HCV transmission (odds ratio 0.26; 95% CI, 0.07–1.01).[28] In an Italian cohort, HCV transmission occurred in 9% of infants born to HCV/HIV-coinfected women, most of whom were on ART. No HCV transmissions occurred in infants born to women with HCV viral loads of <5 log IU/mL.[14]

HIV Transmission

In the absence of ART, maternal HCV/HIV coinfection also may increase the risk of perinatal transmission of HIV.[30,31] The risk of perinatal HIV transmission can likely be reduced in pregnant women with HCV/HIV coinfection by following the standard recommendations for ART for all women with HIV.

Impact of Hepatitis C Virus on HIV Management

Few data exist on the optimal management of pregnant women with HCV/HIV coinfection. Recommendations for ART use during pregnancy for treatment of HIV and prevention of perinatal transmission are the same for women who have HCV/HIV coinfection as for those with HIV monoinfection (see Hepatitis C Virus/HIV Coinfection in the Adult and Adolescent Guidelines). In one Canadian study, HCV/HIV coinfection was associated with an increased risk of HIV viral rebound among women who were on previously effective ART. Although the authors suggest that additional factors (e.g., adherence) may have varied between the groups, these findings support the need to follow recommended HIV RNA monitoring during pregnancy.[32]

Hepatitis C Virus-Specific Therapy in Pregnancy

All currently available DAAs lack sufficient safety data to be recommended during pregnancy. In the past, most anti-HCV therapy included both interferon and ribavirin. Interferons are not recommended for use in pregnancy because they are abortifacient at high doses in monkeys and have direct antigrowth and antiproliferative effects.[33] Some DAA regimens are approved for use with ribavirin in specific nonpregnant populations, due to the suboptimal treatment responses observed with the use of DAAs alone. Any treatment regimens that include ribavirin are **contraindicated** in pregnant women due to the teratogenic and embryocidal effects observed in all animal species exposed to ribavirin. Ribavirin-associated defects in animals include limb abnormalities, craniofacial defects, anencephaly, and anophthalmia. Pregnancies that

occur in women taking ribavirin should be reported to the Ribavirin Pregnancy Registry (online or by phone at 800-593-2214)

There are many interferon-free DAA regimens that have been approved for the treatment of HCV. Determining the optimal regimen for an individual patient is based on many factors, including HCV genotype, prior treatment experience, and stage of liver disease (e.g., compensated or decompensated cirrhosis). There are three main classes of DAAs:[7,34]

- NS5A inhibitors: daclatasvir, elbasvir, ledipasvir, ombitasvir, pibrentasvir, velpatasvir
- NS5B polymerase inhibitors: dasabuvir, sofosbuvir
- NS3/4A protease inhibitors: glecaprevir, grazoprevir, paritaprevir, simeprevir, voxilaprevir.

DAAs are not yet recommended for use in pregnancy because of the lack of PK and safety data; at least one small PK study that is investigating the use of ledipasvir/sofosbuvir in pregnancy is ongoing. In addition, potential drug interactions exist between these newer anti-HCV drugs and ARV drugs that may produce clinically significant changes in serum levels of both ARV drugs and anti-HCV medications. For detailed information on HCV/HIV drug interactions, see the Adult and Adolescent Guidelines, the Adult and Adolescent Opportunistic Infection Guidelines, HCVGuidelines.org, and the HEP Drug Interaction Checker.

Monitoring of Women with HCV/HIV Coinfection during Pregnancy

An elevation in hepatic enzymes following initiation of ART can occur in women with HCV/HIV coinfection—particularly in those with low CD4 cell counts at treatment initiation—as a result of an immune-mediated flare in HCV disease triggered by immune reconstitution with ART. In patients with HIV, HCV infection may increase the hepatotoxic risk of certain ARV agents, specifically protease inhibitors and nevirapine. HCV monoinfection may increase the risk of intrahepatic cholestasis of pregnancy;[35] there are no data about the risk among women with HCV/HIV coinfection. Pregnant women with HCV/HIV coinfection should be counseled about signs and symptoms of liver toxicity, and transaminase levels should be assessed 1 month after initiation of ART and then every 3 months thereafter. If hepatic toxicity occurs, a clinician may need to consider initiating a less hepatotoxic drug regimen, and, if clinical symptoms or significant elevations of transaminases occur, drugs may need to be temporarily discontinued. Differentiating between a flare of HCV disease associated with immune reconstitution and drug toxicity often can be difficult; therefore, consulting an expert in HCV/HIV coinfection is strongly recommended.

Rates of preterm delivery are also high among HCV/HIV-coinfected women. In an Italian cohort of mostly ART-treated women with HCV/HIV coinfection, preterm delivery occurred in 41% of women overall. The rate of preterm delivery was 29% among women with HCV RNA <5 log IU/mL and 43% among women with HCV RNA >5 log IU/mL; the difference in rates of preterm delivery was not statistically significant between the two groups. Women with preterm delivery had significantly higher levels of HCV RNA than those who delivered at term.[14] HCV infection in pregnancy may also be associated with increased risks for gestational diabetes, small-for-gestational-age infants, and low birth weight infants.[5,36] Although no obstetric guidelines suggest increased monitoring among women with HCV infection for diabetes or infant growth,[37] knowledge of these increased risks may inform clinical care.[38]

Mode of Delivery

The majority of studies of scheduled cesarean delivery in women with HCV infection, with or without HIV coinfection, have found that the procedure does not reduce the risk of perinatal transmission of HCV.[28,39-41] Thus, the general recommendations for mode of delivery are the same in women with HCV/HIV coinfection as in those with HIV infection alone (see Transmission and Mode of Delivery).

Evaluation of Infants Exposed to HCV

Infants born to women with HCV/HIV coinfection should be assessed for chronic HCV infection. An HCV antibody test should be performed after age 18 months, when the maternal anti-HCV antibody level has

waned.[42] Sensitivity of HCV RNA testing is low at birth, and viremia can be intermittent or infection may resolve spontaneously; thus, HCV RNA testing should not be performed before age 2 months, and a single negative test is not conclusive evidence of lack of infection.[43] Uptake of HCV testing is very low for HCV-exposed infants; therefore, it is important for providers to counsel patients about the need for pediatric follow-up and testing during the first few years of life.[44,45] The Pediatric Opportunistic Infection Guidelines provide further details about diagnostic evaluation of HCV-exposed infants.

References

1. Benhammou V, Tubiana R, Matheron S, et al. HBV or HCV coinfection in HIV-1-infected pregnant women in France: prevalence and pregnancy outcomes. *J Acquir Immune Defic Syndr*. 2018;77(5):439-450. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29287028.
2. Ghazaryan L, Smith L, Parker M, et al. Hepatitis C seroprevalence among HIV-infected childbearing women in New York state in 2006. *Matern Child Health J*. 2016;20(3):550-555. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26520159.
3. Koneru A, Nelson N, Hariri S, et al. Increased hepatitis C virus (HCV) detection in women of childbearing age and potential risk for vertical transmission - United States and Kentucky, 2011-2014. *MMWR Morb Mortal Wkly Rep*. 2016;65(28):705-710. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27442053.
4. Ly KN, Jiles RB, Teshale EH, Foster MA, Pesano RL, Holmberg SD. Hepatitis C virus infection among reproductive-aged women and children in the United States, 2006 to 2014. *Ann Intern Med*. 2017;166(11):775-782. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28492929.
5. Barritt AS, 4th, Jhaveri R. Treatment of hepatitis C during pregnancy-weighing the risks and benefits in contrast to HIV. *Curr HIV/AIDS Rep*. 2018;15(2):155-161. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29470782.
6. Salemi JL, Spooner KK, Mejia de Grubb MC, Aggarwal A, Matas JL, Salihu HM. National trends of hepatitis B and C during pregnancy across sociodemographic, behavioral, and clinical factors, United States, 1998-2011. *J Med Virol*. 2017;89(6):1025-1032. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27805270.
7. American Association for the Study of Liver Diseases and the Infectious Diseases Society of America. HCV guidance: recommendations for testing, managing, and treating hepatitis C. 2017; http://hcvguidelines.org/.
8. Clinicaltrials.gov. Study of hepatitis C treatment during pregnancy (HIP). 2017; https://clinicaltrials.gov/ct2/show/NCT02683005.
9. Spera AM, Eldin TK, Tosone G, Orlando R. Antiviral therapy for hepatitis C: Has anything changed for pregnant/lactating women? *World J Hepatol*. 2016;8(12):557-565. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27134703.
10. Mack CL, Gonzalez-Peralta RP, Gupta N, et al. NASPGHAN practice guidelines: Diagnosis and management of hepatitis C infection in infants, children, and adolescents. *J Pediatr Gastroenterol Nutr*. 2012;54(6):838-855. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22487950.
11. Bernstein HB, Dunkelberg JC, Leslie KK. Hepatitis C in pregnancy in the era of direct-acting antiviral treatment: potential benefits of universal screening and antepartum therapy. *Clin Obstet Gynecol*. 2018;61(1):146-156. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29351151.
12. Sibiude J, Warszawski J, Tubiana R, et al. High risk of liver enzyme elevation in pregnant women receiving protease inhibitors. Presented at: Conference on Retroviruses and Opportunistic Infections 2016; Boston, MA.
13. Huang QT, Huang Q, Zhong M, et al. Chronic hepatitis C virus infection is associated with increased risk of preterm birth: a meta-analysis of observational studies. *J Viral Hepat*. 2015;22(12):1033-1042. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26081198.
14. Baroncelli S, Pirillo MF, Amici R, et al. HCV-HIV coinfected pregnant women: data from a multicentre study in Italy. *Infection*. 2016;44(2):235-242. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26507133.
15. Alter MJ, Kuhnert WL, Finelli L, Centers for Disease Control Prevention. Guidelines for laboratory testing and result reporting of antibody to hepatitis C virus. *MMWR Recomm Rep*. 2003;52(RR-3):1-13, 15; quiz CE11-14. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12585742.
16. Centers for Disease Control and Prevention. Hepatitis C. 2011. Avialable at: https://www.cdc.gov/std/treatment/2010/hepC.htm.

17. Centers for Disease Control and Prevention. Viral hepatitis-hepatitis C information. 2015. Available at: http://www.cdc.gov/hepatitis/hcv/.

18. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV. Hepatitis B Virus/HIV Coinfection. 2017. Available at: https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/25/hbv-hiv.

19. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Hepatitis C Virus/HIV Coinfection. 2017. Available at: https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv-guidelines/26/hcv-hiv.

20. Centers for Disease Control and Prevention. Guidelines for vaccinating pregnant women. 2017. Available at: https://www.cdc.gov/vaccines/pregnancy/hcp/guidelines.html.

21. Sookoian S. Effect of pregnancy on pre-existing liver disease: chronic viral hepatitis. *Ann Hepatol*. 2006;5(3):190-197. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17060881.

22. Benova L, Mohamoud YA, Calvert C, Abu-Raddad LJ. Vertical transmission of hepatitis C virus: systematic review and meta-analysis. *Clin Infect Dis*. 2014;59(6):765-773. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24928290.

23. Tovo PA, Palomba E, Ferraris G, et al. Increased risk of maternal-infant hepatitis C virus transmission for women coinfected with human immunodeficiency virus type 1. Italian Study Group for HCV Infection in Children. *Clin Infect Dis*. 1997;25(5):1121-1124. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9402369.

24. Gibb DM, Goodall RL, Dunn DT, et al. Mother-to-child transmission of hepatitis C virus: evidence for preventable peripartum transmission. *Lancet*. 2000;356(9233):904-907. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11036896.

25. Mast EE, Hwang LY, Seto DS, et al. Risk factors for perinatal transmission of hepatitis C virus (HCV) and the natural history of HCV infection acquired in infancy. *J Infect Dis*. 2005;192(11):1880-1889. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16267758.

26. Alter MJ. Epidemiology of viral hepatitis and HIV co-infection. *J Hepatol*. 2006;44(1 Suppl):S6-9. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16352363.

27. Polis CB, Shah SN, Johnson KE, Gupta A. Impact of maternal HIV coinfection on the vertical transmission of hepatitis C virus: a meta-analysis. *Clin Infect Dis*. 2007;44(8):1123-1131. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17366462.

28. European Paediatric Hepatitis C Virus Network. A significant sex--but not elective cesarean section--effect on mother-to-child transmission of hepatitis C virus infection. *J Infect Dis*. 2005;192(11):1872-1879. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16267757.

29. Checa Cabo CA, Stoszek SJ, Quarleri J, et al. Mother-to-child transmission of hepatitis C virus (HCV) among HIV/HCV-coinfected women. *J Ped Infect Dis Soc*. 2013;2(2):126-135. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26199724.

30. Hershow RC, Riester KA, Lew J, et al. Increased vertical transmission of human immunodeficiency virus from hepatitis C virus-coinfected mothers. Women and Infants Transmission Study. *J Infect Dis*. 1997;176(2):414-420. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9237706.

31. Petersdorf N, Ross JM, Weiss HA, Barnabas RV, Wasserheit JN, HCV and HIV Transmission Working Group. Systematic review and meta-analysis of hepatitis C virus infection and HIV viral load: new insights into epidemiologic synergy. *J Int AIDS Soc*. 2016;19(1):20944. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27649908.

32. Boucoiran I, Albert AYK, Tulloch K, et al. Human immunodeficiency virus viral load rebound near delivery in previously suppressed, combination antiretroviral therapy-treated pregnant women. *Obstet Gynecol*. 2017;130(3):497-501. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28796673.

33. Boskovic R, Wide R, Wolpin J, Bauer DJ, Koren G. The reproductive effects of beta interferon therapy in pregnancy: a longitudinal cohort. *Neurology*. 2005;65(6):807-811. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16186517.

34. Elbasvir/grazoprevir [package insert]. Food and Drug Administration. 2016. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/208261Orig1s000lbl.pdf.

35. Wijarnpreecha K, Thongprayoon C, Sanguankeo A, Upala S, Ungprasert P, Cheungpasitporn W. Hepatitis C infection and intrahepatic cholestasis of pregnancy: A systematic review and meta-analysis. *Clin Res Hepatol Gastroenterol*. 2017;41(1):39-45. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27542514.

36. Pergam SA, Wang CC, Gardella CM, Sandison TG, Phipps WT, Hawes SE. Pregnancy complications associated with hepatitis C: data from a 2003–2005 Washington state birth cohort. *Am J Obstet Gynecol*. 2008;199(1):38 e31-39. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18486089.

37. American College of Obstetricians Gynecologists. ACOG practice bulletin No. 86: viral hepatitis in pregnancy. *Obstet Gynecol*. 2007;110(4):941-956. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17906043.

38. Society for Maternal-Fetal Medicine, Hughes BL, Page CM, Kuller JA. Hepatitis C in pregnancy: screening, treatment, and management. *Am J Obstet Gynecol*. 2017;217(5):B2-B12. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28782502.

39. Ghamar Chehreh ME, Tabatabaei SV, Khazanehdari S, Alavian SM. Effect of cesarean section on the risk of perinatal transmission of hepatitis C virus from HCV-RNA+/HIV- mothers: a meta-analysis. *Arch Gynecol Obstet*. 2011;283(2):255-260. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20652289.

40. Marine-Barjoan E, Berrebi A, Giordanengo V, et al. HCV/HIV co-infection, HCV viral load and mode of delivery: risk factors for mother-to-child transmission of hepatitis C virus? *AIDS*. 2007;21(13):1811-1815. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17690581.

41. McMenamin MB, Jackson AD, Lambert J, et al. Obstetric management of hepatitis C-positive mothers: analysis of vertical transmission in 559 mother-infant pairs. *Am J Obstet Gynecol*. 2008;199(3):315 e311-315. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18771997.

42. Bal A, Petrova A. Single clinical practice's report of testing initiation, antibody clearance, and transmission of hepatitis C virus (HCV) in infants of chronically HCV-infected mothers. *Open Forum Infect Dis*. 2016;3(1):ofw021. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26985444.

43. Polywka S, Pembrey L, Tovo PA, Newell ML. Accuracy of HCV-RNA PCR tests for diagnosis or exclusion of vertically acquired HCV infection. *J Med Virol*. 2006;78(2):305-310. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16372293.

44. Kuncio DE, Newbern EC, Johnson CC, Viner KM. Failure to test and identify perinatally infected children born to hepatitis C virus-infected women. *Clin Infect Dis*. 2016;62(8):980-985. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26797211.

45. Watts T, Stockman L, Martin J, Guilfoyle S, Vergeront JM. Increased risk for mother-to-infant transmission of hepatitis C virus among medicaid recipients - Wisconsin, 2011-2015. *MMWR Morb Mortal Wkly Rep*. 2017;66(42):1136-1139. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29072864.

HIV-2 Infection and Pregnancy (Last updated December 12, 2019; last reviewed December 12, 2019)

Panel's Recommendations

- HIV-2 infection should be considered in pregnant women who are from—or who have partners who are from—countries in which the disease is endemic and who have positive results on an HIV-1/HIV-2 antibody or HIV-1/HIV-2 antigen/antibody immunoassay. They should be tested with a supplemental HIV-1/HIV-2 antibody differentiation assay. If they have only HIV-2 infection, the test will be negative for HIV-1 antibodies and positive for HIV-2 antibodies **(AII)**.
- Pregnant women living with HIV-2 should be treated as per guidelines for HIV-1 mono-infection but using antiretroviral drugs that are active against HIV-2. Non-nucleoside reverse transcriptase inhibitors and enfuvirtide are not active against HIV-2 and **should not be used** **(AIII)**.
- No randomized clinical trials have been performed to address when to start treatment or what the optimal treatment is for HIV-2 infection **(AIII)**. A regimen with two nucleoside reverse transcriptase inhibitors and integrase strand transfer inhibitors or certain boosted protease inhibitors is recommended for all pregnant women with HIV-2 infection **(AIII)**.
- Dolutegravir (irrespective of trimester), raltegravir, ritonavir-boosted darunavir, or ritonavir-boosted lopinavir plus a dual-nucleoside reverse transcriptase inhibitor (NRTI) backbone of abacavir plus lamivudine or tenofovir disoproxil fumarate plus emtricitabine or lamivudine are recommended for treating HIV-2 mono-infection in pregnant women and in women trying to conceive **(AIII)**. Zidovudine (ZDV) plus lamivudine can be used as an alternative dual-NRTI backbone. See Updated Guidance about the Use of Dolutegravir in Pregnancy in Recommendations for the Use of Antiretroviral Drugs in Pregnancy and Appendix D: Dolutegravir Counseling Guide for Health Care Poviders.
- As with HIV-1, the possibility of hepatitis B virus/HIV-2 coinfection should be considered when choosing an antiretroviral regimen to treat HIV-2 **(AI)**, see Hepatitis B Virus/HIV Coinfection.
- All infants born to women with HIV-2 infection (who do not have HIV-1 infection) should receive the 4-week ZDV prophylactic regimen **(BIII)**.
- In the United States, where safe infant formula is readily available, breastfeeding **is not recommended** for infants born to mothers with HIV-2 infection **(AIII)**.

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*

HIV-2 infection is endemic in West African countries, including the Ivory Coast, Ghana, Cape Verde, The Gambia, Mali, Senegal, Liberia, Guinea, Burkina Faso, Nigeria, Mauritania, Sierra Leone, Guinea Bissau, Niger, Sao Tome, and Togo. It is also endemic in Angola, Mozambique, and in parts of India.[1-4] It also occurs in countries such as France and Portugal, which have large numbers of immigrants from these regions.[5]

HIV-2 remains rare in the United States. Between 1998 and 2010, 242 HIV-2 cases were reported to the Centers for Disease Control and Prevention (CDC), with 166 cases meeting the criteria for HIV-2 diagnosis. These 166 cases constituted only 0.01% of the >1.4 million U.S. cases of HIV infection.[6] Fifty women aged 15 to 44 years at diagnosis were among the 166 cases; 24 (48%) were pregnant at HIV-2 diagnosis or became pregnant after diagnosis.[6] HIV-2 infection should be suspected in pregnant women who are from—or who have partners from—countries in which the disease is endemic and who have positive results on an HIV-1/HIV-2 antibody or HIV-1/HIV-2 antigen/antibody immunoassay. They should be tested with a supplemental HIV-1/HIV-2 antibody differentiation immunoassay. If they have only HIV-2 infection, the test will be negative for HIV-1 antibodies and positive for HIV-2 antibodies. In rare instances, a woman may have dual infection with HIV-1 and HIV-2, and both tests will be positive.

In 2014, CDC released a new HIV testing algorithm. The first step in that algorithm is performing an HIV-1/HIV-2 antigen/antibody combination assay on serum or plasma (e.g., Abbott Architect HIV Ag/Ab combo assay, BioRad GS Combo Ag/Ab EIA, Alere Determine).[7] This test does not distinguish between HIV-1 antibodies and HIV-2 antibodies. Specimens which are reactive on this test must be tested with a Food and Drug Administration (FDA)-approved antibody assay to distinguish HIV-1 antibodies from HIV-2 antibodies. The FDA-approved HIV-2 antibody supplemental test Geenius (Bio-Rad Laboratories) is used as part of the CDC-recommended HIV laboratory testing algorithm. Viral load assays for HIV-2 are not commercially

available, but they may be available under research protocols. The University of Washington[8] and the New York State Department of Health[9] also offer HIV-2 viral load assays. All HIV-2 cases should be reported to the HIV surveillance program of the state or local health department, which can arrange for additional confirmatory testing for HIV-2 by the CDC.[10] No validated HIV-2 genotype or phenotype resistance assays are available in the United States. HIV-2 genotypic resistance assays are available for research use only at the University of Washington. European experts developed a rule set and an automated tool for HIV-2 drug resistance analyses that is freely available online.[11]

HIV-2 has a longer asymptomatic phase than HIV-1, with a slower progression to AIDS. However, without effective antiretroviral therapy (ART), HIV-2 will progress to AIDS and death in the majority of individuals over time.[12] The most common mode of HIV-2 transmission is through heterosexual sex. HIV-2 is less infectious than HIV-1, with a five-fold lower rate of sexual transmission and 20-fold to 30-fold lower rate of vertical transmission.[3,13,14] Several studies confirm that rates of perinatal transmission of HIV-2 are low with and without interventions (0% to 4%), which may be a result of reduced plasma viral loads and less cervical viral shedding in women with HIV-2 than in women with HIV-1.[15-18] HIV-2 also can be transmitted through breastfeeding. HIV-2 infection does not protect against HIV-1, and dual infection, which carries the same prognosis as HIV-1 mono-infection, can occur.[19]

Recommended Antiretroviral Therapy for Pregnant Women Living with HIV-2

Pregnant women living with HIV-2 should be treated according to the guidelines for patients with HIV-1 mono-infection, though clinicians should make sure that the chosen ART regimen is also appropriate for treatment of HIV-2. Once treatment is started, ART should be continued postpartum, as is recommended for all patients with HIV-1. A systematic review analyzed data collected from 1996 to 2012 on treatment outcomes among nonpregnant patients with HIV-2. The review reported a heterogeneity of treatment outcomes among patients who initiated ART, especially in resource-limited settings.[20] Non-nucleoside reverse transcriptase inhibitors (NNRTIs) and enfuvirtide are not active against HIV-2 and should not be used for treatment or prophylaxis.[21,22] The integrase strand transfer inhibitors (INSTIs) raltegravir (RAL), elvitegravir, dolutegravir (DTG), and bictegravir are effective against HIV-2.[23,24] HIV-2 has variable susceptibility to protease inhibitors (PIs), with lopinavir, saquinavir, and darunavir having the most activity.[25] Although DTG may be able to rescue a failing RAL-based regimen in a person with HIV-2, a study has reported the emergence of DTG resistance mutations in people with HIV-2.[26] The CCR5 antagonist maraviroc appears to be active against some strains of HIV-2, although there are no approved assays to determine HIV-2 co-receptor tropism.[27,28] HIV-2 drug resistance has been documented with various antiretroviral (ARV) drugs.[29,30] Among 47 ART-naive persons with HIV-2, ultradeep sequencing showed that three people displayed plasma viruses with a resistance-associated mutation (RAM) above the 20% detection threshold, with a prevalence of transmitted drug resistance for nucleoside reverse transcriptase inhibitors (NRTIs) of 7.9% (95% confidence interval, 0.0% to 16.5%). No RAM above the 20% detection threshold was found for PIs or INSTIs.[31]

The care of pregnant women with HIV-2 mono-infection has been based on expert opinion. A regimen with two NRTIs and an INSTI or a ritonavir-boosted PI currently is recommended for all pregnant women with HIV-2. The following regimens can be used to treat HIV-2, based on the available efficacy and safety data on these drugs from clinical trials of pregnant women with HIV-1:

- DTG (irrespective of trimester), RAL, ritonavir-boosted darunavir, or ritonavir-boosted lopinavir plus a dual-NRTI backbone of abacavir plus lamivudine or tenofovir disoproxil fumarate plus emtricitabine or lamivudine are the recommended regimens for treating HIV-2 mono-infection in pregnant women and women trying to conceive. See Updated Guidance about the Use of Dolutegravir in Pregnancy in Recommendations for the Use of Antiretroviral Drugs in Pregnancy and Appendix D: Dolutegravir Counseling Guide for Health Care Providers.
- Zidovudine (ZDV)/lamivudine can be used as an alternative dual-NRTI backbone.[32,33]
- NNRTIs **should not be used**, because they are not active against HIV-2.

When monitoring the plasma viral loads and CD4 T lymphocyte (CD4) cell counts in pregnant women with HIV-2, clinicians should follow the guidelines outlined for people with HIV-1 (see Monitoring of the Woman and Fetus During Pregnancy). However, disease progression can occur in the setting of undetectable HIV-2 plasma viral load. Patients who have HIV-2 plasma viral loads that are below the limits of detection should still have routine CD4 counts and clinical monitoring (see Plasma HIV-1 RNA (Viral Load) and CD4 Count Monitoring in the Adult and Adolescent Antiretroviral Guidelines).

There are no data to address whether treatment should be continued after pregnancy in women with HIV-2 mono-infection. To date, no randomized trials have addressed the question of an optimal treatment strategy for HIV-2 infection, although clinical trials are underway. The Adult and Adolescent Antiretroviral Guidelines recommend that all patients with HIV-2 should be treated using the guidelines provided for patients with HIV-1 (see the Adult and Adolescent Antiretroviral Guidelines).

All infants born to mothers with HIV-2 (who do not have HIV-1) should receive a 4-week ZDV prophylaxis regimen.[33] The possible risks and benefits of ARV prophylaxis should be discussed with the mothers. As noted above, rates of perinatal transmission of HIV-2 are low with and without interventions, and it is unclear whether infants born to women with undetectable HIV-2 viral loads will benefit from ARV prophylaxis. However, monitoring maternal HIV-2 plasma viral loads and receiving the results in a timely manner can be difficult, as plasma samples must be sent to the University of Washington or New York State Department. Therefore, the Panel recommends that all infants born to mothers with HIV-2 receive prophylaxis. The use of ZDV prophylaxis is recommended in this clinical situation because nevirapine lacks activity against HIV-2.

There are no data on the impact of scheduled cesarean delivery on HIV-2 perinatal transmission. The risk to infants from breastfeeding is lower for HIV-2 than for HIV-1, but breastfeeding should be avoided in the United States and other countries where safe infant formula is readily available.[16]

Infants born to mothers with HIV-2 should be tested for HIV-2 infection with HIV-2–specific virologic assays at time points similar to those used for HIV-1 testing.[34] Quantitative HIV-2 plasma RNA viral load testing for clinical care is available from the University of Washington[8] and the New York State Department of Health.[9] Antibody testing of infants (e.g., with the Bio-Rad Laboratories Multispot HIV-1/HIV-2 test) can also be performed at age 18 months to confirm clearance of HIV-2 antibodies.[33]

References

1. De Cock KM, Brun-Vezinet F. Epidemiology of HIV-2 infection. *AIDS.* 1989;3 Suppl 1:S89-95. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2514761.

2. De Cock KM, Adjorlolo G, Ekpini E, et al. Epidemiology and transmission of HIV-2. Why there is no HIV-2 pandemic. *JAMA*. 1993;270(17):2083-2086. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8147962.

3. Campbell-Yesufu OT, Gandhi RT. Update on human immunodeficiency virus (HIV)-2 infection. *Clin Infect Dis*. 2011;52(6):780-787. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21367732.

4. Heitzinger K, Sow PS, Dia Badiane NM, et al. Trends of HIV-1, HIV-2 and dual infection in women attending outpatient clinics in Senegal, 1990-2009. *Int J STD AIDS*. 2012;23(10):710-716. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23104745.

5. Cazein F, Lot F, Pillonel J, et al. HIV and AIDS surveillance in France, 2006. *Bull Epidemiol Hebd*. 2007(46-47):386-393.

6. Centers for Disease Control and Prevention. HIV-2 infection surveillance--United States, 1987-2009. *MMWR Morb Mortal Wkly Rep*. 2011;60(29):985-988. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21796096.

7. Centers for Disease Control and Prevention. Laboratory testing for the diagnosis of HIV iInfection: updated recommendations. 2014. Available at: http://stacks.cdc.gov/view/cdc/23447.

8. Chang M, Gottlieb GS, Dragavon JA, et al. Validation for clinical use of a novel HIV-2 plasma RNA viral load assay using the Abbott m2000 platform. *J Clin Virol*. 2012;55(2):128-133. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22832059.

9. Styer LM, Miller TT, Parker MM. Validation and clinical use of a sensitive HIV-2 viral load assay that uses a whole virus internal control. *J Clin Virol*. 2013;58 Suppl 1:e127-133. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24342472.

10. Branson BM, Pandori M. 2012 HIV diagnostics conference: the molecular diagnostics perspective. *Expert Rev of Mol Diagn*. 2013;13(3):243-245. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23570401.

11. Charpentier C, Camacho R, Ruelle J, et al. HIV-2EU: supporting standardized HIV-2 drug resistance interpretation in Europe. *Clin Infect Dis*. 2013;56(11):1654-1658. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23429380.

12. Esbjornsson J, Mansson F, Kvist A, et al. Long-term follow-up of HIV-2-related AIDS and mortality in Guinea-Bissau: a prospective open cohort study. *Lancet HIV*. 2018. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30392769.

13. Kanki PJ, Travers KU, S MB, et al. Slower heterosexual spread of HIV-2 than HIV-1. *Lancet*. 1994;343(8903):943-946. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7909009.

14. Matheron S, Courpotin C, Simon F, et al. Vertical transmission of HIV-2. *Lancet*. 1990;335(8697):1103-1104. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1970407.

15. O'Donovan D, Ariyoshi K, Milligan P, et al. Maternal plasma viral RNA levels determine marked differences in mother-to-child transmission rates of HIV-1 and HIV-2 in The Gambia. MRC/Gambia government/university college London medical school working group on mother-child transmission of HIV. *AIDS.* 2000;14(4):441-448. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10770548.

16. Burgard M, Jasseron C, Matheron S, et al. Mother-to-child transmission of HIV-2 infection from 1986 to 2007 in the ANRS French Perinatal Cohort EPF-CO1. *Clin Infect Dis*. 2010;51(7):833-843. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20804413.

17. Adjorlolo-Johnson G, De Cock KM, Ekpini E, et al. Prospective comparison of mother-to-child transmission of HIV-1 and HIV-2 in Abidjan, Ivory Coast. *JAMA*. 1994;272(6):462-466. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8040982.

18. Andreasson PA, Dias F, Naucler A, Andersson S, Biberfeld G. A prospective study of vertical transmission of HIV-2 in Bissau, Guinea-Bissau. *AIDS.* 1993;7(7):989-993. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8357558.

19. Prince PD, Matser A, van Tienen C, Whittle HC, Schim van der Loeff MF. Mortality rates in people dually infected with HIV-1/2 and those infected with either HIV-1 or HIV-2: a systematic review and meta-analysis. *AIDS.* 2014;28(4):549-558. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23921613.

20. Ekouevi DK, Tchounga BK, Coffie PA, et al. Antiretroviral therapy response among HIV-2 infected patients: a systematic review. *BMC Infect Dis*. 2014;14:461. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25154616.

21. Tuaillon E, Gueudin M, Lemee V, et al. Phenotypic susceptibility to nonnucleoside inhibitors of virion-associated reverse transcriptase from different HIV types and groups. *J Acquir Immune Defic Syndr*. 2004;37(5):1543-1549. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15577405.

22. Poveda E, Rodes B, Toro C, Soriano V. Are fusion inhibitors active against all HIV variants? *AIDS Res Hum Retroviruses*. 2004;20(3):347-348. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15117459.

23. Le Hingrat Q, Collin G, Le M, et al. A new mechanism of resistance of HIV-2 to integrase inhibitors: a 5 amino-acids insertion in the integrase C-terminal domain. *Clin Infect Dis*. 2018. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30383215.

24. Smith RA, Raugi DN, Wu VH, et al. Comparison of the antiviral activity of bictegravir against HIV-1 and HIV-2 isolates and integrase inhibitor-resistant HIV-2 mutants. *Antimicrob Agents Chemother*. 2019;63(5). Available at: https://www.ncbi.nlm.nih.gov/pubmed/30803972.

25. Desbois D, Roquebert B, Peytavin G, et al. In vitro phenotypic susceptibility of human immunodeficiency virus type 2 clinical isolates to protease inhibitors. *Antimicrob Agents Chemother*. 2008;52(4):1545-1548. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18227188.

26. Requena S, Trevino A, Cabezas T, et al. Drug resistance mutations in HIV-2 patients failing raltegravir and influence on dolutegravir response. *J Antimicrob Chemother*. 2017;72(7):2083-2088. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28369593.

27. Borrego P, Taveira N. HIV-2 susceptibility to entry inhibitors. *AIDS Rev*. 2013;15(1):49-61. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23449229.

28. Visseaux B, Charpentier C, Hurtado-Nedelec M, et al. In vitro phenotypic susceptibility of HIV-2 clinical isolates to CCR5 inhibitors. *Antimicrob Agents Chemother*. 2012;56(1):137-139. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22064539.

29. Charpentier C, Visseaux B, Benard A, et al. Transmitted drug resistance in French HIV-2-infected patients. *AIDS.* 2013;27(10):1671-1674. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23595155.

30. Menendez-Arias L, Alvarez M. Antiretroviral therapy and drug resistance in human immunodeficiency virus type 2 infection. *Antiviral Res*. 2014;102:70-86. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24345729.

31. Storto A, Visseaux B, Bertine M, et al. Minority resistant variants are also present in HIV-2-infected antiretroviral-naive patients. *J Antimicrob Chemother*. 2018. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29415189.

32. Gilleece Y, Chadwick DR, Breuer J, et al. British HIV association guidelines for antiretroviral treatment of HIV-2-positive individuals 2010. *HIV Med*. 2010;11(10):611-619. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20961377.

33. de Ruiter A, Mercey D, Anderson J, et al. British HIV association and children's HIV association guidelines for the management of HIV infection in pregnant women 2008. *HIV Med*. 2008;9(7):452-502. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18840151.

34. Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV. Guidelines for the use of antiretroviral agents in pediatric HIV infection. 2018. Available at: http://aidsinfo.nih.gov/contentfiles/lvguidelines/pediatricguidelines.pdf.

The Management of Prenatal Care and General Principles of Antiretroviral Therapy and HIV Management in Women with Perinatal HIV Infection (Last updated December 7, 2018; last reviewed December 7, 2018)

Panel's Recommendations
• The management of prenatal care and general principles of antiretroviral therapy (ART) and HIV management do not differ between pregnant women with perinatally acquired HIV (PHIV) and those with nonperinatally acquired HIV **(AII)**.
• Using the same guiding principles that are used for heavily ART-experienced adults, optimal ART regimens should be selected based on resistance testing, prior ART history, and pill burden **(AII)**.
• Consultation with experts in HIV and pregnancy is recommended when the presence of extensive drug resistance warrants the use of antiretroviral drugs for which there is limited experience in pregnancy **(AIII)**.
• Pregnant women with PHIV warrant enhanced focus on adherence interventions during pregnancy and after delivery **(AIII)**.
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*

With the availability of potent antiretroviral therapy (ART), morbidity and mortality have significantly declined in individuals living with HIV, including those with perinatally acquired HIV (PHIV). An increasing number of women with PHIV are now reaching childbearing age and becoming pregnant. A significant number of these pregnancies are unplanned.[1-3] The components of prenatal care and general principles of ART and HIV management do not differ between pregnant women with PHIV and those with nonperinatally acquired HIV (NPHIV) who acquired HIV through sexual contact or injection drug use. However, there are unique challenges in this population related to reproductive health care needs and the prevention of perinatal transmission. Adherence to ART is commonly a major challenge for women with PHIV. In addition, because most of these women are still adolescents and young adults, they may be at higher risk of certain pregnancy complications, such as preterm delivery, small-for-gestational-age (SGA) infants, low birth weight, and preeclampsia.[4-9]

As many as 30% to 70% of pregnant women with PHIV have evidence of HIV drug resistance.[8,10-12] This is due to extensive ART exposure prior to pregnancy, including exposure to suboptimal monotherapy or dual-therapy regimens as children.[8] Optimal ART regimens should be selected on the basis of resistance testing, prior ART history, and the same guiding principles used for ART-experienced adults. Because of the potential for known or suspected complex drug-resistance mutation patterns in individuals who acquired HIV perinatally, clinicians may consider performing phenotypic resistance testing in these women during pregnancy when resistance testing is indicated. Consideration should be given to regimens that optimize dosing intervals and minimize pill burden. Regimens should be constructed using antiretroviral (ARV) drugs that are recommended for use in pregnancy whenever possible. However, in many cases, the presence of extensive drug resistance may warrant the use of ARV drugs for which there is limited experience in pregnancy; consultation with experts in HIV and pregnancy is recommended in such cases.

Women with PHIV are more likely to have lower median CD4 T lymphocyte counts, detectable viral loads, and genotypic drug resistance than women with NPHIV; these factors can have implications during labor and delivery.[8,12-15] Several studies have suggested that pregnant women with PHIV are more likely to have a cesarean delivery in order to prevent HIV transmission; cesarean deliveries are most commonly indicated in these women due to a lack of viral load suppression.[10,13] Cesarean delivery in these young women raises concerns for increased risk of adverse obstetric outcomes if repeated cesarean deliveries are required for future pregnancies. Women with PHIV experience prolonged HIV infection, receive multiple ART regimens, and have an increased likelihood of drug-resistant virus. Despite these factors, many studies have shown that the risk of perinatal transmission does not appear to be increased in this population, as long as these women

receive appropriate prenatal management and ART that results in viral suppression.[8,10,12,13,16-18] However, in a recent analysis of data from SMARTT PHACS that included 2,123 births from 2007 to 2015, mothers with PHIV had a higher perinatal HIV transmission rate (1.1%; 95% CI, 0.3–4.3) than mothers with NPHIV (0.4%; 95% CI, 0.2–1.0%); this higher rate was associated with a greater likelihood of detectable maternal viral load at delivery.[15]

Evidence from studies is conflicting as to whether women with PHIV have higher rates of preterm and SGA infants when compared with women with NPHIV.[19,20] Several studies have demonstrated no associations between perinatal route of maternal HIV infection and preterm birth, SGA infants, or low birth weight.[8,12,19-21] Other studies with smaller sample sizes have reported conflicting results:

- A case series reported high rates of preterm birth (31%) among women with PHIV.[10]
- Jao et al. reported a four-fold increased risk for SGA births among women with PHIV compared to those with NPHIV.[9]
- Munjal et al. reported earlier gestational age at delivery and lower average birth weights in infants born to women with PHIV compared to those with NPHIV.[13]
- Jao et al. found that infants born to women with PHIV had lower mean length-for-age throughout the first year of life than infants born to women with NPHIV.[7]

Women with PHIV also have both poor rates of retention in care and viral suppression for up to 2 years postpartum.[22] In a retrospective analysis of 37 pregnancies among women with PHIV and 40 pregnancies among age-matched women with NPHIV who delivered during the same time period, the viral load declines achieved during pregnancy in women with PHIV were not sustained during postpartum follow-up, in contrast to the age-matched comparison group. During 4 years of follow-up, there were four deaths due to AIDS-related complications among women with PHIV but none among the women with NPHIV.[13] Although genotypic mutations were more common in women with PHIV, loss of viral suppression that resulted in postpartum disease progression was more likely to be related to adherence difficulties, highlighting the need for special focus on adherence interventions after delivery.

Psychosocial challenges in PHIV may be magnified due to the presence of a lifelong chronic illness, high rates of depression,[23] and, frequently the loss of one or both parents. Attention to developmentally appropriate adherence counseling is critical. A systematic review and meta-analysis of 50 eligible studies on ART adherence in individuals living with HIV aged 12 years to 24 years old, reported 62.3% adherence overall among youth with HIV. Youth from U.S. studies had the lowest average rate of adherence at 53%.[24] In a 2014 study of 1,596 people with PHIV who were living in New York City, only 61% were virally suppressed. The authors attributed poor ART adherence to social, behavioral, and developmental factors.[25] A history of depression has also been associated with nonadherence to ART among pregnant women with PHIV.[26] Focused attention on diagnosis and treatment of depression during the preconception period may lead to better medication adherence. Self-motivation and social support were key to achieving medication adherence in a study of adolescents living with HIV in the United Kingdom.[27]

Among adolescents with PHIV, pregnancy may create additional complications in the transition from pediatric/adolescent HIV care to adult care due to the complexity of navigating an adult health care system with multiple providers. However, pregnancy may also be an opportune time for a young woman to transition to adult care. Studies have noted reduced rates of retention in care and viral suppression among pediatric and adolescent persons with HIV who are transitioning to adult health care.[28] Continuing support for adherence to treatment is needed in this population. Coordination of care across multiple disciplines, including HIV primary care, OB/GYN, and perinatal case management, is advised.[29] Integration of reproductive health counseling and pregnancy prevention, including consistent condom use and developmentally appropriate skill building to support disclosure, is recommended.

References

1. Kenny J, Williams B, Prime K, Tookey P, Foster C. Pregnancy outcomes in adolescents in the UK and Ireland growing up with HIV. *HIV Med*. 2012;13(5):304-308. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22136754.

2. Brogly SB, Ylitalo N, Mofenson LM, et al. *In utero* nucleoside reverse transcriptase inhibitor exposure and signs of possible mitochondrial dysfunction in HIV-uninfected children. *AIDS*. 2007;21(8):929-938. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17457086.

3. Badell ML, Lindsay M. Thirty years later: pregnancies in females perinatally infected with human immunodeficiency virus-1. *AIDS Res Treat*. 2012;2012:418630. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22970353.

4. Ganchimeg T, Ota E, Morisaki N, et al. Pregnancy and childbirth outcomes among adolescent mothers: a world health organization multicountry study. *BJOG*. 2014;121 Suppl 1:40-48. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24641534.

5. Ananth CV, Keyes KM, Wapner RJ. Pre-eclampsia rates in the United States, 1980-2010: age-period-cohort analysis. *BMJ*. 2013;347:f6564. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24201165.

6. Witt WP, Cheng ER, Wisk LE, et al. Preterm birth in the United States: the impact of stressful life events prior to conception and maternal age. *Am J Public Health*. 2014;104 Suppl 1:S73-80. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24354830.

7. Jao J, Agwu A, Mhango G, et al. Growth patterns in the first year of life differ in infants born to perinatally vs. nonperinatally HIV-infected women. *AIDS*. 2015;29(1):111-116. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25562495.

8. Badell ML, Kachikis A, Haddad LB, Nguyen ML, Lindsay M. Comparison of pregnancies between perinatally and sexually HIV-infected women: an observational study at an urban hospital. *Infect Dis Obstet Gynecol*. 2013;2013:301763. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24106419.

9. Jao J, Sigel KM, Chen KT, et al. Small for gestational age birth outcomes in pregnant women with perinatally acquired HIV. *AIDS*. 2012;26(7):855-859. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22313958.

10. Williams SF, Keane-Tarchichi MH, Bettica L, Dieudonne A, Bardeguez AD. Pregnancy outcomes in young women with perinatally acquired human immunodeficiency virus-1. *Am J Obstet Gynecol*. 2009;200(2):149 e141-145. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18973871.

11. Cruz ML, Santos E, Benamor Teixeira Mde L, et al. Viral suppression and resistance in a cohort of perinatally-HIV infected (PHIV+) pregnant women. *Int J Environ Res Public Health*. 2016;13(6). Available at: https://www.ncbi.nlm.nih.gov/pubmed/27338425.

12. Lazenby GB, Mmeje O, Fisher BM, et al. Antiretroviral resistance and pregnancy characteristics of women with perinatal and nonperinatal HIV infection. *Infect Dis Obstet Gynecol*. 2016;2016:4897501. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27413359.

13. Munjal I, Dobroszycki J, Fakioglu E, et al. Impact of HIV-1 infection and pregnancy on maternal health: comparison between perinatally and behaviorally infected young women. *Adolescent Health Med Ther*. 2013;4:51-58. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24600295.

14. Byrne L, Sconza R, Foster C, Tookey PA, Cortina-Borja M, Thorne C. Pregnancy incidence and outcomes in women with perinatal HIV infection. *AIDS*. 2017;31(12):1745-1754. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28590327.

15. Goodenough CJ, Patel K, Van Dyke RB, Pediatric HIV AIDS Cohort Study. Is there a higher risk of mother-to-child transmission of HIV among pregnant women with perinatal HIV infection? *Pediatr Infect Dis J*. 2018. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29742647.

16. Phillips UK, Rosenberg MG, Dobroszycki J, et al. Pregnancy in women with perinatally acquired HIV-infection: outcomes and challenges. *AIDS Care*. 2011;23(9):1076-1082. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21562997.

17. Calitri C, Gabiano C, Galli L, et al. The second generation of HIV-1 vertically exposed infants: a case series from the Italian Register for paediatric HIV infection. *BMC Infect Dis*. 2014;14:277. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24885649.

18. Millery M, Vazquez S, Walther V, Humphrey N, Schlecht J, Van Devanter N. Pregnancies in perinatally HIV-infected young women and implications for care and service programs. *JANAC*. 2012;23(1):41-51. Available at: http://www.

ncbi.nlm.nih.gov/pubmed/21820325.

19. Hleyhel M, Tubiana R, Rouzioux C, et al. Pregnancies in women who acquired HIV perinatally. Presented at: Conference on Retroviruses and Opportunistic Infections. 2017. Seattle, WA.

20. Jao J, Kacanek D, Williams P, et al. Birth weight and preterm delivery outcomes of perinatally vs. non-perinatally HIV-infected pregnant women in the U.S.: results from the PHACS SMARTT study and IMPAACT P1025 protocol. *Clin Infect Dis*. 2017 Sep 15;65(6):982-989. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28575201.

21. Agwu AL, Jang SS, Korthuis PT, Araneta MR, Gebo KA. Pregnancy incidence and outcomes in vertically and behaviorally HIV-infected youth. *JAMA*. 2011;305(5):468-470. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21285423.

22. Meade CM, Hussen SA, Momplaisir F, Badell M, Hackett S, Sheth AN. Long term engagement in HIV care among postpartum women with perinatal HIV infection in the United States. *AIDS Care*. 2018;30(4):488-492. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29254363.

23. Mellins CA, Brackis-Cott E, Dolezal C, Abrams EJ. Psychiatric disorders in youth with perinatally acquired human immunodeficiency virus infection. *Pediatr Infect Dis J*. 2006;25(5):432-437. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16645508.

24. Kim SH, Gerver SM, Fidler S, Ward H. Adherence to antiretroviral therapy in adolescents living with HIV: systematic review and meta-analysis. *AIDS*. 2014;28(13):1945-1956. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24845154.

25. Xia Q, Shah D, Gill B, Torian LV, Braunstein SL. Continuum of care among people living with perinatally acquired HIV infection in New York City, 2014. *Public Health Rep*. 2016;131(4):566-573. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27453601.

26. Sheth SS, Coleman J, Cannon T, et al. Association between depression and nonadherence to antiretroviral therapy in pregnant women with perinatally acquired HIV. *AIDS Care*. 2015;27(3):350-354. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25616659.

27. Kim SH, McDonald S, Kim S, Foster C, Fidler S. Importance of self-motivation and social support in medication adherence in HIV-infected Adolescents in the United Kingdom and Ireland: A Multicentre HYPNet Study. *AIDS Patient Care STDS*. 2015;29(6):354-364. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25825814.

28. Hatfield-Timajchy K, Brown JL, Haddad LB, Chakraborty R, Kourtis AP. Parenting among adolescents and young adults with human immunodeficiency virus infection in the United States: challenges, unmet needs, and opportunities. *AIDS Patient Care STDS*. 2016;30(7):315-323. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27410495.

29. Anderson EA, Momplaisir FM, Corson C, Brady KA. Assessing the impact of perinatal HIV case management on outcomes along the HIV care continuum for pregnant and postpartum women living with HIV, Philadelphia 2005-2013. *AIDS Behav*. 2017. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28176167.

Acute HIV Infection (Last updated December 12, 2019; last reviewed December 12, 2019)

Panel's Recommendations

- When acute HIV infection is suspected in pregnancy or during breastfeeding, a plasma HIV RNA test should be obtained in conjunction an antigen/antibody immunoassay test (see Acute and Recent [Early] HIV Infection in the Adult and Adolescent Antiretroviral Guidelines and the Centers for Disease Control and Prevention HIV testing algorithm for more information) **(AII)**.
- Repeat HIV testing in the third trimester is recommended for pregnant women with initial negative HIV test results who are known to be at risk of acquiring HIV, who are receiving care in facilities that have an HIV incidence of ≥1 case per 1,000 pregnant women per year, those who reside in jurisdictions with elevated HIV incidence, or those who reside in states that require third-trimester testing (see Revised Recommendations for HIV Testing of Adults, Adolescents, and Pregnant Women in Health Care Settings) **(AII)**.
- All pregnant women with acute or recent HIV infection should start antiretroviral therapy (ART) as soon as possible to prevent perinatal transmission, with the goal of rapidly suppressing plasma HIV RNA below detectable levels **(AI)**.
- In women with acute HIV infection, baseline genotypic resistance testing should be performed simultaneously with initiation of ART **(AII)**, and the regimen should be adjusted, if necessary, to optimize virologic response **(BIII)**.
- Dolutegravir plus tenofovir disoproxil fumarate (TDF) plus emtricitabine (FTC) is the *Preferred* ART regimen for pregnant and breastfeeding women with acute HIV, irrespective of trimester (see Table 6, Table 7, and Recommendations for Use of Antiretroviral Drugs During Pregnancy and Appendix D: Dolutegravir Counseling Guide for Health Care Providers) **(AII)**.
  - Alternatively, raltegravir plus TDF plus FTC or a regimen that includes a ritonavir-boosted protease inhibitor can be initiated **(AIII)**. See Table 6, Table 7, and Updated Guidance about the Use of Dolutegravir in Pregnancy in Recommendations for Use of Antiretroviral Drugs During Pregnancy for more information.
  - The Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission emphasizes the importance of counseling and informed decision-making regarding all antiretroviral (ARV) regimens for people living with HIV **(AIII)**.
- Lactating women who receive a diagnosis of acute HIV infection should be counseled to discontinue breastfeeding.
- Infants born to women who received a diagnosis of acute HIV infection during pregnancy or breastfeeding are at high risk of perinatal HIV transmission and should receive an ARV regimen that is appropriate for this elevated risk (see Table 8 in Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection) **(All)**. Consulting a pediatric HIV specialist regarding appropriate infant management is strongly recommended (see Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection).

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*

Women may have an increased risk of HIV infection during pregnancy and breastfeeding.[1,2] In a recent study of 2,751 serodifferent couples in seven African countries, 686 pregnancies among HIV-negative women were identified and 82 incident HIV infections occurred. After adjusting for condom use, pre-exposure prophylaxis (PrEP) use, and HIV viral load, the probability of HIV acquisition per condomless sex act was higher in late pregnancy (adjusted relative risk [aRR] 2.82; $P = 0.01$) and the postpartum period (aRR 3.97; $P = 0.01$) than during the nonpregnant period.[1] Women who are at risk for acquiring HIV during pregnancy and the postpartum period should consider using interventions that prevent HIV acquisition, such as PrEP.[3]

Acute or recent HIV infection during pregnancy or breastfeeding is associated with an increased risk of perinatal HIV transmission, and a significant proportion of perinatal transmission cases can be attributed to maternal acute infection.[4] Among 10,308 pregnant women with HIV who delivered live infants from 2005 to 2010 in 15 areas in the United States that conducted Enhanced Perinatal Surveillance, 124 women (1.2%) seroconverted during pregnancy. The rate of perinatal transmission was eight times higher among women who seroconverted during pregnancy (12.9%) than among those who seroconverted prior to pregnancy (1.6%) ($P < 0.0001$).[5] Similarly, among 108 new perinatal HIV infections that were identified between 2006 and 2013 in the United Kingdom, 23 were associated with a concurrent maternal seroconversion.[6] The high rate of transmission in people with acute infection is likely related to the high viral loads in plasma, breast milk, and the genital tract that are present during acute infection;[7] in addition, acute HIV infection symptoms

can be nonspecific, which results in missed opportunities to diagnose and implement interventions that can reduce the risk of perinatal transmission.

Health care providers should maintain a high level of suspicion of acute HIV infection in women who are pregnant or breastfeeding and have clinical signs and symptoms that are compatible with acute infection. Even when women do not report high-risk behaviors, it is still possible that their sexual partners are practicing high-risk behaviors without their knowledge. An estimated 40% to 90% of patients with acute HIV infection will experience symptoms of acute retroviral syndrome, which is characterized by fever, lymphadenopathy, pharyngitis, skin rash, myalgias/arthralgias, and other symptoms.[8-10] Providers often do not recognize acute HIV infection because the symptoms are similar to those of other common illnesses, and individuals with acute HIV infection may also be asymptomatic.

When acute retroviral syndrome is suspected during pregnancy or breastfeeding, a plasma HIV RNA test should be obtained in conjunction with an antigen/antibody immunoassay test. Updated guidance for HIV testing recommends using a Food and Drug Administration (FDA)-approved antigen/antibody combination (fourth-generation) immunoassay that detects HIV-1 and HIV-2 antibodies and HIV-1 p24 antigen for initial testing. These tests are used to screen for established infection with HIV-1 or HIV-2 and for acute HIV-1 infection. More specific guidance on HIV testing can be found in the Acute and Recent (Early) HIV Infection section of the Adult and Adolescent Antiretroviral Guidelines, the Centers for Disease Control and Prevention (CDC) HIV testing algorithm, and the Maternal HIV Testing and Identification of Perinatal HIV Exposure.

Recent HIV infection also can be detected by repeat HIV testing later in pregnancy in women whose initial HIV test was negative.[11] A report from the MIRAD study found that six of 54 women (11%) whose HIV was identified with rapid HIV testing during labor had acute or recent infection.[12] Repeat HIV testing during the third trimester is recommended for pregnant women who are known to be at risk of HIV infection, who receive care in facilities with an HIV incidence of ≥1 case per 1,000 pregnant women per year, or who reside in jurisdictions with elevated HIV incidence (see Prenatal and Perinatal Human Immunodeficiency Virus Testing, Revised Recommendations for HIV Testing of Adults, Adolescents, and Pregnant Women in Health Care Settings, the CDC HIV testing algorithm, and Maternal HIV Testing and Identification of Perinatal HIV Exposure).[13] Despite this recommendation, a retrospective cohort study at a large metropolitan hospital in a high-prevalence jurisdiction reported that repeat prenatal HIV testing was performed in only 28.4% of women.[14]

Acute or recent HIV infection during pregnancy and breastfeeding is associated with a high risk of perinatal transmission of HIV. Therefore, all pregnant women with acute or recent HIV infection should start antiretroviral therapy (ART) as soon as possible, with the goal of preventing perinatal transmission by rapid suppression of plasma HIV RNA below detectable levels. Baseline genotypic resistance testing should be performed to guide adjustment of an optimal antiretroviral (ARV) drug regimen. Data from the United States and Europe demonstrate that in 6% to 16% of patients, transmitted virus may be resistant to ≥1 ARV drug.[15,16] If results of resistance testing are already available or the source virus's resistance pattern is known, that information can be used to guide the selection of the drug regimen.

A regimen that includes dolutegravir (DTG) plus tenofovir disoproxil fumarate (TDF) plus emtricitabine (FTC) should be initiated in pregnant women and breastfeeding women with acute HIV infection (see Recommendations for Use of Antiretroviral Drugs During Pregnancy, Table 6, and Table 7). DTG exposure around the time of conception has been associated with a small but significant increase in the risk of infant neural tube defects (NTDs) in Botswana (0.3%). Although this risk was higher than the risk for NTDs in infants born to women who were receiving efavirenz (EFV; 0.05%) and women without HIV (0.08%), there are not enough data to determine the risk of NTDs with preconception use of all *Preferred* and *Alternative* regimens, including DTG, in the United States. Based on the available evidence, the Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission recommends DTG as a *Preferred* drug for pregnant women, irrespective of trimester. When DTG use is continued after delivery,

clinicians should discuss reproductive desires as well as the risks and benefits of conceiving on DTG and contraceptive options with the patient. For additional information and recommendations on the use of DTG, see Recommendations for Use of Antiretroviral Drugs During Pregnancy and Appendix D: Dolutegravir Counseling Guide for Health Care Providers.

DTG is associated with higher rates of virologic suppression, faster rates of viral load decline, and a higher genetic barrier to drug resistance than other *Preferred* and *Alternative* agents. DTG plus TDF plus FTC is considered a reasonable ARV regimen for treatment of acute infection in nonpregnant adults, but data are limited regarding the transmission of integrase strand transfer inhibitor (INSTI)-resistant HIV and the efficacy of this regimen when treating early infection. *Alternative* regimens for treatment of acute infection during pregnancy and breastfeeding include raltegravir (RAL) plus TDF plus FTC or a regimen that includes a ritonavir-boosted protease inhibitor-based regimen (see Table 6 and Table 7). TDF plus FTC is the *Preferred* nucleoside reverse transcriptase inhibitor (NRTI) backbone for treatment of acute infection. Abacavir **is not recommended** for empiric treatment of acute infection unless the patient previously tested negative for HLA-B*5701; this will avoid delays in ART initiation while awaiting HLA-B*5701 test results.

Several studies have demonstrated that the use of INSTI-based regimens is associated with shorter time to viral suppression compared with other ARV regimens. An observational study evaluated time to viral suppression among 86 nonpregnant adults with newly diagnosed HIV infection: 36 participants (42%) had acute HIV infection, 27 (31%) had early HIV infection, and 23 (27%) had established HIV infection. ART was initiated within 30 days of diagnosis, and the median time to documented viral suppression was 12 weeks. Time to viral suppression was significantly shorter in those who received an INSTI-based regimen than in those who received a PI-based regimen. Median time to viral suppression was 12 weeks in those who received INSTIs (interquartile range [IQR] 4–24 weeks) and 24 weeks in those who received PIs (IQR 12–24 weeks; $P = 0.022$). The baseline viral loads did not differ between these two groups.[17] In the ADVANCE study, 1,053 ART-naive individuals were randomized to receive DTG plus FTC plus TDF versus DTG plus FTC plus tenofovir alafenamide (TAF), or EFV plus FTC plus TDF. At 48 weeks, 84% of participants in the DTG plus FTC plus TAF group, 85% in the DTG plus FTC plus TDF group, and 79% in the EFV-based ART group had achieved HIV RNA <50 copies/mL. While both DTG-based regimens were noninferior to the EFV regimen, the time to viral suppression was substantially shorter among participants in the DTG arms.[18]

While no data are available to inform the treatment of acute HIV during pregnancy, two recent studies in women who presented to care late in pregnancy demonstrated more rapid viral decline on INSTI-based regimens than on EFV-based ART. In the DolPHIN-2 study, 268 ART-naive pregnant women in Uganda and South Africa with a median gestational age of 31 weeks were randomized to receive either DTG plus two NRTIs or EFV plus two NRTIs. At delivery, women in the DTG arm were significantly more likely to have achieved HIV RNA <50 copies/mL than those in the EFV arm (73.8% vs. 42.6%; adjusted risk ratio 1.66; 95% confidence interval, 1.3–2.1; $P < 0.0001$).[19] Similarly, IMPAACT 1081 randomized 408 ART-naive, late-presenting pregnant women in South America, Africa, Thailand, and the United States to receive RAL plus two NRTIs or EFV plus two NRTIs. Fifty percent of these women presented to care at 20 weeks to <28 weeks gestation and 50% presented at 28 weeks to <37 weeks gestation. Median time to achieve viral loads <200 copies/mL was 8 days for women who received RAL-based ART and 15 days for those who received EFV-based treatment. Viral load decline was greater in women who received RAL-based ART than in those who received EFV-based ART at Weeks 2, 4, and 6 after initiation.[20]

When acute HIV infection is diagnosed during pregnancy, and particularly when it is documented in late pregnancy, cesarean delivery may be necessary when there is insufficient time to fully suppress a patient's viral load. When acute HIV infection is diagnosed during breastfeeding, breastfeeding should be discontinued. In nursing mothers with suspected seroconversion, breastfeeding should be interrupted, and it should not resume if infection is confirmed (see Guidance for Counseling and Managing Women Living with HIV in the United States Who Desire to Breastfeed). Women can continue to express and store breast milk while awaiting confirmation of infection status.

Given the high risk of transmission to the infant with acute maternal infection, an infant should receive an ARV regimen that is appropriate for this elevated risk when acute HIV infection is diagnosed during pregnancy or breastfeeding (see Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection). Consulting a pediatric HIV specialist regarding appropriate infant management is strongly recommended. All women who receive a diagnosis of acute infection should be asked whether they know the HIV status of their partner. HIV testing of the sexual partners of all pregnant women who test HIV positive should be encouraged, and PrEP should be offered to partners who test HIV negative.

References

1. Thomson KA, Hughes J, Baeten JM, et al. Increased risk of HIV acquisition among women throughout pregnancy and during the postpartum period: a prospective per-coital-act analysis among women with HIV-infected partners. *J Infect Dis*. 2018;218(1):16-25. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29514254.

2. Drake AL, Wagner A, Richardson B, John-Stewart G. Incident HIV during pregnancy and postpartum and risk of mother-to-child HIV transmission: a systematic review and meta-analysis. *PLoS Med*. 2014;11(2):e1001608. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24586123.

3. Mofenson LM. Risk of HIV acquisition during pregnancy and postpartum: a call for action. *J Infect Dis*. 2018;218(1):1-4. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29506075.

4. Nesheim S, Harris LF, Lampe M. Elimination of perinatal HIV infection in the USA and other high-income countries: achievements and challenges. *Curr Opin HIV AIDS*. 2013;8(5):447-456. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23925002.

5. Singh S, Lampe MA, Surendera B, S. R, Borkowf CB, Nesheim SR. HIV seroconversion during pregnancy and mother-to-child HIV transmission: data from the enhanced perinatal surveillance projects, United States, 2005-2010. Presented at: Conference on Retroviruses and Opportunistic Infections. 2013. Atlanta, Georgia.

6. Peters H, Thorne C, Tookey PA, Byrne L. National audit of perinatal HIV infections in the UK, 2006-2013: what lessons can be learnt? *HIV Med.* 2018;19(4):280-289. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29336508.

7. Morrison CS, Demers K, Kwok C, et al. Plasma and cervical viral loads among Ugandan and Zimbabwean women during acute and early HIV-1 infection. *AIDS*. 2010;24(4):573-582. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20154581.

8. Yerly S, Hirschel B. Diagnosing acute HIV infection. *Expert Rev Anti Infect Ther*. 2012;10(1):31-41. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22149612.

9. Richey LE, Halperin J. Acute human immunodeficiency virus infection. *Am J Med Sci*. 2013;345(2):136-142. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23095473.

10. Crowell TA, Colby DJ, Pinyakorn S, et al. Acute retroviral syndrome is associated with high viral burden, CD4 depletion, and immune activation in systemic and tissue compartments. *Clin Infect Dis*. 2018;66(10):1540-1549. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29228130.

11. Wertz J, Cesario J, Sackrison J, Kim S, Dola C. Acute HIV infection in pregnancy: the case for third trimester rescreening. *Case Rep Infect Dis*. 2011;2011:340817. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22567467.

12. Nesheim S, Jamieson DJ, Danner SP, et al. Primary human immunodeficiency virus infection during pregnancy detected by repeat testing. *Am J Obstet Gynecol*. 2007;197(2):149 e141-145. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17689629.

13. Branson BM, Handsfield HH, Lampe MA, et al. Revised recommendations for HIV testing of adults, adolescents, and pregnant women in health-care settings. *MMWR Recomm Rep*. 2006;55(RR-14):1-17; quiz CE11-14. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16988643.

14. Liao C, Golden WC, Anderson JR, Coleman JS. Missed opportunities for repeat HIV testing in pregnancy: implications for elimination of mother-to-child transmission in the United States. *AIDS Patient Care STDS*. 2017;31(1):20-26. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27936863.

15. Rhee SY, Blanco JL, Jordan MR, et al. Geographic and temporal trends in the molecular epidemiology and genetic mechanisms of transmitted HIV-1 drug resistance: an individual-patient- and sequence-level meta-analysis. *PLoS Med*. 2015;12(4):e1001810. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25849352.

16. Buchacz K, Young B, Palella FJ Jr, et al. Trends in use of genotypic resistance testing and frequency of major drug resistance among antiretroviral-naive persons in the HIV Outpatient Study, 1999-2011. *J Antimicrob Chemother*. 2015;70(8):2337-2346. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25979729.

17. Hoenigl M, Chaillon A, Moore DJ, et al. Rapid HIV viral load suppression in those Initiating antiretroviral therapy at first visit after HIV diagnosis. *Sci Re*p. 2016;6:32947. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27597312.

18. 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.

19. Kintu K, Malaba T, Nakibuka J, et al. Rct of dolutegravir vs. efavirenz-based therapy initiated in late pregnancy: DolPHIN-2. Abstract 40. Conference on Retroviruses and Opportunistic Infections. 2019. Seattle, Washington. Available at: http://www.croiconference.org/sessions/rct-dolutegravir-vs-efavirenz-based-therapy-initiated-late-pregnancy-dolphin-2.

20. Mirochnick M, Shapiro D, Morrison L, et al. Randomized trial of raltegravir-ART vs. efavirenz-ART when initiated during pregnancy. Abstract 39. Presented at: Conference on Retroviruses and Opportunistic Infections. 2019. Seattle, Washington.

Intrapartum Care (Last updated December 7, 2018; last reviewed December 7, 2018)

Intrapartum Antiretroviral Therapy/Prophylaxis

Panel's Recommendations

- Women should continue taking their antepartum combination antiretroviral therapy (ART) on schedule as much as possible during labor and before scheduled cesarean delivery **(AIII)**.
- Intravenous (IV) zidovudine:
  - Should be administered to women living with HIV if HIV RNA is known or suspected to be >1,000 copies/mL (or if HIV RNA is unknown) near delivery **(AI)**.
  - Is not required for women who are receiving ART regimens and who have HIV RNA ≤50 copies/mL during late pregnancy and near delivery and no concerns regarding adherence to the ART regimen **(BII)**.
  - May be considered for women with HIV RNA between 50 and 999 copies/mL. There are inadequate data to determine whether administration of IV zidovudine to women with HIV RNA levels between 50 and 999 copies/mL provides any additional protection against perinatal transmission. This decision can be made on a case by case basis, taking into consideration the woman's recent ART adherence, her preferences, and involving expert consultation if needed **(CII)**.
- Scheduled cesarean delivery at 38 weeks' gestation (compared to 39 weeks for most indications) is recommended for women who have HIV RNA >1,000 copies/mL near delivery (see Transmission and Mode of Delivery) **(AI)**.
- Women who present in labor with unknown HIV status should undergo expedited antigen/antibody HIV testing **(AII)**.
  - If the results are positive, an HIV-1/HIV-2 antibody differentiation test and an HIV-1 RNA assay should be done as soon as possible and maternal (IV zidovudine)/infant (combination antiretroviral [ARV] prophylaxis) ARV drugs should be initiated pending results of the differentiation test **(AII)**.
  - If the maternal HIV differentiation test is positive or if acute infection is suspected because the differentiation test is negative but the HIV RNA test is positive, infant ARV drugs should be managed as discussed in Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV **(AI)**. Women with positive expedited testing should not initiate breastfeeding until HIV infection is definitively ruled out (see Postpartum Follow-Up of Women Living with HIV Infection) **(AII)**.
  - If the maternal HIV differentiation test is negative and acute HIV infection has been reasonably excluded with a negative HIV RNA test, the maternal and infant ARV drugs should be stopped **(AIII)**.

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*

Women Who Have Received Antepartum Antiretroviral Drugs

Use of Intravenous Zidovudine During Labor

The PACTG 076 zidovudine regimen included a continuous intravenous (IV) infusion of zidovudine during labor for all women. Antiretroviral therapy (ART) regimens are now recommended for treatment of HIV and prevention of perinatal transmission of HIV in all pregnant women, regardless of CD4 T lymphocyte (CD4) cell count and HIV viral load; the additional benefit of IV zidovudine in women receiving combination regimens has not been evaluated in randomized clinical trials.

The French Perinatal Cohort evaluated transmission in >11,000 pregnant women with HIV who were receiving antiretroviral (ARV) drugs (10% of women were receiving zidovudine alone, 18% were receiving dual-ARV regimens, and 72% were receiving triple-ARV regimens) and who delivered between 1997 and 2010, stratified by viral load at delivery; 95% of these women received IV intrapartum zidovudine.[1] The overall rate of perinatal transmission was 0.9% (95/10,239 infants) with IV zidovudine and 1.8% (9/514 infants, $P = 0.06$) without IV zidovudine. Among women with HIV RNA <1,000 copies/mL at delivery, no transmission occurred among 369 women who did not receive IV zidovudine compared to a transmission rate of 0.6% (47/8,132, $P > 0.20$) among those who received IV zidovudine. Among women with HIV RNA >1,000 copies/mL whose infants received only zidovudine for prophylaxis, the risk of transmission

was 10.2% without maternal IV zidovudine and 2.5% with maternal IV zidovudine ($P < 0.01$) The risk of transmission was no different (4.8% vs. 4.1%, $P = 0.83$) if the neonate received intensified prophylaxis with two or more ARV drugs. In a cohort of 717 women who delivered between 1996 and 2008 in Miami, the majority of whom were receiving an ART regimen and had HIV RNA <1,000 copies/mL at delivery, lack of receipt of IV zidovudine during labor was not associated with an increased risk of transmission.[2] Among a European cohort of infants considered at high risk of transmission, lack of IV zidovudine during labor was associated with transmission on univariate analysis but was not significantly associated with transmission once the results were adjusted for maternal HIV RNA and other factors (adjusted odds ratio with IV zidovudine = 0.79; 95% CI, 0.55–1.15; $P = 0.23$).[3] In a cohort of Irish women with HIV RNA <1,000 copies/mL who received ART for at least 4 weeks before delivery, no transmission occurred among 61 women who received either no zidovudine during labor or <4 hours of IV zidovudine.[4]

Based on the results of these studies, IV zidovudine should continue to be administered to women with HIV RNA >1,000 copies/mL near delivery (or to women living with HIV who have unknown HIV RNA levels), regardless of antepartum regimen. IV zidovudine is not required for women receiving ART and have HIV RNA ≤1,000 copies/mL in late pregnancy and/or near delivery and have no concerns about adherence to or tolerance of their ART regimens. However, many experts feel that there are inadequate data to determine whether administration of intrapartum IV zidovudine to women with HIV RNA between 50 and 999 copies/mL provides any additional protection against perinatal transmission. They recommend intrapartum IV zidovudine administration to women with HIV RNA levels in this range, as the transmission risk is slightly higher (approximately 1% to 2%) when HIV RNA is in the range of 50 to 999 copies/mL compared to <50 copies/mL (transmission risk is ≤1%).[1,5,6] In addition, a recent study noted that 6% of women with suppressed HIV RNA levels during pregnancy had viral load rebound near delivery.[7] Regardless of viral load, the clinician may elect to use or not use intrapartum IV zidovudine based on clinical judgment.

In women with HIV RNA >1,000 copies/mL who are undergoing a scheduled cesarean delivery for prevention of transmission, IV zidovudine administration should begin 3 hours before the scheduled operative delivery. This recommendation is based on a pharmacokinetic (PK) study of zidovudine given orally during pregnancy and as a continuous infusion during labor. Maternal zidovudine levels were measured at baseline, after the initial IV loading dose, and then every 3 to 4 hours until delivery. Zidovudine levels were also measured in cord blood.[8] Systemic and intracellular zidovudine levels increased from baseline but appeared to stabilize after 3 hours of infusion; cord blood zidovudine levels were associated with maternal levels and maternal infusion duration. If cesarean delivery is being performed for other indications and maternal viral load is ≤1,000 copies/mL near the time of delivery, administration of IV zidovudine is not required.

If zidovudine was not used in the antenatal ART regimen because of known or suspected zidovudine resistance, intrapartum use of the drug is still recommended in women with HIV RNA >1,000 copies/mL near delivery unless a woman has a documented history of hypersensitivity. This intrapartum use of the drug is recommended because of the unique characteristics of zidovudine and its proven record in reducing perinatal transmission, even in the presence of maternal resistance to the drug (see Antiretroviral Drug Resistance and Resistance Testing in Pregnancy).

In some international studies, oral (rather than IV) zidovudine has been administered during labor. Data are limited on the PKs of oral versus IV zidovudine during labor. In studies of oral dosing in labor, zidovudine levels were lower than with IV dosing, and PK parameters suggested erratic absorption during labor.[9,10] Therefore, in women with HIV RNA >1,000 copies/mL near delivery for whom zidovudine is recommended, IV would be preferred to oral administration in the United States; in situations where IV administration is not possible, oral administration of zidovudine using a 600-mg loading dose and 400 mg every 3 hours[10] can be considered.

Continuation of Antenatal Antiretroviral Drugs during Labor

Women who are receiving an antepartum ART regimen should continue that regimen on schedule as much as possible during the intrapartum period to provide maximal virologic suppression and to minimize the

chance of developing drug resistance. If the woman is to receive IV zidovudine and oral zidovudine as part of the antepartum regimen, the oral zidovudine component of the regimen can be held while she receives IV zidovudine. When cesarean delivery is planned, oral medications can be administered preoperatively with sips of water. Medications requiring food ingestion for absorption can be taken with liquid dietary supplements, contingent on consultation with the attending anesthesiologist during the preoperative period. If the maternal ARV drug regimen must be interrupted temporarily (meaning for <24 hours) during the peripartum period, all drugs should be stopped and reinstituted simultaneously to minimize the chance that resistance will develop.

Women Who Have Received Antepartum Antiretroviral Drugs but Have Suboptimal Viral Suppression Near Delivery

Women who have received ART regimens may not achieve complete viral suppression by the time of delivery because of factors such as difficulty with adherence, viral resistance, or late entry into care. Regardless of the reason, all women who have HIV RNA levels >1,000 copies/mL or presumed >1,000 copies/mL near the time of delivery should be offered a scheduled cesarean delivery at 38 weeks, which may significantly reduce the risk of transmission (see Transmission and Mode of Delivery).

Women with HIV RNA levels above 1,000 copies/mL at the time of delivery should receive IV zidovudine along with oral administration of their other ARVs, as described above. While additional maternal ART, such as single-dose nevirapine, is not recommended, in certain high-risk situations, additional medications for prophylaxis in infants may be warranted. These situations include cases where maternal HIV RNA levels are high at or near the time of delivery, especially if delivery is not a scheduled cesarean delivery (see Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV and Table 9).

Women Who Have Not Received Antepartum Antiretroviral Drugs

Women Who Present in Labor without Documentation of HIV Status

All women without documentation of HIV status at the time of labor should be screened for HIV with expedited testing unless they decline (i.e., "opt-out" screening). Expedited repeat HIV testing is also recommended for women presenting in labor who tested negative for HIV in early pregnancy, but who are at increased risk of HIV infection and were not retested in the third trimester.[11] Factors that may increase the risk of infection include diagnosis of a sexually transmitted disease, illicit drug use, exchange of sex for money or drugs, multiple sexual partners during pregnancy, a sexual partner at risk of or with known HIV infection, signs/symptoms of acute HIV infection, or living in a region with an elevated incidence of HIV in women of childbearing age.[11]

Initial testing for HIV should be done with a Food and Drug Administration (FDA)-approved antigen/antibody combination immunoassay that detects HIV-1 and HIV-2 antibodies, and an HIV RNA assay to screen for both acute and established HIV-1 infection. No further testing is required for specimens that are nonreactive on the initial immunoassay. Women with a positive initial antigen/antibody combination immunoassay result should be tested with an FDA-approved antibody immunoassay that differentiates HIV-1 antibodies from HIV-2 antibodies. Reactive results on the initial antigen/antibody combination immunoassay and the HIV-1/HIV-2 antibody differentiation immunoassay should be interpreted as positive for HIV-1 antibodies; HIV-2 antibodies; or HIV antibodies, undifferentiated (see Revised Recommendations for HIV Testing in Adults, Adolescents, and Pregnant Women in Health-Care Settings and the resource page for laboratory testing for HIV). Those with high HIV-1 RNA and a negative confirmatory HIV assay most likely have acute HIV infection.

Expedited HIV testing should be available on a 24-hour basis at all facilities with a maternity service and/or neonatal intensive care unit. Statutes and regulations regarding expedited testing vary from state to state (see State HIV Testing Laws from the Clinician Consultation Center for a review of these laws). Current information about testing also should be available at all facilities with a maternity service and/or neonatal intensive care unit.

Women who test positive on the initial test should be presumed to have HIV until follow-up testing clarifies their infection status. IV zidovudine should be started immediately in all women with positive initial HIV tests in labor to prevent perinatal transmission of HIV, as discussed below. Women with positive initial testing should not initiate breastfeeding until HIV infection is definitively ruled out.

During the postpartum period, clinicians should follow up with these women on the results of confirmatory HIV-1/HIV-2 antibody differentiation immunoassay and HIV-1 RNA testing and provide appropriate assessments of their health status as soon as possible, including CD4 cell count and HIV genotype for resistance. Arrangements also should be made for establishing HIV care and providing ongoing psychosocial support after discharge. The infant should receive combination ARV prophylaxis as outlined in the section on Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV. If the follow-up antibody testing is negative, results of the HIV RNA test should be reviewed to rule out acute infection as a cause of the initial positive test before ART is stopped (see Acute HIV Infection).

Choice of Intrapartum/Postpartum Antiretroviral Regimen for Women who Have Not Received Antepartum Antiretroviral Therapy

All women with HIV who have not received antepartum ARV drugs should start IV zidovudine immediately to prevent perinatal transmission of HIV. Although intrapartum/neonatal ARV medications will not prevent perinatal transmission that occurs before labor, most transmission occurs near to or during labor and delivery. Pre-exposure prophylaxis for the fetus can be provided by giving mothers a drug that rapidly crosses the placenta, producing fetal systemic ARV drug levels during intensive exposure to HIV in maternal genital secretions and in blood during birth. In general, zidovudine and other nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and the integrase inhibitor raltegravir cross the placenta well, whereas protease inhibitors do not (see Table 10). A small PK study and placental perfusion data suggest moderate-to-high placental transfer of elvitegravir.[12,13] For dolutegravir, a PK study found the median cord blood/maternal plasma concentration ratio was 1.25 in 18 infants, corroborating data from case reports and placental perfusion models showing moderate-to-high placental transfer of dolutegravir.[14-16] Considerations for postpartum regimen choice are similar to those for women who have never received ART (see Pregnant Women Living with HIV Who Have Never Received Antiretroviral Drugs).

A large international trial (NICHD-HPTN 040/PACTG 1043) demonstrated that adding ARV agents to the neonatal portion of the intrapartum/neonatal zidovudine regimen can further reduce perinatal transmission of HIV for mothers who have received no antepartum ARV drugs (see Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV). In this study, women who had not received antepartum ARV drugs received IV zidovudine if HIV infection was diagnosed during labor or no zidovudine if HIV was diagnosed immediately postpartum; their infants received either 6 weeks of zidovudine alone or zidovudine in combination with other agents. The combination infant regimens resulted in a 50% reduction in transmission when compared with zidovudine alone.[17] Adding maternal single-dose nevirapine to a regimen of maternal short-course zidovudine and infant single-dose nevirapine did not reduce the risk of perinatal transmission in the Mashi trial conducted by Shapiro et al. in Botswana. Therefore, intrapartum maternal single-dose nevirapine is not recommended for a woman who has received no antepartum ARV drugs.[18] The efficacy of newer drugs, such as integrase inhibitors, in this situation has not been evaluated. In the United States, where replacement feeding is affordable, feasible, acceptable, sustainable, and safe, women diagnosed with HIV infection during labor or the early postpartum period should be counseled against breastfeeding.

References

1. Briand N, Warszawski J, Mandelbrot L, et al. Is intrapartum intravenous zidovudine for prevention of mother-to-child HIV-1 transmission still useful in the combination antiretroviral therapy era? *Clin Infect Di*s. 2013;57(6):903-914. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23728147.

2. Cotter AM, Brookfield KF, Duthely LM, Gonzalez Quintero VH, Potter JE, O'Sullivan MJ. Duration of membrane rupture and risk of perinatal transmission of HIV-1 in the era of combination antiretroviral therapy. *Am J Obstet Gynecol*. 2012;207(6):482 e481-485. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23103331.

3. Chiappini E, Galli L, Giaquinto C, et al. Use of combination neonatal prophylaxis for the prevention of mother-to-child transmission of HIV infection in European high-risk infants. *AIDS*. 2013;27(6):991-1000. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23211776.

4. Wong VV. Is peripartum zidovudine absolutely necessary for patients with a viral load less than 1,000 copies/mL? *J Obstet Gynaecol*. 2011;31(8):740-742. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22085066.

5. Townsend CL, Byrne L, Cortina-Borja M, et al. Earlier initiation of ART and further decline in mother-to-child HIV transmission rates, 2000-2011. *AIDS*. 2014;28(7):1049-1057. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24566097.

6. Myer L, Phillips TK, McIntyre JA, et al. HIV viraemia and mother-to-child transmission risk after antiretroviral therapy initiation in pregnancy in Cape Town, South Africa. *HIV Med*. 2017;18(2):80-88. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27353189.

7. Boucoiran I, Albert AYK, Tulloch K, et al. Human immunodeficiency virus viral load rebound near delivery in previously suppressed, combination antiretroviral therapy-treated pregnant women. *Obstet Gynecol*. 2017;130(3):497-501. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28796673.

8. Rodman JH, Flynn PM, Robbins B, et al. Systemic pharmacokinetics and cellular pharmacology of zidovudine in human immunodeficiency virus type 1-infected women and newborn infants. *J Infect Dis*. 1999;180(6):1844-1850. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10558940.

9. Bhadrakom C, Simonds RJ, Mei JV, et al. Oral zidovudine during labor to prevent perinatal HIV transmission, Bangkok: tolerance and zidovudine concentration in cord blood. Bangkok collaborative perinatal HIV transmission study group. *AIDS*. 2000;14(5):509-516. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10780713.

10. Mirochnick M, Rodman JH, Robbins BL, et al. Pharmacokinetics of oral zidovudine administered during labour: a preliminary study. *HIV Med*. 2007;8(7):451-456. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17760737.

11. Branson BM, Handsfield HH, Lampe MA, et al. Revised recommendations for HIV testing of adults, adolescents, and pregnant women in health-care settings. *MMWR Recomm Rep*. 2006;55(RR-14):1-17; quiz CE11-14. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16988643.

12. Best B, Caparelli E, Stek A, et al. Elvitegravir/cobicistat pharmacokinetics in pregnancy and postpartum. Presented at: Conference on Retroviruses and Opportunistic Infections. 2017. Seattle, WA.

13. Faure-Bardon V, Mandelbrot L, Duro D, Dussaux C, Le M, Peytavin G. Placental transfer of elvitegravir and cobicistat in an ex vivo human cotyledon double perfusion model. *AIDS*. 2018;32(3):321-325. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29112064.

14. Lewis JM, Railton E, Riordan A, Khoo S, Chaponda M. Early experience of dolutegravir pharmacokinetics in pregnancy: high maternal levels and significant foetal exposure with twice-daily dosing. *AIDS*. 2016;30(8):1313-1315. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27128333.

15. Rimawi BH, Johnson E, Rajakumar A, et al. Pharmacokinetics and placental transfer of elvitegravir and dolutegravir, and other antiretrovirals during pregnancy. *Antimicrob Agents Chemother*. 2017. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28348149.

16. 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.

17. Nielsen-Saines K, Watts DH, Veloso VG, et al. Three postpartum antiretroviral regimens to prevent intrapartum HIV infection. *N Engl J Med*. 2012;366(25):2368-2379. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22716975.

18. Shapiro RL, Thior I, Gilbert PB, et al. Maternal single-dose nevirapine versus placebo as part of an antiretroviral strategy to prevent mother-to-child HIV transmission in Botswana. *AIDS*. 2006;20(9):1281-1288. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16816557.

Transmission and Mode of Delivery (Last updated December 7, 2018; last reviewed December 7, 2018)

Panel's Recommendations
• Scheduled cesarean delivery at 38 weeks gestation to minimize perinatal transmission of HIV is recommended for women with HIV RNA levels >1,000 copies/mL or unknown HIV levels near the time of delivery, irrespective of administration of antepartum antiretroviral therapy (ART) **(AII)**.
• Scheduled cesarean delivery performed solely for prevention of perinatal transmission in women receiving ART with HIV RNA ≤1,000 copies/mL **is not routinely recommended** given the low rate of perinatal transmission in this group **(AII)**.
• In women with HIV RNA levels ≤1,000 copies/mL, if scheduled cesarean delivery or induction is indicated, it should be performed at the standard time for obstetrical indications **(AII)**.
• In women with an HIV RNA >1,000 copies/mL or unknown HIV RNA level who present in spontaneous labor or with ruptured membranes, there is insufficient evidence to determine whether cesarean delivery reduces the risk of perinatal HIV transmission. Management of women originally scheduled for cesarean delivery because of HIV who present in labor must be individualized at the time of presentation **(BII)**. In these circumstances, consultation with an expert in perinatal HIV (e.g., telephone consultation with the National Perinatal HIV/AIDS Clinical Consultation Center at 888-448-8765) may be helpful in rapidly developing an individualized delivery plan.
• In women on ART with HIV RNA ≤1,000 copies/mL, duration of ruptured membranes is not associated with an increased risk of perinatal transmission, and vaginal delivery is recommended **(BII)**.
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*

Basis for Current Recommendations

Scheduled cesarean delivery, defined as cesarean delivery performed before the onset of labor and before rupture of membranes, is recommended for prevention of perinatal transmission of HIV in women with HIV RNA levels >1,000 copies/mL near delivery and for women with unknown HIV RNA levels.

This recommendation is based on findings from a multicenter, randomized clinical trial[1] and from a large individual patient data meta-analysis.[2] These two studies were conducted when the majority of women with HIV received no antiretroviral (ARV) drugs or zidovudine as a single drug and before the availability of viral load information. Study results have since been extrapolated to make current recommendations about the mode of delivery in an era when antiretroviral therapy (ART) during pregnancy is recommended and viral load information is readily available.

HIV RNA Level >1000 copies/mL as a Threshold for Recommendation of Scheduled Cesarean Delivery

The American Congress of Obstetricians and Gynecologists (ACOG) recommends that women with HIV RNA >1,000 copies/mL be counseled regarding the potential benefits of scheduled cesarean delivery.[3] Initially, the threshold of 1,000 copies/mL was based largely on data from the Women and Infants Transmission Study, a large prospective cohort study that reported no HIV transmission among 57 women with HIV RNA levels <1,000 copies/mL.[4] Studies reported since then have demonstrated that HIV transmission can occur in infants born to women with low viral loads. Most studies do not specify the exact time that the HIV RNA levels closest to delivery were measured. The Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission recommends viral load testing at approximately 34–36 weeks gestation to inform decisions about mode of delivery and to inform decisions about optimal treatment of the newborn. A Canadian retrospective analysis reported that 6% of women (n = 318) who had had an undetectable HIV RNA level at some point during pregnancy had detectable virus at delivery, thus demonstrating that viral rebound near delivery may occur even among women in care.[5]

In an analysis of 957 women with plasma viral loads ≤1,000 copies/mL, cesarean delivery (scheduled or urgent) reduced the risk of HIV transmission when adjusting for potential confounders including receipt of maternal ARV medications (adjusted odds ratio [AOR] 0.30; $P = 0.022$); however, zidovudine alone was the

regimen primarily used as prophylaxis.[6] Among infants born to 834 women with HIV RNA ≤1,000 copies/mL receiving ARV medications, 8 (1%) were born with HIV. In a report based on data from a comprehensive national surveillance system in the United Kingdom and Ireland, 3 (0.1%) of 2,309 and 12 (1.2%) of 1,023 infants born to women with HIV RNA levels <50 copies/mL and 50 to 999 copies/mL, respectively, were born with HIV, of which some infections appear to represent *in utero* transmission.[7]

Some studies demonstrate that transmission can occur even at very low HIV RNA levels. However, given the low rate of transmission among women with very low viral loads, it is unclear whether scheduled cesarean delivery confers any additional benefit in reducing transmission. Furthermore, there is evidence that complication rates for cesarean deliveries are higher in women with HIV than in women without HIV.[8] Therefore, decisions about mode of delivery for women receiving ART with HIV RNA levels ≤1,000 copies/mL should be individualized based on discussion between an obstetrician and a pregnant woman. Women should be informed that there is no evidence that a scheduled cesarean delivery performed solely for prevention of perinatal transmission is of any benefit in women receiving ART with HIV RNA ≤1,000 copies/mL and therefore **is not routinely recommended** for these women.

Scheduled Cesarean Delivery in the Antiretroviral Therapy Era

In surveillance data from the United Kingdom and Ireland published in 2008, pregnant women receiving ART (i.e., ≥3 drugs) had transmission rates of about 1%, unadjusted for mode of delivery.[7] Given the low transmission rates achievable with use of maternal ART, the benefit of scheduled cesarean delivery is difficult to evaluate. Most of the women included in both the randomized clinical trial[1] and meta-analysis[2] documenting the benefits of cesarean delivery were receiving either no ARV drugs or zidovudine alone. However, other data partially address this issue.

In a report on births to women with HIV from the United Kingdom and Ireland between 2000 and 2011, perinatal transmission rates in women on ART with HIV RNA <1,000 copies/mL who had a planned cesarean delivery (13/3,544; 0.3%) were not significantly different than those in women who had a planned vaginal delivery (6/2238; 0.3%).[9] Similarly, data from the French Perinatal Cohort showed no difference in transmission rates between vaginal delivery and planned cesarean delivery among women on ART with suppressed viral loads, 0.3% in both groups of women. For preterm deliveries in women with HIV RNA <1,000 copies/mL, transmission rates were slightly higher among planned vaginal deliveries than among planned cesarean deliveries, but the number of women with viral loads <400 copies/ml was low and the differences across viral load levels were not statistically significant (1/9 [11.1%] vs. 1/17 [5.9%] for HIV RNA 400–1,000 copies/mL; 1/39 [2.6%] vs. 1/56 [1.8%] for HIV RNA 50–400 copies/mL; 1/189 [0.5%] vs. 0/143 [0%] for HIV RNA <50 copies/mL, for planned vaginal deliveries and elective cesarean deliveries, respectively).[10] Among 290 deliveries in Finland from 1993 to 2013, 75.4% of women delivered vaginally, 12.5% by elective cesarean, and 12.5% by emergency cesarean; 80% had HIV RNA <50 copies/mL. There were no perinatal HIV transmissions across the delivery methods.[11] Therefore, no evidence to date suggests any benefit from scheduled cesarean delivery in women who have been receiving ART for several weeks and who and are virally suppressed at or near delivery.

When the delivery method selected is scheduled cesarean delivery and the maternal viral load is >1,000 copies/mL, a 1-hour loading dose followed by a continuous intravenous (IV) zidovudine infusion for 2 hours (3 hours total) before scheduled cesarean delivery should be administered. In a study of the pharmacokinetics of IV zidovudine in 28 pregnant women, the ratio of cord blood-to-maternal-zidovudine concentration was significantly greater in women who received IV zidovudine for 3 to 6 hours before delivery than in those who received the infusion for <3 hours before delivery (1.0 vs. 0.55, respectively).[12] This suggests that an interval of ≥3 hours may provide adequate time for ZDV to cross the placenta and equilibrate with maternal concentrations, although the relationship between specific cord blood zidovudine levels or cord blood-to-maternal-zidovudine levels and efficacy in preventing perinatal transmission of HIV is unknown.

Because unscheduled cesarean delivery is performed for both maternal and fetal indications, when an unscheduled cesarean delivery is indicated in a woman who has a viral load >1,000 copies/mL, consideration

can be given to shortening the interval between initiation of IV zidovudine administration and delivery. For example, some experts recommend administering the 1-hour loading dose of IV zidovudine and not waiting to complete additional administration before proceeding with delivery.

Women Presenting Late in Pregnancy

Women with HIV who present late in pregnancy and are not receiving ARV drugs may not have HIV RNA results available before delivery. Without current therapy, HIV RNA levels are unlikely to be ≤1,000 copies/mL at baseline. Even when ART is initiated immediately, reduction in plasma HIV RNA to undetectable levels may take several weeks, depending on the baseline viral load and kinetics of viral decay for a particular drug regimen.[13-15] In this instance, scheduled cesarean delivery is likely to provide additional benefit in reducing the risk of perinatal transmission of HIV for women, unless viral suppression can be documented before 38 weeks gestation. Although some experts would recommend a cesarean delivery in a woman who has virologic suppression for a brief period (e.g., <2 weeks), given this scenario, many others would support a vaginal delivery as long as the woman's plasma HIV RNA level was <1000 copies/mL by the day of delivery.

Timing of Vaginal Delivery

A comparison of 613 women (with HIV RNA level <1,000 copies/mL) who delivered vaginally at 38 to 40 weeks gestation and 303 women who delivered vaginally at ≥40 weeks gestation demonstrated no difference (0.3 vs. 0.5%) in perinatal HIV transmission by estimated gestational age at delivery, which suggests that women without an indication for scheduled cesarean delivery for prevention of perinatal HIV transmission should be delivered according to standard obstetrical indications.[16]

Timing of Scheduled Cesarean Delivery

For the general obstetric population, ACOG recommends that a scheduled cesarean delivery not be performed before 39 weeks gestation because of the risk of iatrogenic prematurity.[17,18] However, when cesarean delivery is indicated to prevent transmission of HIV, ACOG recommends scheduling cesarean delivery at 38 weeks gestation to decrease the likelihood of onset of labor or rupture of membranes before delivery.[3] In all women undergoing repeat cesarean delivery, the risk of any neonatal adverse event—including neonatal death, respiratory complications, hypoglycemia, newborn sepsis, or admission to the neonatal intensive care unit—is 15.3% at 37 weeks gestation, 11.0% at 38 weeks gestation, and 8.0% at 39 weeks gestation.[18] Gestational age should be determined by best obstetrical dating criteria, including last menstrual period and early ultrasound for dating purposes. Amniocentesis to document lung maturity should be avoided when possible in women with HIV and is rarely indicated before a scheduled cesarean section for prevention of HIV transmission.

Among 1,194 infants born to mothers with HIV, nine (1.6%) born vaginally and 18 (4.4%) delivered by scheduled cesarean had respiratory distress syndrome (RDS) ($P < 0.001$). There was no statistically significant association between mode of delivery and infant RDS in an adjusted model that included infant gestational age and birth weight.[19] Although newborn complications may be increased in planned cesarean delivery <39 weeks gestation, the benefits of planned cesarean delivery at 38 weeks are generally thought to outweigh the risks if the procedure is performed for prevention of HIV transmission. When scheduled cesarean delivery is performed in women with HIV with an HIV RNA ≤1,000 copies/mL for an indication other than decreasing HIV transmission, cesarean delivery should be scheduled based on ACOG guidelines for women without HIV.

Risk of Maternal Complications

Administration of perioperative antimicrobial prophylaxis is recommended for all women to decrease maternal infectious morbidity associated with cesarean delivery. Most studies have demonstrated that women with HIV have higher rates of postoperative complications, mostly infectious, than women without HIV and that their risk of complications is related to degree of immunosuppression and the receipt of suppressive ART.[20-25] Furthermore, a Cochrane review of six studies in women with HIV concluded that urgent cesarean delivery was associated with the highest risk of postpartum morbidity, scheduled cesarean delivery was intermediate in risk, and vaginal delivery had the lowest risk of morbidity.[26,27] Complication rates in women with HIV in most studies[1,28-32] were

within the range reported in populations of women without HIV with similar risk factors and not of sufficient frequency or severity to outweigh the potential benefit of reduced perinatal HIV transmission. A U.S. study of nationally representative data from a large administrative database demonstrated that—even in the era of ART—infectious complications, surgical trauma, prolonged hospitalization, and in-hospital deaths remain higher among women with HIV than among women without HIV.[8] The rate of any complication associated with cesarean delivery was 117 per 1,000 deliveries among women with HIV and 67 per 1,000 deliveries among women without HIV. A meta-analysis of primarily observational studies in women with HIV also reported higher morbidity with elective cesarean delivery than with vaginal delivery (OR 3.12) and no reduction in perinatal HIV transmission among the mothers on ART.[33] Therefore, women with HIV should be counseled regarding the specific risks associated with undergoing cesarean delivery in the setting of HIV infection.

In addition, caution should be exercised in proceeding with a cesarean delivery in circumstances where there is no clear evidence of benefit, especially in younger women who are likely to have additional pregnancies and perhaps multiple cesarean deliveries. Increased risk of abnormal placentation (e.g., placenta previa, placenta accrete, placenta increta, placenta percreta) and intrapartum hemorrhage are associated with increasing numbers of cesarean deliveries. These risks should be considered and discussed with the woman before proceeding with a cesarean delivery.[34,35]

Managing Women Who Present in Early Labor or with Ruptured Membranes

Most studies have shown a similar risk of HIV transmission for cesarean delivery performed for obstetric indications after labor and membrane rupture as for vaginal delivery. In one study, the HIV transmission rate was similar in women undergoing emergency cesarean delivery and those delivering vaginally (1.6% vs. 1.9%, respectively).[7] A meta-analysis of studies in women with HIV, most of whom were receiving no ARV drugs or only zidovudine, demonstrated a 2% increased transmission risk for every additional hour of ruptured membranes.[36] However, it is not clear how soon after the onset of labor or the rupture of membranes the benefit of cesarean delivery is lost.[37] A prospective study of 707 women in Ireland showed that among the 493 women on ART with HIV RNA levels <1,000 copies/mL, no cases of perinatal transmission occurred with membranes ruptured for up to 25 hours. Only a viral load of >10,000 copies/mL was an independent risk factor for perinatal transmission.[38] A prospective review of 2,398 women with HIV in the UK and Ireland, most of whom were virally suppressed, showed no association between duration of ruptured membranes and perinatal HIV transmission in 2,116 term deliveries, regardless of maternal viral load. Eighty-nine percent of the women had HIV RNA levels <50 copies/mL; among the remaining 11%, 9% had HIV RNA levels 50–399 copies/mL, 1% 400–999 copies/mL, 0.4% 1,000–9,999 copies/mL, and 0.6% >10,000 copies/mL. Among mother-baby pairs with perinatal transmission and no evidence of *in utero* transmission, 2 mothers had undetectable HIV RNA levels (<50 copies/mL), one had an HIV RNA level of 50–399 copies/mL, and 2 had levels >10,000 copies/mL. Among term deliveries, median duration of rupture of membranes was 3 hours and 30 minutes; 71 (3.4%) had rupture of membranes >24 hours, and 24 (1.1%) had rupture of membranes >48 hours. The study authors concluded that obstetric care of women on ART at term with ruptured membranes should be "normalized."[39,40] Because it is not clear whether cesarean delivery after onset of labor reduces the risk of perinatal HIV transmission, management of women originally scheduled for cesarean delivery who present in labor must be individualized at the time of presentation. In these circumstances, consultation with an expert in perinatal HIV may be helpful. Because the delivery plan in the setting of labor must be made quickly, telephone consultation via a 24-hour, 7-day-a-week hotline (e.g., the National Perinatal HIV/AIDS Clinical Consultation Center [888-448-8765] may be helpful in rapidly developing an individualized plan).

The woman's oral ARV drug regimen should be continued, and IV zidovudine initiated (if previously planned) regardless of the mode of delivery.

When membrane rupture occurs before 37 weeks gestation, decisions about timing of delivery should be based on best obstetrical practices, considering risks to the infant of prematurity and of HIV transmission. Steroids should be given, when appropriate, to accelerate fetal lung maturity because no data exist to suggest that these recommendations need to be altered for women with HIV. When the decision is made to deliver, route of delivery should be according to obstetrical indications.

Operative Vaginal Delivery

In the past, before data from the era of ART was available, HIV was considered a relative contraindication to operative vaginal delivery with forceps or vacuum, but data from the era of ART had been lacking. Peters et al. reviewed the deliveries of 9,072 women living with HIV in the United Kingdom between 2008 and 2016. The percentage of women with viral suppression was 80% for the deliveries from 2007 through 2011 and 90% for those from 2012 through 2014. Among the 3,023/3,663 vaginal deliveries with data as to whether forceps or vacuum device were used, 249 (8.2%) involved operative delivery (5.6% using forceps, 2.4% using vacuum device, 0.1% using both forceps and vacuum device, and 0.2% device type unknown). Among the 222 infants with known HIV status at 18 months of age, there was 1 case of HIV transmission with multiple possible causes and not enough evidence to confirm intrapartum transmission. The study authors concluded that operative delivery is a safe option for women who are virally suppressed.[41]

References

1. European Mode of Delivery Collaboration. Elective caesarean-section versus vaginal delivery in prevention of vertical HIV-1 transmission: a randomised clinical trial. *Lancet*. 1999;353(9158):1035-1039. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10199349.

2. International Perinatal HIV Group. The mode of delivery and the risk of vertical transmission of human immunodeficiency virus type 1--a meta-analysis of 15 prospective cohort studies. The International Perinatal HIV Group. *N Engl J Med*. 1999;340(13):977-987. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10099139.

3. American College of Obstetricians and Gynecologists. ACOG Committee Opinion No. 751: labor and delivery management of women with Human Immunodeficiency Virus infection. *Obstet Gynecol*. 2018;132(3):e131-e137. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30134427.

4. Garcia PM, Kalish LA, Pitt J, et al. Maternal levels of plasma human immunodeficiency virus type 1 RNA and the risk of perinatal transmission. Women and infants transmission study group. *N Engl J Med*. 1999;341(6):394-402. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10432324.

5. Boucoiran I, Albert AYK, Tulloch K, et al. Human immunodeficiency virus viral load rebound near delivery in previously suppressed, combination antiretroviral therapy-treated pregnant women. *Obstet Gynecol*. 2017;130(3):497-501. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28796673.

6. Ioannidis JP, Abrams EJ, Ammann A, et al. Perinatal transmission of human immunodeficiency virus type 1 by pregnant women with RNA virus loads <1000 copies/ml. *J Infect Dis*. 2001;183(4):539-545. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11170978.

7. Townsend CL, Cortina-Borja M, Peckham CS, de Ruiter A, Lyall H, Tookey PA. Low rates of mother-to-child transmission of HIV following effective pregnancy interventions in the United Kingdom and Ireland, 2000–2006. *AIDS*. 2008;22(8):973-981. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18453857.

8. Kourtis AP, Ellington S, Pazol K, Flowers L, Haddad L, Jamieson DJ. Complications of cesarean deliveries among HIV-infected women in the United States. *AIDS*. 2014;28(17):2609-2618. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25574961.

9. Townsend CL, Byrne L, Cortina-Borja M, et al. Earlier initiation of ART and further decline in mother-to-child HIV transmission rates, 2000-2011. *AIDS*. 2014;28(7):1049-1057. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24566097.

10. Briand N, Jasseron C, Sibiude J, et al. Cesarean section for HIV-infected women in the combination antiretroviral therapies era, 2000-2010. *Am J Obstet Gynecol*. 2013;209(4):335 e331-335 e312. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23791563.

11. Aho I, Kaijomaa M, Kivela P, et al. Most women living with HIV can deliver vaginally: national data from Finland 1993–2013. *PLoS One*. 2018;13(3):e0194370. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29566017.

12. Rodman JH, Flynn PM, Robbins B, et al. Systemic pharmacokinetics and cellular pharmacology of zidovudine in human immunodeficiency virus type 1-infected women and newborn infants. *J Infect Dis*. 1999;180(6):1844-1850. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10558940.

13. European Collaborative Study, Patel D, Cortina-Borja M, Thorne C, Newell ML. Time to undetectable viral load after highly active antiretroviral therapy initiation among HIV-infected pregnant women. *Clin Infect Dis*. 2007;44(12):1647-1656. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17516411.

14. Aziz N, Sokoloff A, Kornak J, et al. Time to viral load suppression in antiretroviral-naive and -experienced HIV-infected pregnant women on highly active antiretroviral therapy: implications for pregnant women presenting late in gestation. *BJOG*. 2013;120(12):1534-1547. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23924192.

15. Read PJ, Mandalia S, Khan P, et al. When should HAART be initiated in pregnancy to achieve an undetectable HIV viral load by delivery? *AIDS*. 2012;26(9):1095-1103. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22441248.

16. Scott RK, Chakhtoura N, Burke MM, Cohen RA, Kreitchmann R. Delivery after 40 weeks of gestation in pregnant women with well-controlled human immunodeficiency virus. *Obstet Gynecol*. 2017;130(3):502-510. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28796679.

17. American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 97: Fetal lung maturity. *Obstet Gynecol*. 2008;112(3):717-726. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18757686.

18. Tita AT, Landon MB, Spong CY, et al. Timing of elective repeat cesarean delivery at term and neonatal outcomes. *N Engl J Med*. 2009;360(2):111-120. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19129525.

19. Livingston EG, Huo Y, Patel K, et al. Mode of delivery and infant respiratory morbidity among infants born to HIV-1-infected women. *Obstet Gynecol*. 2010;116(2 Pt 1):335-343. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20664394.

20. Grubert TA, Reindell D, Kastner R, Lutz-Friedrich R, Belohradsky BH, Dathe O. Complications after caesarean section in HIV-1-infected women not taking antiretroviral treatment. *Lancet*. 1999;354(9190):1612-1613. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10560681.

21. Maiques-Montesinos V, Cervera-Sanchez J, Bellver-Pradas J, Abad-Carrascosa A, Serra-Serra V. Post-cesarean section morbidity in HIV-positive women. *Acta Obstet Gynecol Scand*. 1999;78(9):789-792. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10535342.

22. Rodriguez EJ, Spann C, Jamieson D, Lindsay M. Postoperative morbidity associated with cesarean delivery among human immunodeficiency virus-seropositive women. *Am J Obstet Gynecol*. 2001;184(6):1108-1111. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11349171.

23. Semprini AE, Castagna C, Ravizza M, et al. The incidence of complications after caesarean section in 156 HIV-positive women. *AIDS*. 1995;9(8):913-917. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7576327.

24. Urbani G, de Vries MM, Cronje HS, Niemand I, Bam RH, Beyer E. Complications associated with cesarean section in HIV-infected patients. *Int J Gynaecol Obstet*. 2001;74(1):9-15. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11430935.

25. Vimercati A, Greco P, Loverro G, Lopalco PL, Pansini V, Selvaggi L. Maternal complications after caesarean section in HIV infected women. *Eur J Obstet Gynecol Reprod Biol*. 2000;90(1):73-76. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10767514.

26. Read JS, Newell MK. Efficacy and safety of cesarean delivery for prevention of mother-to-child transmission of HIV-1. *Cochrane Database Syst Rev*. 2005(4):CD005479. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16235405.

27. Livingston EG, Huo Y, Patel K, et al. Complications and route of delivery in a large cohort study of HIV-1-infected women-IMPAACT P1025. *J Acquir Immune Defic Syndr*. 2016;73(1):74-82. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27082506.

28. Faucher P, Batallan A, Bastian H, et al. Management of pregnant women infected with HIV at Bichat Hospital between 1990 and 1998: analysis of 202 pregnancies. *Gynecol Obstet Fertil*. 2001;29(3):211-225. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11300046.

29. Fiore S, Newell ML, Thorne C, European HIV in Obstetrics Group. Higher rates of post-partum complications in HIV-infected than in uninfected women irrespective of mode of delivery. *AIDS*. 2004;18(6):933-938. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15060441.

30. Marcollet A, Goffinet F, Firtion G, et al. Differences in postpartum morbidity in women who are infected with the human immunodeficiency virus after elective cesarean delivery, emergency cesarean delivery, or vaginal delivery. *Am J Obstet Gynecol*. 2002;186(4):784-789. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11967508.

31. Read JS, Tuomala R, Kpamegan E, et al. Mode of delivery and postpartum morbidity among HIV-infected women: the women and infants transmission study. *J Acquir Immune Defic Syndr*. 2001;26(3):236-245. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11242196.

32. Watts DH, Lambert JS, Stiehm ER, et al. Complications according to mode of delivery among human immunodeficiency virus-infected women with CD4 lymphocyte counts of < or = 500/microL. *Am J Obstet Gynecol*. 2000;183(1):100-107.

Available at: http://www.ncbi.nlm.nih.gov/pubmed/10920316.

33. Kennedy CE, Yeh PT, Pandey S, Betran AP, Narasimhan M. Elective cesarean section for women living with HIV: a systematic review of risks and benefits. *AIDS*. 2017;31(11):1579-1591. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28481770.

34. Silver RM, Landon MB, Rouse DJ, et al. Maternal morbidity associated with multiple repeat cesarean deliveries. *Obstet Gynecol*. 2006;107(6):1226-1232. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16738145.

35. Greenbaum S, Wainstock T, Dukler D, Leron E, Erez O. Underlying mechanisms of retained placenta: Evidence from a population based cohort study. *Eur J Obstet Gynecol Reprod Biol*. 2017;216:12-17. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28692888.

36. International Perinatal HIVG. Duration of ruptured membranes and vertical transmission of HIV-1: a meta-analysis from 15 prospective cohort studies. *AIDS*. 2001;15(3):357-368. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11273216.

37. Jamieson DJ, Read JS, Kourtis AP, Durant TM, Lampe MA, Dominguez KL. Cesarean delivery for HIV-infected women: recommendations and controversies. *Am J Obstet Gynecol*. 2007;197(3 Suppl):S96-100. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17825656.

38. Cotter AM, Brookfield KF, Duthely LM, Gonzalez Quintero VH, Potter JE, O'Sullivan MJ. Duration of membrane rupture and risk of perinatal transmission of HIV-1 in the era of combination antiretroviral therapy. *Am J Obstet Gynecol*. 2012;207(6):482 e481-485. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23103331.

39. Peters H, Byrne L, De Ruiter A, et al. Duration of ruptured membranes and mother-to-child HIV transmission: a prospective population-based surveillance study. *BJOG*. 2015. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26011825.

40. Eppes C. Is it time to leave the avoidance of rupture of membranes for women infected with HIV and receiving cART in the past? *BJOG*. 2015. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25998194.

41. Peters H, Francis K, Harding K, Tookey PA, Thorne C. Operative vaginal delivery and invasive procedures in pregnancy among women living with HIV. *Eur J Obstet Gynecol Reprod Biol*. 2017;210:295-299. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28092853.

Other Intrapartum Management Considerations (Last updated December 7, 2018; last reviewed December 7, 2018)

Panel's Recommendations

- Artificial rupture of membranes (ROM) can be performed for standard obstetric indications in virologically suppressed women with HIV who are on antiretroviral therapy (ART) **(BII)**.
- The following procedures should generally be avoided because of a potential increased risk of HIV perinatal transmission, unless there are clear obstetric indications:
  - Artificial ROM in the setting of viremia **(BIII)**
  - Routine use of fetal scalp electrodes for fetal monitoring **(BIII)**
  - Operative delivery with forceps or a vacuum extractor **(BIII)**
- The ART regimen a woman is receiving should be taken into consideration when treating excessive postpartum bleeding resulting from uterine atony:
  - In women who are receiving a cytochrome P450 (CYP) 3A4 enzyme inhibitor (e.g., a protease inhibitor, integrase inhibitor, cobicistat), methergine should be used only if no alternative treatments for postpartum hemorrhage are available and the need for pharmacologic treatment outweighs the risks. If methergine is used, it should be administered at the lowest effective dose for the shortest possible duration **(BIII)**.
  - In women who are receiving a CYP3A4 enzyme inducer such as nevirapine, efavirenz, or etravirine, additional uterotonic agents may be needed because of the potential for decreased methergine levels and inadequate treatment effect **(BIII)**.

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*

Data on the association between the duration of rupture of membranes (ROM) and perinatal transmission of HIV in the era of effective antiretroviral therapy (ART) are reassuring. A prospective cohort study of 707 pregnant women on ART included 493 women with delivery HIV RNA <1,000 copies/mL with no cases of perinatal transmission for up to 25 hours of membrane rupture; logistic regression found that a viral load >10,000 copies/mL was the only independent risk factor for transmission.[1] A large, prospective, population-based surveillance study in the United Kingdom and Ireland evaluated data collected from 2007 through 2012 on 2,116 pregnancies; this data included information on the duration of ROM. The infants in this study were delivered at term vaginally or by emergency cesarean delivery to women with HIV who were on ART. The median duration of ROM was 3 hours 30 minutes (interquartile range [IQR] 1–8 hours) and the overall perinatal transmission rate was not significantly different with longer durations of ROM (0.64% with a duration of ROM ≥4 hours compared with 0.34% for a duration of ROM <4 hours; odds ratio [OR] 1.90, 95% CI, 0.45–7.97]). In women with viral loads <50 copies/mL, there was no difference between the perinatal transmission rate for a duration of ROM ≥4 hours and the rate for a duration of ROM <4 hours (0.14% for ≥4 hours vs. 0.12% for <4 hours; OR 1.14, 95% CI, 0.07–18.27). Among infants born preterm, no transmissions occurred during 163 deliveries where the maternal viral load was <50 copies/mL.[2] If spontaneous ROM occurs before labor or early in labor, interventions to decrease the interval to delivery (e.g., administration of oxytocin) can be considered based on obstetric considerations in virologically suppressed women with HIV. Women with detectable viral loads should not undergo artificial ROM unless there is a clear obstetric indication.

Obstetric procedures that increase the risk of fetal exposure to maternal blood, such as invasive fetal monitoring, have been associated with an increased risk of perinatal transmission rates in some studies, primarily those performed in the pre-ART era.[3-6] Data are limited on the use of fetal scalp electrodes during labor in women who are receiving suppressive ART and who have undetectable viral loads; routine use of fetal scalp electrodes for fetal monitoring should generally be avoided in the setting of maternal HIV infection.

Similarly, data are limited regarding the potential risk of perinatal transmission of HIV associated with operative vaginal delivery using forceps or the vacuum extractor and/or the use of episiotomy;[4,6] existing data

are mostly from the pre-ART era. A prospective, population-based surveillance study in the United Kingdom and Ireland reported 251 operative deliveries (using forceps or vacuum) from January 2008 through March 2016. One infant who was delivered operatively is known to have acquired HIV, although there were other significant risk factors that may have contributed to this transmission.[7] Although information on HIV RNA levels was not included in this report, during this time period 80% to 90% of pregnant women living with HIV in the United Kingdom achieved viral suppression by the time of delivery.[7,8] Operative deliveries should be performed only if there are clear obstetric indications. There are no data from the ART era regarding the risk of perinatal HIV transmission associated with episiotomy or with vaginal or perineal tears, specifically in the absence of maternal viremia; indications for episiotomy should be the same as they are for women without HIV (e.g., a need for expedited vaginal delivery, a need for operative vaginal delivery, shoulder dystocia).

Delayed cord clamping has been associated with improved iron stores in both term and preterm infants as well as a lower incidence of necrotizing enterocolitis and intraventricular hemorrhage in preterm infants born to mothers without HIV. The American College of Obstetricians and Gynecologists now recommends this practice in vigorous term and preterm infants, with clamping delayed for ≥30 to 60 seconds after birth.[9-11] In the setting of HIV infection, a recent study of 64 mother-infant pairs in which 32 infants had early cord clamping (i.e., performed 30 seconds after birth) and 32 infants had delayed cord clamping (i.e., performed 120 seconds after birth) found that mean hemoglobin levels at 24 hours of life were significantly higher in the delayed cord clamping group ($P = 0.05$). This difference persisted at 1 month of age ($P < 0.05$), despite differential prescribing of iron supplementation to infants with anemia. All mothers were on stable antiretroviral (ARV) regimens. During 18 months of follow-up, there were no HIV transmissions and no increased risk of jaundice or polycythemia with delayed cord clamping.[12]

Intrapartum Epidural Use and Pharmacologic Interactions with Antiretroviral Drugs

Ritonavir inhibition of cytochrome P450 (CYP) 3A4 decreases the elimination of fentanyl by 67%, raising concerns about a possible increased risk of respiratory depression, particularly with patient-controlled analgesia during labor, in women receiving ritonavir-containing regimens. However, a pharmacokinetic simulation study suggests that even with maximal clinical dosing regimens of epidural fentanyl over 24 hours, ritonavir-induced CYP3A4 inhibition is unlikely to produce the plasma fentanyl concentrations associated with a decrease in minute ventilation.[13] This suggests that epidural anesthesia can be used safely regardless of ART regimen.

Postpartum Hemorrhage, Antiretroviral Drugs, and Methergine Use

Oral or parenteral methergine or other ergot alkaloids are often used as first-line treatment for postpartum hemorrhage caused by uterine atony. However, methergine should not be coadministered with drugs that are potent CYP3A4 enzyme inhibitors, including protease inhibitors (PIs). Concomitant use of ergotamines with PIs and/or cobicistat has been associated with exaggerated vasoconstrictive responses.[14] When uterine atony results in excessive postpartum bleeding in women who are receiving PIs or cobicistat, methergine should be used only if alternative treatments such as prostaglandin F2-alpha, misoprostol, or oxytocin are unavailable or are contraindicated. If no alternative medications are available and the need for pharmacologic treatment outweighs the risks, methergine should be used at the lowest effective dose for the shortest possible duration. In contrast, additional uterotonic agents may be needed when using other ARV drugs that are CYP3A4 inducers (e.g., nevirapine, efavirenz, etravirine) because of the potential for decreased methergine levels and inadequate treatment effect.

References

1. Cotter AM, Brookfield KF, Duthely LM, Gonzalez Quintero VH, Potter JE, O'Sullivan MJ. Duration of membrane rupture and risk of perinatal transmission of HIV-1 in the era of combination antiretroviral therapy. *Am J Obstet Gynecol*. 2012;207(6):482 e481-485. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23103331.

2. Peters H, Francis K, Harding K, Tookey PA, Thorne C. Operative vaginal delivery and invasive procedures in

pregnancy among women living with HIV. *Eur J Obstet Gynecol Reprod Biol*. 2016;210:295-299. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28092853.

3. Boyer PJ, Dillon M, Navaie M, et al. Factors predictive of maternal-fetal transmission of HIV-1. Preliminary analysis of zidovudine given during pregnancy and/or delivery. *JAMA*. 1994;271(24):1925-1930. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7911164.

4. Mandelbrot L, Mayaux MJ, Bongain A, et al. Obstetric factors and mother-to-child transmission of human immunodeficiency virus type 1: the French perinatal cohorts. SEROGEST French Pediatric HIV Infection Study Group. *Am J Obstet Gynecol*. 1996;175(3 Pt 1):661-667. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8828431.

5. Mofenson LM, Lambert JS, Stiehm ER, et al. Risk factors for perinatal transmission of human immunodeficiency virus type 1 in women treated with zidovudine. Pediatric AIDS Clinical Trials Group Study 185 Team. *N Engl J Med*. 1999;341(6):385-393. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10432323.

6. Shapiro DE, Sperling RS, Mandelbrot L, Britto P, Cunningham BE. Risk factors for perinatal human immunodeficiency virus transmission in patients receiving zidovudine prophylaxis. Pediatric AIDS Clinical Trials Group protocol 076 Study Group. *Obstet Gynecol*. 1999;94(6):897-908. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10576173.

7. Peters H, Francis K, Sconza R, et al. UK mother-to-child HIV transmission rates continue to decline: 2012–2014. *Clin Infect Dis*. 2017;64(4):527-528. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28174911.

8. Townsend CL, Byrne L, Cortina-Borja M, et al. Earlier initiation of ART and further decline in mother-to-child HIV transmission rates, 2000–2011. *AIDS*. 2014;28(7):1049-1057. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24566097.

9. McDonald SJ, Middleton P, Dowswell T, Morris PS. Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes. *Cochrane Database Syst Rev*. 2013;7:CD004074. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23843134.

10. Rabe H, Diaz-Rossello JL, Duley L, Dowswell T. Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes. *Cochrane Database Syst Rev*. 2012;8:CD003248. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22895933.

11. American College of Obstetricians and Gynecologists. Committee Opinion No. 684: Delayed umbilical cord clamping after birth. *Obstet Gynecol*. 2017;129(1):e5-e10. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28002310.

12. Pogliani L, Erba P, Nannini P, Giacomet V, Zuccotti GV. Effects and safety of delayed versus early umbilical cord clamping in newborns of HIV-infected mothers. *J Matern Fetal Neonatal Med*. 2017:1-4. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28969479.

13. Cambic CR, Avram MJ, Gupta DK, Wong CA. Effect of ritonavir-induced cytochrome P450 3A4 inhibition on plasma fentanyl concentrations during patient-controlled epidural labor analgesia: a pharmacokinetic simulation. *Int J Obstet Anesth*. 2014;23(1):45-51. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24333052.

14. Navarro J, Curran A, Burgos J, et al. Acute leg ischaemia in an HIV-infected patient receiving antiretroviral treatment. *Antivir Ther*. 2017;22(1):89-90. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27546463.

Postpartum Care (Last updated December 7, 2018; last reviewed December 7, 2018)

Panel's Recommendations
• Antiretroviral therapy (ART) is currently recommended for all individuals living with HIV to reduce the risk of disease progression and to prevent the sexual transmission of HIV **(AI)**.
• Any plans for modifying ART after delivery should be made in consultation with the woman and her HIV care provider, ideally before delivery, taking into consideration the recommended regimens for nonpregnant adults **(AIII)**.
• Because the immediate postpartum period poses unique challenges to antiretroviral (ARV) adherence, arrangements for new or continued supportive services should be made before hospital discharge **(AII)**.
• Contraceptive counseling should start during the prenatal period; a contraceptive plan should be developed prior to hospital discharge **(AIII)**.
• Women with a positive rapid HIV antibody test during labor require immediate linkage to HIV care and comprehensive follow-up, including confirmation of HIV infection **(AII)**.
• Prior to hospital discharge, the woman should be given ARV medications for herself and her newborn to take at home **(AIII)**.
• Breastfeeding is not recommended for women in the United States with confirmed or presumed HIV infection, because safer alternatives are available **(AI)**.
• Infant feeding counseling, including a discussion of potential barriers to formula feeding, should begin during the prenatal period, and this information should be reviewed after delivery **(AIII)**.
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*

Postpartum Follow-Up of Women Living with HIV

The postpartum period provides an opportunity to review and optimize women's health care. Comprehensive medical care and supportive services are particularly important for women living with HIV and their families, who often face multiple medical and social challenges. Components of comprehensive care include the following services as needed:

- Primary care, gynecologic/obstetric care, and HIV specialty care for the woman with HIV;
- Pediatric care for her infant;
- Family planning services;
- Mental health services;
- Substance abuse treatment;
- Support services;
- Coordination of care through case management for a woman, her child(ren), and other family members; *and*
- Prevention of secondary transmission for serodiscordant partners, including counseling on the use of condoms, antiretroviral therapy (ART) to maintain virologic suppression in the partner with HIV (i.e., treatment as prevention), and the potential use of pre-exposure prophylaxis (PrEP) by the partner without HIV.

Support services should be tailored to the individual woman's needs and can include case management; child care; respite care; assistance with basic life needs, such as housing, food, and transportation; peer counseling; and legal and advocacy services. Ideally, this care should begin before pregnancy and continue throughout

pregnancy and the postpartum period.

Immediate linkage to care, comprehensive medical assessment, counseling, and follow-up are required for all women with HIV and particularly for women who have a positive HIV test during labor or at delivery. The American College of Obstetricians and Gynecologists recommends that all women have contact with their obstetrician-gynecologists or other obstetric care providers within the first 3 weeks postpartum.[1] Women with HIV should have a follow-up appointment with the health care provider who manages their HIV care, whether that is an obstetrician or an HIV health care provider, within the first 2 to 4 weeks after hospital discharge.

When care is not co-located or not within the same health care system, a case manager can facilitate care coordination. Women who are receiving case management are also more likely to have virologic suppression and be retained in care.[2] It is especially critical to ensure continuity of ART between the antepartum and postpartum periods. Prior to discharge, the mother should receive HIV medications for herself and her newborn. Special hospital programs may need to be established to support dispensing ART to mothers before discharge.

Decisions about any changes to an ART regimen after delivery should be made after consulting with the woman and her HIV care provider, ideally prior to delivery. There are ART regimens that are recommended for nonpregnant adults (see the Adult and Adolescent Guidelines) that may not have the same designation for use during pregnancy due to insufficient data or pharmacokinetic concerns. See Table 6 and Table 7 for specific recommendations regarding regimens to use in pregnant women and women who are trying to conceive.

ART is currently recommended for all individuals with HIV to reduce the risk of disease progression and to prevent HIV secondary transmission.[3] The START and TEMPRANO trials were randomized clinical trials that demonstrated that early ART can reduce the risk of disease progression even in individuals with CD4 T lymphocyte cell counts >500 cells/mm^3, and the HPTN 052 randomized clinical trial demonstrated that early ART can reduce the risk of sexual transmission to a discordant partner by 96%.[4-6] It is important to counsel a woman that no single method (including treatment) is 100% protective against HIV transmission; however, with full, sustained HIV suppression, the risk of sexual transmission is negligible.

Helping women with HIV understand the need for lifelong ART is a priority during postpartum care. Several studies have demonstrated significant decreases in ART adherence postpartum.[7-11] During the postpartum period, women may have difficulty with medical appointment follow-up, which can affect ART adherence. Systematic monitoring of retention in HIV care is recommended for all individuals living with HIV, but special attention is warranted during the postpartum period. A number of studies have suggested that postpartum depression is common among women with HIV.[12-20] The U.S. Preventive Services Task Force recommends screening all women for postpartum depression[21] using a validated tool; this is especially important for women living with HIV who appear to be at increased risk for postpartum depression and poor ART adherence during the postpartum period. Women should be counseled that postpartum physical and psychological changes (and the stresses and demands of caring for a new baby) may make adherence more difficult and that additional support may be needed during this period.[2,22-25]

Poor adherence has been shown to be associated with virologic failure, development of resistance, and decreased long-term effectiveness of ART.[26-28] In women who achieve viral suppression by the time of delivery, postpartum simplification to once-daily, coformulated regimens—which are often the preferred initial regimens for nonpregnant adults—could promote adherence during this challenging time. Efforts to maintain adequate adherence during the postpartum period may ensure effectiveness of therapy (see Adherence in the Adult and Adolescent Guidelines). For women who are continuing ART and who received increased protease inhibitor doses during pregnancy, available data suggest that doses can be reduced to standard doses immediately after delivery.

The postpartum period is a critical time for addressing safer sex practices in order to reduce secondary transmission of HIV to partners,[29] and clinicians should begin discussing these practices with the patient during the prenatal period. Topics that should be discussed during counseling on prevention of secondary

transmission to the partner without HIV include condoms, ART for the partner with HIV to maintain viral suppression below the limit of detection, and the potential use of PrEP by the partner without HIV. With full, sustained HIV suppression in the woman—with or without reliable PrEP use by her partner without HIV—the possibility of transmission is negligible (for additional information, see Reproductive Options).

It is important to integrate comprehensive family planning and preconception care into all health care visits, with special attention given to these topics during the routine prenatal and postpartum visits. Lack of breastfeeding is associated with earlier return of fertility; ovulation returns as early as 6 weeks postpartum, and it can occur earlier in some women—even before resumption of menses—putting them at risk of pregnancy shortly after delivery.[30] If a long-acting reversible contraceptive (LARC), such as an injectable, implant, or intrauterine device (IUD), is desired by the patient, it should be inserted prior to hospital discharge or during the obstetrical care visit at 3 weeks postpartum. If a LARC is postponed to the postpartum visit, Depo-Provera is an option to be given as a contraceptive to avoid unplanned pregnancy in the interim, particularly if the postpartum appointment is missed. Interpregnancy intervals of <18 months have been associated with an increased risk of poor perinatal and maternal outcomes in women without HIV.[31] Because of the stresses and demands of a new baby, women may be more receptive to the use of effective contraception, yet they are simultaneously at higher risk of nonadherence to contraception and, thus, unintended pregnancy.[32]

The potential for drug-drug interactions between several antiretroviral (ARV) drugs and hormonal contraceptives is discussed in Preconception Counseling and Care for Women of Childbearing Age Living with HIV and Table 3. A systematic review conducted for the World Health Organization summarized the research on hormonal contraception, IUD use, and risk of HIV infection and concluded that women with HIV can use all forms of contraception.[33,34] Findings from a systematic review of hormonal contraceptive methods and risk of HIV transmission to partners without HIV concluded that oral contraceptives and medroxyprogesterone do not increase risk of HIV transmission in women who are on ART, although the data are limited and have methodological issues.[35] Permanent sterilization is appropriate only for women who are certain they do not desire future pregnancies.

Avoidance of breastfeeding has been and continues to be a standard, strong recommendation for women living with HIV in the United States, because maternal ART dramatically reduces but does not eliminate breastmilk transmission, and safe infant feeding alternatives are readily available. There are also other concerns, including the potential for drug toxicity in the neonate or, should HIV transmission occur, the risk that the infant will develop ARV drug resistance due to subtherapeutic drug levels in breastmilk. However, clinicians should be aware that women may face social, familial, and personal pressures to consider breastfeeding despite this recommendation; this may be particularly problematic for women from cultures where breastfeeding is important, as they may fear that formula feeding would reveal their HIV status.[36,37] It is therefore important to address these possible barriers to formula feeding during the antenatal period (see Guidelines for Counseling and Managing Women Living with HIV in the United States Who Desire to Breastfeed). Women who have an initial positive HIV test should not breastfeed unless a confirmatory HIV test is negative (for detailed guidance on maternal HIV testing, please see Maternal HIV Testing and Identification of Perinatal HIV Exposure). If HIV infection is confirmed, a full health assessment is warranted, including counseling related to newly diagnosed HIV infections, a discussion of the need for lifelong ART, an assessment of the need for opportunistic infection prophylaxis, and an evaluation for associated medical conditions. The newborn should receive appropriate testing and ARV drug management. Other children and partner(s) should be referred for HIV testing. Similarly, women with HIV should be made aware of the risks of HIV transmission via premastication (prechewing or prewarming in the mother's mouth) of infant food.[38] It is not yet known whether there is a risk of HIV transmission with premastication of food when the mother's viral load is below the limit of detection.

References

1. American College of Obstetricians and Gynecologists. ACOG Committee Opinion No. 736: optimizing postpartum care. *Obstet Gynecol*. 2018;131(5):e140-e150. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29683911.
2. Anderson EA, Momplaisir FM, Corson C, Brady KA. Assessing the impact of perinatal HIV case management on outcomes along the HIV care continuum for pregnant and postpartum women living with HIV, Philadelphia 2005–2013. *AIDS Behav*. 2017. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28176167.
3. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV. 2018. Available at: http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf.
4. Danel C, Gabillard D, Le Carrou J, et al. Early ART and IPT in HIV-infected African adults with high CD4 count (TEMPRANO trial). Presented at: 22nd on Retroviruses and Opportunistic Infections. 2015. Seattle, WA.
5. National Institute of Allergy and Infectious Diseases. Starting antiretroviral treatment early improves outcomes for HIV-infected individuals. NIH News. 2015. Available at: http://www.niaid.nih.gov/news/newsreleases/2015/Pages/START.aspx.
6. Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med*. 2011;365(6):493-505. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21767103.
7. Kreitchmann R, Harris R, Kakehasi Fea. Adherence during pregnancy and post-partum: Latin America. Abstract 1016. Presented at: 6th International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention. 2011. Rome, Italy.
8. Kaida A, Kanters S, Chaworth-Musters T, et al. Antiretroviral adherence during pregnancy and postpartum among HIV-positive women receiving highly active antiretroviral therapy (HAART) in British Columbia (BC), Canada (1997–2008). CDB397-CD-ROM. Presented at: 6th International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention. 2011. Rome, Italy.
9. Mellins CA, Chu C, Malee K, et al. Adherence to antiretroviral treatment among pregnant and postpartum HIV-infected women. *AIDS Care*. 2008;20(8):958-968. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18608073.
10. Nachega J, Uthman C, Mills E, Muessig K, et al. Adherence to antiretroviral therapy (ART) during and after pregnancy in low, middle and high income countries: a systematic review and meta-analysis. Abstract 1006. Presented at: 19th Conference on Retroviruses and Opportunistic Infections. 2012. Seattle, WA.
11. Adams JW, Brady KA, Michael YL, Yehia BR, Momplaisir FM. Postpartum engagement in HIV care: an important predictor of long-term retention in care and viral suppression. *Clin Infect Dis*. 2015;61(12):1880-1887. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26265499.
12. Ross R, Sawatphanit W, Mizuno M, Takeo K. Depressive symptoms among HIV-positive postpartum women in Thailand. *Arch Psychiatr Nurs*. 2011;25(1):36-42. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21251600.
13. Chibanda D, Mangezi W, Tshimanga M, et al. Postnatal depression by HIV status among women in Zimbabwe. *J Womens Health (Larchmt)*. 2010;19(11):2071-2077. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20849286.
14. Rubin LH, Cook JA, Grey DD, et al. Perinatal depressive symptoms in HIV-infected versus HIV-uninfected women: a prospective study from preconception to postpartum. *J Womens Health (Larchmt)*. 2011;20(9):1287-1295. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21732738.
15. Kapetanovic S, Christensen S, Karim R, et al. Correlates of perinatal depression in HIV-infected women. *AIDS Patient Care STDS*. 2009;23(2):101-108. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19196032.
16. Bonacquisti A, Geller PA, Aaron E. Rates and predictors of prenatal depression in women living with and without HIV. *AIDS Care*. 2014;26(1):100-106. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23750820.
17. Aaron E, Bonacquisti A, Geller PA, Polansky M. Perinatal depression and anxiety in women with and without human immunodeficiency virus infection. *Womens Health Issues*. 2015;25(5):579-585. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26093677.
18. Ion A, Wagner AC, Greene S, Loutfy MR, Team HIVMS. HIV-related stigma in pregnancy and early postpartum of mothers living with HIV in Ontario, Canada. *AIDS Care*. 2017;29(2):137-144. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27449254.
19. Wielding S, Scott A. What women want: social characteristics, gender-based violence and social support preferences in a cohort of women living with HIV. *Int J STD AIDS*. 2017;28(5):486-490. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27270691.

20. Gauthreaux C, Negron J, Castellanos D, et al. The association between pregnancy intendedness and experiencing symptoms of postpartum depression among new mothers in the United States, 2009 to 2011: A secondary analysis of PRAMS data. *Medicine (Baltimore)*. 2017;96(6):e5851. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28178128.

21. O'Connor E, Rossom RC, Henninger M, Groom HC, Burda BU. Primary care screening for and treatment of depression in pregnant and postpartum women: evidence report and systematic review for the US preventive services task force. *JAMA*. 2016;315(4):388-406. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26813212.

22. Cohn SE, Umbleja T, Mrus J, Bardeguez AD, Andersen JW, Chesney MA. Prior illicit drug use and missed prenatal vitamins predict nonadherence to antiretroviral therapy in pregnancy: adherence analysis A5084. *AIDS Patient Care STDS*. 2008;22(1):29-40. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18442305.

23. Ickovics JR, Wilson TE, Royce RA, et al. Prenatal and postpartum zidovudine adherence among pregnant women with HIV: results of a MEMS substudy from the perinatal guidelines evaluation project. *J Acquir Immune Defic Syndr*. 2002;30(3):311-315. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12131568.

24. Bardeguez AD, Lindsey JC, Shannon M, et al. Adherence to antiretrovirals among US women during and after pregnancy. *J Acquir Immune Defic Syndr*. 2008;48(4):408-417. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18614923.

25. Buchberg MK, Fletcher FE, Vidrine DJ, et al. A mixed-methods approach to understanding barriers to postpartum retention in care among low-income, HIV-infected women. *AIDS Patient Care STDS*. 2015;29(3):126-132. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25612217.

26. Paterson DL, Swindells S, Mohr J, et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. *Ann Intern Med*. 2000;133(1):21-30. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10877736.

27. Le Moing V, Chene G, Carrieri MP, et al. Clinical, biologic, and behavioral predictors of early immunologic and virologic response in HIV-infected patients initiating protease inhibitors. *J Acquir Immune Defic Syndr.* 2001;27(4):372-376. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11468425.

28. Murri R, Ammassari A, Gallicano K, et al. Patient-reported nonadherence to HAART is related to protease inhibitor levels. *J Acquir Immune Defic Syndr*. 2000;24(2):123-128. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10935687.

29. Cates W, Jr., Steiner MJ. Dual protection against unintended pregnancy and sexually transmitted infections: what is the best contraceptive approach? *Sex Transm Dis*. 2002;29(3):168-174. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11875378.

30. Jackson E, Glasier A. Return of ovulation and menses in postpartum nonlactating women: a systematic review. *Obstet Gynecol*. 2011;117(3):657-662. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21343770.

31. Sholapurkar SL. Is there an ideal interpregnancy interval after a live birth, miscarriage or other adverse pregnancy outcomes? *J Obstet Gynaecol*. 2010;30(2):107-110. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20143964.

32. Sha BE, Tierney C, Cohn SE, et al. Postpartum viral load rebound in HIV-1-infected women treated with highly active antiretroviral therapy: AIDS Clinical Trials Group Protocol A5150. *HIV Clin Trials*. 2011;12(1):9-23. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21388937.

33. World Health Organization. Review of priorities in research: hormnonal contraception and IUDs and HIV infection. 2010. Available at: http://www.who.int/reproductivehealth/publications/rtis/rhr_10_21/en/.

34. Polis CB, Curtis KM. Use of hormonal contraceptives and HIV acquisition in women: a systematic review of the epidemiological evidence. *Lancet Infect Dis*. 2013;13(9):797-808. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23871397.

35. Haddad LB, Polis CB, Sheth AN, et al. Contraceptive methods and risk of HIV acquisition or female-to-male transmission. *Curr HIV/AIDS Rep*. 2014;11(4):447-458. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25297973.

36. Levison J, Weber S, Cohan D. Breastfeeding and HIV-infected women in the United States: harm reduction counseling strategies. *Clin Infect Dis*. 2014;59(2):304-309. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24771330.

37. Tariq S, Elford J, Tookey P, et al. "It pains me because as a woman you have to breastfeed your baby": decision-making about infant feeding among African women living with HIV in the UK. *Sex Transm Infect*. 2016;92(5):331-336. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26757986.

38. Gaur AH, Dominguez KL, Kalish ML, et al. Practice of feeding premasticated food to infants: a potential risk factor for HIV transmission. *Pediatrics*. 2009;124(2):658-666. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19620190.

Guidance for Counseling and Managing Women Living with HIV in the United States Who Desire to Breastfeed (Last updated March 27, 2018; last reviewed March 27, 2018)

Panel's Recommendations
• Breastfeeding **is not recommended** for women living with HIV in the United States **(AII)**. • Women who have questions about breastfeeding or who desire to breastfeed should receive patient-centered, evidence-based counseling on infant feeding options **(AIII)**. • When women with HIV choose to breastfeed despite intensive counseling, they should be counseled to use harm-reduction measures to minimize the risk of HIV transmission to their infants **(BIII)**.
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

Avoidance of breastfeeding is the standard, strong recommendation for women living with HIV in the United States, because

- Maternal antiretroviral therapy (ART) reduces but does not eliminate the risk of HIV transmission via breast milk;
- Safe and affordable infant feeding alternatives are readily accessible in the United States; and
- There is a paucity of safety data on most modern ART regimens during breastfeeding.

The recommendations in the United States differ from those in many low- and middle-income countries, where cost limits access to formula and where inadequate quantities of formula and/or unsafe water mixed into formula have been associated with high rates of infant mortality.[1] Women from areas in the United States without access to safe water may face similar challenges. Infant replacement feeding using formula, banked breast milk, or a properly screened HIV-negative wet nurse remains the only way to eliminate the risk of HIV transmission through infant feeding. However, women may face environmental, social, familial, and personal pressures to consider breastfeeding, despite the risk of HIV transmission via breast milk.[2-4]

A qualitative study of mothers living with HIV in Canada found that infant feeding is a social, cultural, and emotional issue, often underpinned by HIV-related stigma.[4] Some women, especially those from a country or cultural background where breastfeeding is the norm, fear that not breastfeeding will lead to disclosure of their HIV status.[2] Multiple experts have called for a patient-centered, harm-reduction approach to counseling women living with HIV on infant feeding options in high-resource countries.[2,5,6] This section of the guidelines is intended to provide tools to help providers counsel women living with HIV on the potential risks associated with breastfeeding and to provide a harm-reduction approach for women who choose to breastfeed despite intensive counseling. **This section is not intended to be an endorsement of breastfeeding, nor is it a recommendation to breastfeed for women living with HIV in the United States.**

Breastfeeding and Strategies to Reduce Risk of HIV Transmission

Both the evidence regarding the risks of HIV transmission via breastfeeding and the strategies to reduce this type of transmission come from studies conducted in low- and middle-income countries, where rates of infant mortality are high and many families do not have access to safe water and affordable formula. Without maternal ART and infant antiretroviral (ARV) prophylaxis, the risk of a woman with HIV transmitting the virus to a breastfeeding infant is 15% to 20% over 2 years.[7,8]

Studies have shown that maternal ART throughout pregnancy and breastfeeding and infant ARV prophylaxis during breastfeeding can reduce, but not eliminate, the risk of HIV transmission through breast milk.[9-13] However, most of these studies only provided ARV drugs to women or their infants through 6 months postpartum and collected limited data on maternal plasma HIV viral load during breastfeeding.

As ART has become more widely available for women during pregnancy and the postpartum period, studies have looked at women who started ART earlier in pregnancy and continued ART longer than in previous studies. A study of women with CD4 T lymphocyte cell counts ≥350 cells/mm^3 compared extended infant nevirapine to maternal ART, with both treatments continued through cessation of breastfeeding or 18 months postpartum, whichever came first. This study estimated transmission rates of 0.3% at 6 months and 0.6% at 12 months in both arms.[14] Importantly, cases of HIV transmission via breastfeeding have occurred despite undetectable maternal plasma viral loads.[15]

Prior to the current accessibility of ART in low-income countries, studies demonstrated that exclusive breastfeeding during the first 6 months of life is associated with lower HIV transmission than mixed feeding (a term used to describe infants fed breast milk plus other liquid or solid foods, including formula).[16,17] After 6 months, when complementary foods are required for adequate infant nutrition, demand for breast milk decreases and gradual weaning can occur. Rapid weaning over several days is not recommended. Studies from low-income countries that were conducted before ART was widely accessible for breastfeeding women observed the potential for increased HIV shedding into breast milk and an increased risk of HIV transmission during rapid weaning.[18-20]

Safety of Maternal and Infant Use of Antiretroviral Drugs during Breastfeeding

Studied NNRTIs (nevirapine, efavirenz, and etravirine) get into breast milk, but to a lower extent than the levels in maternal plasma. Studied PIs (lopinavir, nelfinavir, ritonavir, indinavir, atazanavir) reach very low concentrations in breast milk, with little to no drug detectable in the blood of the breastfed infant.[21] NRTIs show more variability than PIs and NNRTIs. Tenofovir disoproxil fumarate has very little transfer into breast milk, with no detectable drug concentration in the blood of the breastfed infant.[21-23] Emtricitabine and lamivudine have more accumulation in breast milk and can sometimes be detected in the blood of the breastfeed infant (in 19% and 36% of infants, respectively).[21] For more details on ARV passage into breastmilk, see the individual drug sections in Appendix B.

A review of studies of women with and without HIV taking TDF during pregnancy found generally normal infant growth.[21,24] One reviewed study showed a decrease in bone mineral content among the babies of mothers on combination ART (whether the mothers received tenofovir diphosphate (DP)-based ART or zidovudine-based ART) compared to the babies of mothers receiving zidovudine alone. Another study showed a decrease in bone mineral content among breastfeeding mothers receiving tenofovir DP-based ART compared to mothers who received no ART, but whether these findings will persist after discontinuation of breastfeeding is not known.[24]

Serious adverse infant events associated with ART in breastfeeding mothers appear to be relatively uncommon. In two studies that compared the efficacy of maternal ART (zidovudine-based ART in one study and TDF-based ART in the other) to infant nevirapine prophylaxis with no maternal ART during breastfeeding for prevention of postnatal HIV transmission, no significant differences in adverse events were observed between study arms.[10,14] One study reported that anemia occurred more frequently among infants who were exposed to zidovudine-based ART during breastfeeding than among infants who were not exposed to ART.[25] An infant who acquires HIV while breastfeeding is at risk of developing ARV drug resistance due to subtherapeutic drug levels in breast milk, especially if the breastfeeding woman develops viremia.[26,27]

As noted above, extended infant ARV prophylaxis during breastfeeding has similar rates of serious adverse events compared to maternal ART. In one study, the rate of adverse events in infants receiving 6 months of nevirapine was not significantly different from those receiving nevirapine placebo. A second study comparing

two infant ARV prophylaxis regimens (lopinavir/ritonavir vs. lamivudine) found no significant difference in the rates of adverse events in infants receiving the two regimens.[10-12,14] Studies to date have only examined short-term adverse events, and there is little data on whether there might be long-term consequences of these drug exposures.

Approach to Counseling and Management

Formula, banked donor milk, and milk from an HIV-negative wet nurse who has been properly screened remain the only completely reliable methods of preventing HIV transmission during breastfeeding. The Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission recommends that women living with HIV in the United States not breastfeed their infants. However, patient-centered counseling on infant feeding must balance maternal psychosocial concerns, infant health benefits of breastfeeding, and risks of HIV transmission. Providers can initiate counseling with a nonjudgmental inquiry about infant feeding early in pregnancy, and then engage the mother by offering joint problem solving and shared decision making. One approach is to say to all pregnant women living with HIV "In the United States, we recommend formula feeding to avoid the risk of HIV transmission to your baby through breast milk. Do you have any questions or concerns about this?" For women who are considering breastfeeding, we recommend engaging each woman privately in a nonjudgmental conversation about the motivation behind her desire to breastfeed, as well as consultation with the clinician(s) who will be managing the infant's care.

If, despite extensive counseling, a woman decides to breastfeed, harm-reduction measures should be taken to reduce the risk of HIV transmission. These include:

- Demonstrating maternal ART adherence and engagement in care both during pregnancy and throughout breastfeeding.
- Documenting consistent viral suppression prior to delivery and throughout breastfeeding. This can be accomplished by monitoring maternal plasma viral loads every 1 to 2 months during breastfeeding. If maternal viral load becomes detectable, consult an expert immediately.
- Breastfeeding exclusively for up to 6 months postpartum, followed by breastfeeding in combination with the introduction of complementary foods.
- Developing a plan for weaning with input from the family and providers. Rapid weaning over a few days is not recommended.
- Infants should receive at least 6 weeks of infant ARV prophylaxis with zidovudine and/or nevirapine. In non-breastfeeding infants, there is high quality evidence that 4 weeks to 6 weeks of infant prophylaxis with zidovudine prevents HIV transmission (see Antiretroviral Management of Newborns with Perinatal HIV Exposure of Perinatal HIV). The most extensively studied infant prophylaxis in breastfeeding infants is daily infant nevirapine, which has been shown to be safe and effective when used for extended prophylaxis in infants whose mothers are not receiving ART.[11,14] If the mother is receiving ART, infant ARV prophylaxis can be discontinued after 6 weeks. Some experts in the United States have felt more comfortable with continuing infant ARV prophylaxis through 1 month after cessation of weaning, even when the mother is receiving ART. However, during the HPTN 046 trial, in which the mothers received ART, there was no difference in postnatal transmission when the infant received nevirapine or placebo, suggesting no additive effect.[11]
- Monitoring the infant for HIV acquisition during breastfeeding. A reasonable approach to infant monitoring would include virologic HIV testing at the standard time points (see Maternal HIV Testing and Identification of Perinatal HIV Exposure) and then every 3 months throughout breastfeeding, followed by monitoring at 4 to 6 weeks, 3 months, and 6 months after cessation of breastfeeding.

- In the unlikely case of HIV transmission via breastfeeding, it is important to promptly initiate a full combination ARV treatment regimen for the infant. Resistance testing should be done on the infant viral isolate. If resistance is identified, the treatment regimen can be adjusted appropriately.
- Maternal mastitis and infant thrush should be promptly identified and treated, as both conditions increase the risk of HIV transmission through breastfeeding. Milk from the affected breast should be pumped and discarded until mastitis resolves.

The immediate postpartum period poses unique challenges to adherence to medical care and ART. Close follow-up and enhanced support services should be considered for women planning to breastfeed (see Postpartum Follow-Up of Women Living with HIV Infection).

Clinicians caring for a woman with HIV who is considering breastfeeding should consult with an expert and, if necessary, the Perinatal HIV Hotline (888-448-8765).

References

1. World Health Organization. Guideline: Updates on HIV and Infant Feeding: The Duration of Breastfeeding, and Support from Health Services to Improve Feeding Practices Among Mothers Living with HIV. Geneva. 2016.
2. Yudin MH, Kennedy VL, MacGillivray SJ. HIV and infant feeding in resource-rich settings: considering the clinical significance of a complicated dilemma. *AIDS Care*. 2016;28(8):1023-1026. Available at https://www.ncbi.nlm.nih.gov/pubmed/26881474.
3. Levison J, Weber S, Cohan D. Breastfeeding and HIV-infected women in the United States: harm reduction counseling strategies. *Clin Infect Dis*. 2014;59(2):304-309. Available at http://www.ncbi.nlm.nih.gov/pubmed/24771330.
4. Greene S, Ion A, Elston D, et al. "Why aren't you breastfeeding?": How mothers living with HIV talk about infant feeding in a "Breast Is Best" world. *Health Care Women Int*. 2015;36(8):883-901. Available at https://www.ncbi.nlm.nih.gov/pubmed/24527767.
5. Morrison P, Israel-Ballard K, Greiner T. Informed choice in infant feeding decisions can be supported for HIV-infected women even in industrialized countries. *AIDS*. 2011;25(15):1807-1811. Available at https://www.ncbi.nlm.nih.gov/pubmed/21811145.
6. Johnson G, Levison J, Malek J. Should providers discuss breastfeeding with women living with HIV in high-income countries? an ethical analysis. *Clin Infect Dis*. 2016;63(10):1368-1372. Available at https://www.ncbi.nlm.nih.gov/pubmed/27572099.
7. Nduati R, John G, Mbori-Ngacha D, et al. Effect of breastfeeding and formula feeding on transmission of HIV-1: a randomized clinical trial. *JAMA*. 2000;283(9):1167-1174. Available at https://www.ncbi.nlm.nih.gov/pubmed/10703779.
8. World Health Organization. HIV Transmission through breastfeeding: a review of available evidence; 2007 update. 2008. Available at http://apps.who.int/iris/bitstream/10665/43879/1/9789241596596_eng.pdf.
9. White AB, Mirjahangir JF, Horvath H, Anglemyer A, Read JS. Antiretroviral interventions for preventing breast milk transmission of HIV. *Cochrane Database Syst Rev*. 2014(10):CD011323. Available at https://www.ncbi.nlm.nih.gov/pubmed/25280769.
10. Chasela CS, Hudgens MG, Jamieson DJ, et al. Maternal or infant antiretroviral drugs to reduce HIV-1 transmission. *N Engl J Med*. 2010;362(24):2271-2281. Available at http://www.ncbi.nlm.nih.gov/pubmed/20554982.
11. Coovadia HM, Brown ER, Fowler MG, et al. Efficacy and safety of an extended nevirapine regimen in infant children of breastfeeding mothers with HIV-1 infection for prevention of postnatal HIV-1 transmission (HPTN 046): a randomised, double-blind, placebo-controlled trial. *Lancet*. 2012;379(9812):221-228. Available at http://www.ncbi.nlm.nih.gov/pubmed/22196945.
12. Nagot N, Kankasa C, Tumwine JK, et al. Extended pre-exposure prophylaxis with lopinavir-ritonavir versus lamivudine to prevent HIV-1 transmission through breastfeeding up to 50 weeks in infants in Africa (ANRS 12174): a randomised controlled trial. *Lancet*. 2016;387(10018):566-573. Available at http://www.ncbi.nlm.nih.gov/pubmed/26603917.

13. Kesho Bora Study G, de Vincenzi I. Triple antiretroviral compared with zidovudine and single-dose nevirapine prophylaxis during pregnancy and breastfeeding for prevention of mother-to-child transmission of HIV-1 (Kesho Bora study): a randomised controlled trial. *Lancet Infect Dis*. 2011;11(3):171-180. Available at http://www.ncbi.nlm.nih.gov/pubmed/21237718.

14. Flynn PM, Taha TE, Cababasay M, et al. Prevention of HIV-1 transmission through breastfeeding: efficacy and safety of maternal antiretroviral therapy versus infant nevirapine prophylaxis for duration of breastfeeding in HIV-1-infected women with high CD4 cell count (IMPAACT PROMISE): a randomized, open label, clinical trial. *J Acquir Immune Defic Syndr*. 2017. Available at https://www.ncbi.nlm.nih.gov/pubmed/29239901.

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. Coovadia HM, Rollins NC, Bland RM, et al. Mother-to-child transmission of HIV-1 infection during exclusive breastfeeding in the first 6 months of life: an intervention cohort study. *Lancet*. 2007;369(9567):1107-1116. Available at https://www.ncbi.nlm.nih.gov/pubmed/17398310.

17. Coutsoudis A, Pillay K, Spooner E, Kuhn L, Coovadia HM. Influence of infant-feeding patterns on early mother-to-child transmission of HIV-1 in Durban, South Africa: a prospective cohort study. South African Vitamin A Study Group. *Lancet*. 1999;354(9177):471-476. Available at https://www.ncbi.nlm.nih.gov/pubmed/10465172.

18. Kuhn L, Aldrovandi GM, Sinkala M, et al. Effects of early, abrupt weaning on HIV-free survival of children in Zambia. *N Engl J Med*. 2008;359(2):130-141. Available at https://www.ncbi.nlm.nih.gov/pubmed/18525036.

19. Thea DM, Aldrovandi G, Kankasa C, et al. Post-weaning breast milk HIV-1 viral load, blood prolactin levels and breast milk volume. *AIDS*. 2006;20(11):1539-1547. Available at https://www.ncbi.nlm.nih.gov/pubmed/16847409.

20. Kuhn L, Kim HY, Walter J, et al. HIV-1 concentrations in human breast milk before and after weaning. *Sci Transl Med*. 2013;5(181):181ra151. Available at https://www.ncbi.nlm.nih.gov/pubmed/23596203.

21. Waitt C, Olagunju A, Nakalema S, et al. Plasma and breast milk pharmacokinetics of emtricitabine, tenofovir and lamivudine using dried blood and breast milk spots in nursing African mother-infant pairs. *J Antimicrob Chemother*. 2018. Available at https://www.ncbi.nlm.nih.gov/pubmed/29309634.

22. Mugwanya KK, Hendrix CW, Mugo NR, et al. Pre-exposure prophylaxis use by breastfeeding HIV-uninfected women: a prospective short-ferm study of antiretroviral excretion in breast milk and infant absorption. *PLoS Med*. 2016;13(9):e1002132. Available at https://www.ncbi.nlm.nih.gov/pubmed/27676257.

23. Palombi L, Pirillo MF, Marchei E, et al. Concentrations of tenofovir, lamivudine and efavirenz in mothers and children enrolled under the Option B-Plus approach in Malawi. *J Antimicrob Chemother*. 2016;71(4):1027-1030. Available at https://www.ncbi.nlm.nih.gov/pubmed/26679247.

24. Mofenson LM, Baggaley RC, Mameletzis I. Tenofovir disoproxil fumarate safety for women and their infants during pregnancy and breastfeeding. *AIDS*. 2017;31(2):213-232. Available at https://www.ncbi.nlm.nih.gov/pubmed/27831952.

25. Dryden-Peterson S, Shapiro RL, Hughes MD, et al. Increased risk of severe infant anemia after exposure to maternal HAART, Botswana. *J Acquir Immune Defic Syndr*. 2011;56(5):428-436. Available at http://www.ncbi.nlm.nih.gov/pubmed/21266910.

26. Fogel J, Li Q, Taha TE, et al. Initiation of antiretroviral treatment in women after delivery can induce multiclass drug resistance in breastfeeding HIV-infected infants. *Clin Infect Dis*. 2011;52(8):1069-1076. Available at http://www.ncbi.nlm.nih.gov/pubmed/21460326.

27. Zeh C, Weidle PJ, Nafisa L, et al. HIV-1 drug resistance emergence among breastfeeding infants born to HIV-infected mothers during a single-arm trial of triple-antiretroviral prophylaxis for prevention of mother-to-child transmission: a secondary analysis. *PLoS Med*. 2011;8(3):e1000430. Available at http://www.ncbi.nlm.nih.gov/pubmed/21468304.

Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV (Last Updated December 7, 2018; last reviewed December 7, 2018)

Panel's Recommendations

- All newborns perinatally exposed to HIV should receive postpartum antiretroviral (ARV) drugs to reduce the risk of perinatal transmission of HIV **(AI)**.
- Newborn ARV regimens—at gestational-age-appropriate doses—should be initiated as close to the time of birth as possible, preferably within 6 to 12 hours of delivery **(AII)**.
- The selection of a newborn ARV regimen should be determined based on maternal and infant factors that influence risk of perinatal transmission of HIV **(AIII)**. The uses of ARV regimens in newborns include:
  - **ARV Prophylaxis:** The administration of one or more ARV drugs to a newborn without documented HIV infection to reduce the risk of perinatal acquisition of HIV.
  - **Empiric HIV Therapy:** The administration of a three-drug ARV regimen to newborns at highest risk of perinatal acquisition of HIV. Empiric HIV therapy is intended to be preliminary treatment for a newborn who is later documented to have HIV but also serves as prophylaxis against HIV acquisition for those newborns who are exposed to HIV *in utero*, during the birthing process, or during breastfeeding and who do not acquire HIV.
  - **HIV Therapy:** The administration of a three-drug ARV regimen at treatment dosages (antiretroviral therapy [ART]) to newborns with documented HIV infection (see Diagnosis of HIV Infection).
- For newborns whose mothers have received ART during pregnancy with sustained viral suppression near delivery and for whom there are no concerns related to maternal adherence, a 4-week zidovudine ARV prophylaxis regimen can be used **(BII)**.
- Newborns at higher risk of perinatal acquisition of HIV should receive a multi-drug ARV prophylaxis regimen or empiric HIV therapy based on clinician assessment of risk (see Tables 8 and 9 for recommended regimens). Newborns at higher risk of HIV acquisition include those born to women with HIV who:
  - Have not received antepartum or intrapartum ARV drugs **(AI)**, *or*
  - Have received only intrapartum ARV drugs **(AI)**, *or*
  - Have received antepartum ARV drugs but without viral suppression near delivery **(AII)**, *or*
  - Have primary or acute HIV infection during pregnancy **(AII)**, *or*
  - Have primary or acute HIV infection during breastfeeding **(AII)**.
- Newborns of women with unknown HIV status who test HIV positive on expedited testing performed during labor or shortly after birth should initiate an ARV regimen (ARV prophylaxis or empiric HIV therapy based on clinician assessment of risk) **(AII)**. If supplemental testing is negative, the ARV regimen can be discontinued **(AII)**.
- For newborns with HIV infection, ART should be initiated **(AI)**.
- The use of ARV drugs other than zidovudine, lamivudine, and nevirapine cannot be recommended for any indication in premature newborns (<37 weeks gestational age) because of lack of dosing and safety data **(BIII)**.
- Providers with questions about ARV management of perinatal HIV exposure should consult the National Perinatal HIV Hotline (1-888-448-8765), which provides free clinical consultation on all aspects of perinatal HIV, including newborn care **(AIII)**.

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*

General Considerations for Antiretroviral Management of Newborns Exposed to HIV or Born with HIV

All newborns with perinatal exposure to HIV should receive antiretroviral (ARV) drugs in the neonatal period to reduce perinatal transmission of HIV, with selection of the appropriate ARV regimen guided by the level of transmission risk. The most important factors that influence the risk of HIV transmission to a newborn exposed to HIV are whether the mother has received antepartum/intrapartum antiretroviral therapy (ART) and her viral load. The risk of transmission is increased in the absence of maternal ART or if

maternal antepartum/intrapartum treatment was started after early pregnancy or was ineffective in producing virologic suppression; higher maternal viral load, especially in later pregnancy, correlates with higher risk of transmission. There is a spectrum of transmission risk that depends on these and other maternal and infant factors, including mode of delivery, gestational age at delivery, and maternal health status. HIV transmission can occur *in utero*, intrapartum, or during breastfeeding.

Historically, the use of ARV drugs in the newborn period was referred to as ARV prophylaxis since it primarily focused on protection against newborn perinatal acquisition of HIV. More recently, clinicians have begun to identify newborns at highest risk for HIV acquisition and initiate three-drug ARV regimens as empiric treatment of HIV. In this guideline, the following terms will be used:

- **ARV Prophylaxis:** The administration of ARV drugs to a newborn without documented HIV infection to reduce the risk of HIV acquisition. ARV prophylaxis includes administration of a single agent, usually zidovudine, as well as combinations of two or three ARV drugs.
- **Empiric HIV Therapy:** The administration of a three-drug ARV regimen to newborns at highest risk of HIV acquisition. Empiric HIV therapy is intended to be early treatment for a newborn who is later documented to have acquired HIV, but also serves as ARV prophylaxis against HIV acquisition for those newborns who are exposed to HIV *in utero*, during the birthing process, or during breastfeeding and who do not acquire HIV.
- **HIV Therapy:** The administration of a three-drug ARV treatment regimen to newborns with documented HIV (see Diagnosis of HIV Infection). HIV therapy is lifelong.

The terms ARV prophylaxis and empiric HIV therapy describe the clinician's intent in prescribing ARV drugs and may be overlapping. For example, an empiric HIV therapy regimen also provides ARV prophylaxis for a newborn. However, two-drug (and some three-drug) ARV prophylaxis regimens, notably those that use prophylactic rather than therapeutic dosages of nevirapine, are not considered empiric HIV therapy.

The interval during which newborn ARV prophylaxis or empiric HIV therapy can be initiated and still be beneficial is undefined; however, most studies support providing ARVs as early as possible after delivery.[1-6]

Table 8 provides an overview of neonatal ARV management recommendations according to risk of perinatal transmission of HIV to the newborn and Table 8 summarizes the dosing recommendations for ARV dosing in newborns. Additional information about dose selection for newborns, including premature infants (<37 weeks gestational age), can be found in Pediatric Antiretroviral Drug Information. In addition, the National Perinatal HIV Hotline (888-448-8765) is a federally funded service providing free clinical consultation for difficult cases to providers caring for pregnant women living with HIV and their newborns, and can provide referral to local or regional pediatric HIV specialists.

Table 8. Newborn Antiretroviral Management According to Risk of HIV Infection in the Newborn

Drug selection and dosing considerations are related to the age and gestational age of the newborn. Consultation is available through the National Perinatal HIV Hotline (888-448-8765).

Category	Description	Neonatal ARV Management
Low Risk of Perinatal HIV Transmission	• Mothers who received ART during pregnancy with sustained viral suppression near delivery and no concerns related to adherence	ZDV for 4 weeks
Higher Risk of Perinatal HIV Transmission[a,b]	• Mothers who received neither antepartum nor intrapartum ARV drugs • Mothers who received only intrapartum ARV drugs • Mothers who received antepartum and intrapartum ARV drugs but who have detectable viral load near delivery, particularly if delivery was vaginal • Mothers with acute or primary HIV infection during pregnancy or breastfeeding (in which case, the mother **should discontinue** breastfeeding).[c]	2-drug ARV prophylaxis (NICHD-HPTN 040/PACTG 1043 regimen) with 6 weeks ZDV and 3 doses of NVP (prophylactic dosage, with doses given within 48 hours of birth, 48 hours after first dose, and 96 hours after second dose) *or* Empiric HIV therapy using either ZDV, 3TC, and NVP (treatment dosage) *or* ZDV, 3TC, and RAL administered from birth to age 6 weeks.[d]
Presumed Newborn HIV Exposure	• Mothers with unknown HIV status who test HIV positive at delivery or postpartum or whose newborns have a positive HIV antibody test	ARV management as above (for higher risk of perinatal HIV transmission) Infant ARVs should be discontinued immediately if supplemental testing confirms that the mother does not have HIV.
Newborn with HIV[e]	• Positive newborn HIV virologic test/NAT	3-drug ARV regimen using treatment dosages

[a] See text for evidence supporting a 2-drug ARV prophylaxis regimen and empiric HIV therapy.

[b] See the Intrapartum Care section for guidance on indications for scheduled cesarean delivery and intrapartum IV ZDV to reduce the risk of perinatal HIV transmission for mothers with an elevated viral load at delivery.

[c] Most Panel members would opt to administer empiric HIV therapy to infants whose mothers had acute HIV during pregnancy because of the higher risk for *in utero* transmission. If acute HIV is diagnosed during breastfeeding, mother should stop breastfeeding.

[d] The optimal duration of empiric HIV therapy in newborns at higher risk of perinatal HIV transmission is unknown. Some Panel members opt to discontinue NVP, RAL, and/or 3TC when a birth NAT returns negative, while others would continue empiric HIV therapy for infants at highest risk of HIV acquisition for 6 weeks. In all cases, ZDV should be continued for 6 weeks. It is recommended that providers consult with an expert in pediatric HIV infection to determine therapy duration based on case-specific risk factors and interim HIV NAT results.

[e] Most Panel members do not recommend delaying the initiation of ART pending results of the confirmatory HIV NAT, given low likelihood of a false-positive HIV NAT.

Note: ARV drugs should be initiated as close to the time of birth as possible, preferably within 6 to 12 hours of delivery. See Table 9 for dosing specifics.

Key to Acronyms: 3TC = lamivudine; ART = antiretroviral therapy; ARV =antiretroviral; IV = intravenous; NAT = nucleic acid test; NVP = nevirapine; the Panel = Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission; RAL = raltegravir; ZDV = zidovudine

Table 9. Antiretroviral Dosing Recommendations for Newborns (page 1 of 3)

Newborns at Low Risk of Perinatal HIV Transmission	
Recommended Regimen	**Recommended Duration**
• ZDV	• ZDV administered for 4 weeks
Newborns at Higher Risk of Perinatal HIV Transmission	
Recommended Regimen	**Recommended Duration**
• 2-drug ARV prophylaxis with ZDV and 3 doses of NVP (NICHD-HPTN 040/PACTG 1043 regimen), *or*	• ZDV administered for 6 weeks; 3 doses of NVP during the first week of life
• Empiric HIV therapy with ZDV/3TC/NVP, *or*	• ZDV administered for 6 weeks; 3TC and NVP administered for 2–6 weeks, up to 6 weeks of age[a]
• Empiric HIV therapy with ZDV/3TC/RAL	• ZDV administered for 6 weeks; 3TC and RAL administered for 2–6 weeks, up to 6 weeks of age[a]
Newborns with HIV Infection	
Recommended Regimen	**Recommended Duration**
• HIV therapy with ZDV/3TC/NVP, *or*	• Lifelong therapy
• HIV therapy with ZDV/3TC/RAL	• Lifelong therapy

<table>
<tr><th colspan="4">Indication</th></tr>
<tr><th>Drug</th><th>Low Risk Prophylaxis</th><th>Higher Risk Prophylaxis: 2-Drug</th><th>Higher Risk Prophylaxis: Empiric and HIV Therapy</th></tr>
<tr><td>ZDV

Note: For newborns unable to tolerate oral agents, the IV dose is 75% of the oral dose while maintaining the same dosing interval.</td><td colspan="2">≥35 Weeks Gestation at Birth:
• ZDV 4 mg/kg/dose orally twice daily

Simplified Weight-Band Dosing for Newborns ≥35 Weeks Gestation at Birth:
<table><tr><th>Weight Band (kg)</th><th>Volume (mL) ZDV 10 mg/mL Oral Syrup Twice Daily</th></tr><tr><td>2 to <3 kg</td><td>1 mL</td></tr><tr><td>3 to <4 kg</td><td>1.5 mL</td></tr><tr><td>4 to <5 kg</td><td>2 mL</td></tr></table></td><td>≥35 Weeks Gestation at Birth
Birth–4 Weeks:
• ZDV 4 mg/kg/dose orally twice daily
Age >4 Weeks:
• ZDV 12 mg/kg/dose orally twice daily

Simplified Weight-Band Dosing for Newborns Aged ≥35 Weeks Gestation from Birth to 4 Weeks:
<table><tr><th>Weight Band (kg)</th><th>Volume (mL) ZDV 10 mg/mL Oral Syrup Twice Daily</th></tr><tr><td>2 to <3 kg</td><td>1 mL</td></tr><tr><td>3 to <4 kg</td><td>1.5 mL</td></tr><tr><td>4 to <5 kg</td><td>2 mL</td></tr></table></td></tr>
<tr><td></td><td colspan="2">≥30 to <35 Weeks Gestation at Birth
Birth to Age 2 Weeks:
• ZDV 2 mg/kg/dose orally twice daily
Age 2 Weeks to 4–6 Weeks:
• ZDV 3 mg/kg/dose orally twice daily</td><td>≥30 to <35 Weeks Gestation at Birth
Birth to Age 2 Weeks:
• ZDV 2 mg/kg/dose orally twice daily
Age 2 Weeks to 6–8 Weeks:
• ZDV 3 mg/kg/dose orally twice daily
Age >6–8 Weeks:
• ZDV 12 mg/kg/dose orally twice daily</td></tr>
<tr><td></td><td colspan="2"><30 Weeks Gestation at Birth
Birth to Age 4–6 Weeks:
• ZDV 2 mg/kg/dose orally twice daily</td><td><30 Weeks Gestation at Birth
Birth to Age 4 Weeks:
• ZDV 2 mg/kg/dose orally twice daily
Age 4 to 8–10 Weeks:
• ZDV 3 mg/kg/dose orally twice daily
Aged >8–10 Weeks:
• ZDV 12 mg/kg/dose orally twice daily</td></tr>
</table>

Table 9. Antiretroviral Dosing Recommendations for Newborns (page 2 of 3)

Indication			
Drug	**Low Risk Prophylaxis**	**Higher Risk Prophylaxis: 2-Drug**	**Higher Risk Prophylaxis: Empiric and HIV Therapy**
3TC	N/A	N/A	≥32 Weeks Gestation at Birth *Birth to Age 4 Weeks:* • 3TC 2 mg/kg/dose orally twice daily *Age >4 Weeks:* • 3TC 4 mg/kg/dose orally twice daily
NVP	N/A	≥32 Weeks Gestation at Birth: • NVP in 3 doses given 1. Within 48 hours of birth, 2. 48 hours after the 1st dose, *and* 3. 96 hours after the 2nd dose Birth Weight 1.5 to 2 kg: • NVP 8 mg per dose orally. **Note:** No calculation is required for this dose; **this is the actual dose, not a mg/kg dose**. Birth Weight >2 kg: • NVP 12 mg per dose orally. **Note:** No calculation is required for this dose; **this is the actual dose, not a mg/kg dose**.	≥37 Weeks Gestation at Birth *Birth to Age 4 Weeks:* • NVP 6 mg/kg/dose orally twice daily[b] *Age >4 Weeks:* • NVP 200 mg/m^2 of BSA/dose orally twice daily 34 to <37 Weeks Gestation at Birth *Birth to Age 1 Week:* • NVP 4 mg/kg/dose orally twice daily *Age 1 to 4 Weeks:* • NVP 6 mg/kg/dose orally twice daily *Age >4 Weeks:* • NVP 200 mg/m^2 of BSA/dose orally twice daily **Note:** NVP dose adjustment at 4 weeks of age is optional for empiric HIV therapy.
RAL **Note:** If the mother has taken RAL 2–24 hours prior to delivery, the neonate's first dose of RAL should be delayed until 24–48 hours after birth; additional ARVs should be started as soon as possible.	N/A	N/A	≥37 Weeks Gestation at Birth and Weighing ≥2 kg[c] *Birth to Age 6 Weeks:*

Body Weight (kg)	**Volume (Dose) of Suspension, RAL 10 mg/mL, to be Administered**
Birth to 1 Week: Once Daily Dosing	**Approximately 1.5 mg/kg/dose**
2 to <3 kg	0.4 mL (4 mg) once daily
3 to <4 kg	0.5 mL (5 mg) once daily
4 to <5 kg	0.7 mL (7 mg) once daily
1 to 4 Weeks: Twice Daily Dosing	**Approximately 3 mg/kg/dose**
2 to <3 kg	0.8 mL (8 mg) twice daily
3 to <4 kg	1 mL (10 mg) twice daily
4 to <5 kg	1.5 mL (15 mg) twice daily
4 to 6 Weeks: Twice Daily Dosing	**Approximately 6 mg/kg/dose**
3 to <4 kg	2.5 mL (25 mg) twice daily
4 to <6 kg	3 mL (30 mg) twice daily

[a] The optimal duration of empiric HIV therapy in newborns at higher risk of perinatal HIV transmission is unknown. Some Panel members opt to discontinue NVP, RAL, and/or 3TC when birth NAT returns negative, while others would continue empiric HIV therapy for infants at the highest risk of HIV acquisition for 6 weeks. In all cases in which the newborn is at higher risk of HIV acquisition, ZDV should be continued for 6 weeks. Consultation with an expert in pediatric HIV to select a therapy duration based on case-specific risk factors and interim HIV NAT results is recommended.

Table 9. Antiretroviral Dosing Recommendations for Newborns (page 3 of 3)

[b] Investigational NVP treatment dose recommended by the Panel; FDA has not approved a dose of NVP for infants <1 month of age.

[c] RAL dosing is increased at 1 and 4 weeks of age because metabolism by UGT1A1 is low at birth and increases rapidly during the next 4 to 6 weeks of life. No dosing information is available for preterm or low birthweight infants.

Key to Acronyms: 3TC = lamivudine; ARV =antiretroviral; BSA = body surface area; FDA = Food and Drug Administration; IV = intravenous; N/A = no recommendation; NAT = nucleic acid test; NVP = nevirapine; the Panel = the Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission; RAL = raltegravir; UGT1A1 = uridine diphosphate glucotransferase; ZDV = zidovudine

Recommendations for Antiretrovirals in Specific Clinical Situations

In the following sections and Table 8, the Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission (the Panel) presents available data and recommendations for management of newborns with documented HIV and newborns born to mothers who:

- Received antepartum/intrapartum ARV drugs with effective viral suppression
- Are at higher risk of transmitting HIV to their newborns, including mothers who:
  - Received neither antepartum nor intrapartum ARV drugs
  - Received only intrapartum ARV drugs, *or*
  - Received antepartum and intrapartum ARV drugs but who had detectable viral load near delivery, particularly if delivery was vaginal
- Have acute or primary HIV infection during pregnancy or breastfeeding
- Have unknown HIV status
- Have known ARV drug-resistant virus

Newborns Born to Mothers Who Received Antepartum/Intrapartum Antiretroviral Drugs with Effective Viral Suppression

The risk of HIV acquisition in newborns born to women who received ART regimens during pregnancy and labor and had undetectable viral loads at delivery is <1%. In the PACTG 076 study, zidovudine alone was shown to effectively reduce perinatal HIV transmission and is recommended as prophylaxis for neonates whose mothers received ART that resulted in consistent virologic suppression during pregnancy. The optimal minimum duration of neonatal zidovudine prophylaxis has not been established in clinical trials. A 6-week newborn zidovudine regimen was studied in PACTG 076. However, in the United Kingdom and many other European countries, where a 4-week neonatal zidovudine prophylaxis regimen has been recommended for newborns born to mothers who have received ART regimens during pregnancy and have viral suppression, there has been no apparent increase in the overall HIV perinatal transmission rate.[7,8] Compared with the 6-week zidovudine regimen, a 4-week zidovudine regimen has been reported to allow earlier recovery from anemia in otherwise healthy newborns.[9]

Therefore, the Panel now recommends a 4-week neonatal zidovudine prophylaxis regimen for newborns if the mother has received ART during pregnancy with viral suppression (usually defined as confirmed HIV RNA level below the lower limits of detection of an ultrasensitive assay) at or after 36 weeks gestation, and there are no concerns related to maternal adherence. Dosing recommendations for zidovudine are available for premature newborns and an intravenous preparation is available. Table 9 shows recommended neonatal zidovudine dosing based on gestational age and birthweight.

Newborns Born to Mothers Who Have Received No Antepartum or Intrapartum Antiretroviral Drugs, Who Have Received Intrapartum Antiretroviral Drugs Only, Who Have Received Antiretroviral Drugs and Do Not Have Viral Suppression Near Delivery, or Who Have Acquired HIV During Pregnancy or Breastfeeding

All newborns born to mothers with detectable viral load at the time of delivery, who received only intrapartum ARV drugs, or who have received no ARV drugs during pregnancy or delivery, are at higher risk of HIV acquisition and **should receive a multi-drug ARV prophylaxis regimen** or **empiric HIV therapy**.[5,10-14] The experience with these regimens is described below. Currently, the optimal duration of an empiric HIV therapy regimen in newborns at higher risk of perinatal HIV transmission is unknown. When birth HIV nucleic acid test (NAT) returns negative, some Panel members would opt to discontinue nevirapine, raltegravir, and/or lamivudine, while others would continue empiric HIV therapy for 6 weeks. In all cases in which the newborn is at higher risk of HIV acquisition, zidovudine should be continued for 6 weeks. Consultation with an expert in pediatric HIV is recommended to select a duration of therapy based on case-specific risk factors and interim HIV NAT results.

For those women who received ARV drugs during pregnancy but have a detectable viral load near delivery (on or after 36 weeks gestation), the level of maternal viremia that would trigger the use of a multi-drug ARV prophylaxis regimen or empiric HIV therapy is not definitively known. In two large observational studies of women on combination antenatal ARV drugs, perinatal transmission rates were 0.05% and 0.3% when the mother had viral load measurements <50 copies/mL at delivery. Rates of transmission in these studies increased to 1.1% and 1.5% when viral load measurements were 50 to 399 copies/mL and 2.8% and 4.1% when viral load measurements were >400 copies/mL.[15,16] However, there has been no study to compare the relative efficacy of a multi-drug ARV prophylaxis regimen or empiric HIV therapy to standard newborn prophylaxis at these different thresholds of maternal viremia. While some Panel members would recommend a multi-drug ARV prophylaxis regimen or empiric HIV therapy with any level of detectable viremia, others reserve multi-drug ARV prophylaxis regimens and empiric HIV therapy until higher levels of maternal viral load are documented. The decision whether to initiate a multi-drug ARV prophylaxis regimen or empiric HIV therapy should be made following discussion with the parents weighing the risks and benefits of the proposed regimen.

Primary or acute HIV infection during pregnancy is associated with an increased risk of perinatal transmission of HIV. A multi-drug ARV prophylaxis regimen or empiric HIV therapy should be administered to the infant until maternal HIV can be confirmed or ruled out. (see Acute HIV Infection).

In summary, in these scenarios where the infant is at higher risk of HIV transmission, the Panel recommends either a multi-drug ARV prophylaxis regimen, specifically the NICHD-HPTN 040/PACTG 1043 regimen, or empiric HIV therapy. The data supporting the use these regimens are summarized below. Choosing between these regimens will depend on clinician assessment of the likelihood of HIV transmission.

Multi-Drug Antiretroviral Prophylaxis

There is a paucity of data from randomized clinical trials to guide the optimal selection of a newborn multi-ARV prophylaxis regimen. To date, the NICHD-HPTN 040/PACTG 1043 trial is the only randomized clinical trial of multi-ARV prophylaxis in newborns at higher risk of HIV acquisition. In this study, 1,746 formula-fed infants born to women with HIV who did not receive any ARV drugs during pregnancy were randomized to 1 of 3 newborn prophylaxis regimens: the standard 6-week zidovudine regimen; 6 weeks of zidovudine plus three doses of nevirapine given during the first week of life (first dose at birth–48 hours, second dose 48 hours after the first dose, and third dose 96 hours after the second dose); and 6 weeks of zidovudine plus 2 weeks of lamivudine/nelfinavir. Forty-one percent of the mothers received zidovudine during labor. The risk of intrapartum transmission was significantly lower in the 2- and 3-drug arms (2.2% and 2.5%, respectively, vs. 4.9% for 6 weeks of zidovudine alone; $P = 0.046$ for each experimental arm vs. zidovudine alone).[5] The NICHD-HPTN 040/PACTG 1043 regimen was associated with nucleoside reverse transcriptase inhibitor (NRTI) resistance in 3 of 53 (5.7%) participants with *in utero* infection who were

treated with zidovudine alone, and in 6 of 33 (18.2%) participants treated with zidovudine plus nevirapine ($P > 0.05$). In addition, the third drug in the three-arm regimen was nelfinavir, which has highly variable pharmacokinetics (PKs) in this age group and did not reach the nelfinavir target plasma concentration in 46% of study participants.[17] Although transmission rates with the two regimens were similar, neutropenia was significantly more common with the three-drug regimen than with the two-drug or zidovudine-alone regimen (27.5% vs. 15%, $P < 0.0001$).

Data from Europe and the United States indicate increasing use of multi-drug ARV prophylaxis regimens in newborns exposed to HIV. In the United Kingdom and Ireland, use of the regimens increased from 9% of newborns exposed to HIV between 2001 to 2004 to 13% between 2005 to 2008 and, in a poll of 134 U.S.-based providers, 62% reported using multi-ARV prophylaxis regimens in high-risk newborns.[18-20] However, interpretation of these observational studies is complicated by the definition of ARV prophylaxis, use of prophylaxis versus treatment dosing of nevirapine, and combining multiple different ARV prophylaxis regimens to compare safety and efficacy with zidovudine monotherapy. Many studies include single-dose nevirapine combined with another ARV, usually zidovudine, as two-drug HIV prophylaxis. Most do not report whether nevirapine was administered at the recommended prophylaxis dose or at a higher dose as part of empiric HIV therapy. So, despite increasing use of various ARV prophylaxis regimens, comprehensive data on efficacy and safety are lacking. For newborns at higher risk of HIV acquisition (Table 8), the Panel recommends the NICHD-HPTN 040/PACTG 1043 2-drug regimen of 6 weeks of zidovudine plus 3 doses of nevirapine as an option for management.

Empiric HIV Therapy

The other option that the Panel recommends for newborns at higher risk of perinatal acquisition of HIV is a three-drug ARV empiric HIV therapy regimen consisting of zidovudine, lamivudine, and either nevirapine (at treatment dosage) or raltegravir.

Enthusiasm for the three drug approach followed a case of a "functional cure" of HIV in an newborn reported in 2013.[21] The newborn was born by vaginal delivery at 35 weeks' gestation to a woman who received no prenatal care and whose HIV infection was diagnosed by expedited testing during labor; delivery occurred before maternal intrapartum ARV drugs could be given. When the newborn was 30 hours old, a regimen of zidovudine, lamivudine, and nevirapine (the latter drug administered at a higher treatment dose rather than standard prophylactic dosing) was initiated. The newborn was found to have a positive HIV DNA polymerase chain reaction (PCR) in a sample obtained at age 30 hours and an HIV RNA level of 19,812 copies/mL on an HIV RNA PCR assay performed at age 31 hours. Based on these test results, the newborn was continued on treatment for HIV, thought to be acquired *in utero*. At age 18 months, the mother discontinued the child's ART; levels of plasma RNA, proviral DNA, and HIV antibodies remained undetectable in the child for >2 years without ART. Unfortunately, virologic rebound was identified shortly before the child turned 4 years of age. Of interest is the subsequently reported case of an infant treated from birth and virologically suppressed for 4 years who had virologic rebound within days of ART discontinuation.[22]

Further support of empiric HIV therapy comes from Canadian investigators who have reported outcomes in 136 newborns considered at higher risk of HIV acquisition (i.e., born to women with HIV who had detectable viral loads and/or poor adherence to therapy prior to delivery) who received a triple-ARV regimen within 72 hours of birth. Of these 136 newborns, 12 (9%) were found to be have acquired HIV and no major regimen-related toxicities were identified.[23] However, there was no control group to permit comparison of safety or efficacy of this approach relative to single-drug or two-drug regimens. Another Canadian study compared the safety of empiric HIV therapy in 148 newborns with high-risk exposure (i.e., incomplete maternal virologic suppression at delivery or, in the absence of maternal viral load results, a maternal history of incomplete adherence or non-adherence to ART, or late pregnancy initiation of ART) to zidovudine alone in 145 low-risk newborns in a control group. Thirteen newborns in the empiric HIV therapy group acquired HIV, including five with a positive HIV NAT within the first 48 hours of life, suggesting *in utero* infection. No newborn in the low-risk zidovudine-only group acquired HIV. Non-specific signs and symptoms (e.g., vomiting,

diarrhea, rash, jitteriness, irritability) potentially attributable to medication-related adverse effects were reported among the newborns receiving empiric HIV therapy but not among those receiving zidovudine only (10.2% vs. 0%, $P < 0.001$). ARV drugs were also more likely to be discontinued prematurely in the newborns receiving empiric HIV therapy than in those receiving only zidovudine (9.5% vs. 2.1%, $P = 0.01$).[24]

Empiric HIV therapy in newborns is consistent with the Centers for Disease Control and Prevention's recommendations for occupational and non-occupational HIV post-exposure prophylaxis in adults, circumstances in which the risk of infection is often lower than for newborns at higher risk of HIV acquisition.[25,26] The use of empiric HIV therapy in newborns was limited until the availability of new PK and safety information about ARVs in the neonatal period. Although the use of nevirapine to prevent perinatal transmission has been found to be safe in neonates and low-birthweight newborns, these prophylaxis-dose regimens target trough drug levels are ≥10-fold lower than targeted therapeutic levels. However recent studies of therapeutic dosages of nevirapine and raltegravir have established safe doses that achieve targeted PK parameters.[27-31]

At this time, if an empiric HIV therapy regimen is selected, the Panel recommends a combination of zidovudine, lamivudine, and nevirapine (treatment dosage) or zidovudine, lamivudine, and raltegravir (see Tables 8 and 9). The optimal duration of empiric HIV therapy in newborns at higher risk of perinatal HIV transmission is unknown. Some Panel members opt to discontinue additional medications if returned birth NAT results are negative, while others would continue empiric HIV therapy for 6 weeks depending on risk for HIV transmission. In all cases, zidovudine should be continued for 6 weeks. Consultation with an expert in pediatric HIV to select a therapy duration based on case-specific risk factors and interim HIV NAT results is recommended.

Newborns Born to Mothers with Unknown HIV Status at Presentation in Labor

Expedited HIV testing is recommended during labor for women with unknown HIV status and, if not performed during labor, as soon as possible after birth for the mothers and/or their newborns (see Identification of Perinatal Exposure). Expedited test results should be available within 60 minutes. If maternal or infant expedited testing is positive, the newborn **should be immediately initiated on a multi-drug ARV prophylaxis regimen or empiric HIV therapy**, without waiting for the results of supplemental tests. Expedited HIV testing should be available on a 24-hour basis at all facilities with a maternity service and/or neonatal intensive care unit or special care or newborn nursery.

A positive initial test result in mothers or newborns should be presumed to indicate maternal HIV until supplemental testing clarifies maternal and newborn status. If appropriate test results for a mother (or newborn) are negative, newborn ARV drugs can be discontinued. Clinicians should be aware of their state laws, as there is variability in the HIV testing allowed without parental consent.

A nursing mother who is suspected of having HIV based on an initial positive antibody or antibody/antigen test result should stop breastfeeding until HIV is confirmed or ruled out.

Pumping and temporarily discarding or freezing breast milk can be recommended. If HIV is ruled out, breastfeeding can resume. If HIV is confirmed, breastfeeding should be discontinued permanently.[32]

Newborns Born to Mothers with Antiretroviral Drug-Resistant Virus

The optimal ARV regimen for newborns delivered by women with ARV drug-resistant virus is unknown. It is also unknown whether resistant virus in the mother increases the risk of HIV acquisition by the infant. The ARV regimen for newborns born to mothers with known or suspected drug resistance should be determined in consultation with a pediatric HIV specialist before delivery or through consultation via the National Perinatal HIV Hotline (888-448-8765). However, there is no evidence that neonatal prophylaxis regimens customized based on presence of maternal drug resistance are more effective than standard neonatal prophylaxis regimens.

Data from the WITS study suggest that, in women who have mixed zidovudine-resistant and zidovudine-sensitive viral populations, the zidovudine-sensitive virus may be preferentially transmitted.[33,34] Thus, the selection of the newborn ARV regimen should be based on other risk factors (Table 8).

Some studies have suggested that ARV drug-resistant virus may have decreased replicative capacity (reduced viral fitness) and transmissibility.[34] However, perinatal transmission of multidrug-resistant virus has been reported both in the United States and in international settings.[35-39]

Newborns with HIV Infection

Until recently, neonatal ARV regimens were designed for prophylaxis against perinatal HIV transmission and to be as simple as possible for practical use. There was little reason to develop ARV regimens for treatment of neonates, as the long turnaround times to receive HIV NAT results meant that neonatal infections were generally not diagnosed in the first weeks of life. HIV NAT results are now available within a few days and HIV in newborns is being diagnosed as early as the first days of life. A positive HIV NAT must be repeated to confirm HIV. However, most Panel members do not recommend delaying the initiation of ART while waiting for the results of the confirmatory HIV NAT, given the low likelihood of a false-positive HIV NAT. However, evidence that very early treatment (before age 2 weeks) will lead to prolonged remission or better outcomes in newborns with HIV is lacking. Earlier diagnosis of HIV in newborns and the increasing use of empiric HIV therapy in newborns at higher risk for HIV acquisition have necessitated investigation of dosing and safety of ARV drugs in term and preterm newborns. Although still incomplete, especially for preterm newborns, PK and safety profiles of ARV drugs are increasingly available. As already noted, the recommended neonatal ARV doses for prophylaxis and for treatment are the same with the important exception of nevirapine (see Pediatric Antiretroviral Drug Information).

Sufficient data exist to provide dosing recommendations appropriate for the treatment of HIV in neonates using the following medications (see Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection):

- From birth in term and preterm newborns: zidovudine, lamivudine, nevirapine
- From birth in term newborns: emtricitabine, raltegravir
- From age 2 weeks in term newborns: lopinavir/ritonavir (LPV/r)

Dosing recommendations for *premature* newborns are available for zidovudine, lamivudine, and nevirapine only. Neonatal dosing advice, including for premature newborns, is summarized in Table 9. For more detailed information about neonatal dosing recommendations and considerations of these drugs, please see the Pediatric Antiretroviral Drug Information.

Newborns of Mothers Diagnosed with HIV while Breastfeeding

Women with suspected HIV (e.g., a positive initial screening test) should stop breastfeeding until HIV is ruled out. Pumping and temporarily discarding or freezing breast milk can be recommended to mothers who are suspected of having HIV but whose HIV serostatus is not yet confirmed and who want to continue to breastfeed. If HIV is ruled out, breastfeeding can resume. Breastfeeding is not recommended for women with confirmed HIV in the United States, including those receiving ART (see Guidance for Counseling and Managing Women Living with HIV in the United States Who Desire to Breastfeed).[40]

The risk of HIV acquisition associated with breastfeeding depends on multiple newborn and maternal factors, including maternal viral load and CD4 T lymphocyte (CD4) cell count.[41] Newborns of women who develop acute HIV while breastfeeding are at greater risk of acquiring HIV than are those whose mothers have chronic HIV infection[42] because acute HIV infection is accompanied by a rapid increase in viral load and a corresponding decrease in CD4 cell count.[43]

Other than discontinuing breastfeeding, optimal strategies for managing a newborn who was breastfed by a

mother with HIV (often because the mother just learned of her own HIV diagnosis) have yet to be defined. Some Panel members would consider the use of post-exposure prophylaxis in newborns for 4 to 6 weeks after cessation of breastfeeding. Post-exposure prophylaxis, however, is less likely to be effective in this circumstance than with other non-occupational exposures because the exposure to breast milk is likely to have occurred during a prolonged period rather than a single exposure to the virus.[44]

Several studies of newborns breastfed by women with chronic HIV infection in low-resource settings have shown that daily newborn nevirapine, lamivudine, LPV/r, or nevirapine plus zidovudine can reduce the risk of postnatal infection during breastfeeding.[45-49] No trials have evaluated the use of multi-ARV regimens to prevent transmission after cessation of breastfeeding in mothers with acute HIV infection.

Given the higher risk of postnatal transmission from a breastfeeding woman with acute HIV infection, an alternative approach favored by some Panel members would be to offer empiric HIV therapy until infant HIV status can be determined. If the infant's initial HIV NAT is negative, the optimal duration of empiric HIV therapy is unknown. A 28-day course may be reasonable based on current recommendations for non-occupational HIV exposure.[44] As in other situations, decisions regarding ARV management should be accompanied by consultation with a pediatric HIV specialist and maternal counseling on the potential risks and benefits of this approach. The National Perinatal HIV Hotline (888-448-8765) is a federally funded service providing free clinical consultation for difficult cases to providers caring for pregnant women living with HIV and their newborns, and can provide referral to local or regional pediatric HIV specialists.

Newborns should be tested for HIV prior to initiation of empiric HIV therapy, 4 to 6 weeks and 4 to 6 months after diagnosis of maternal HIV infection and cessation of breastfeeding to determine their HIV status. An additional virologic test should be performed 2 to 4 weeks after discontinuation of empiric HIV therapy (see Diagnosis section). If a newborn is already receiving an ARV prophylaxis regimen other than empiric HIV therapy and is found to have HIV, prophylaxis should be discontinued and treatment for HIV initiated. Resistance testing should be performed, and the ART regimen modified if needed (see the Pediatric Antiretroviral Guidelines).

Short-Term Antiretroviral Drug Safety

Newborn prophylaxis with zidovudine has been associated with only minimal toxicity, consisting primarily of transient hematologic toxicity (mainly anemia), which generally resolves by age 12 weeks (see Initial Postnatal Management). Data on toxicities in newborns exposed to multiple ARV drugs are limited.

Other than zidovudine, lamivudine is the NRTI with the most experience in use for neonatal prophylaxis. In early studies, neonatal exposure to combination zidovudine/lamivudine was generally limited to 1[13,50,51] or 2 weeks.[5] Six weeks of newborn zidovudine/lamivudine exposure has also been reported. These studies suggest that hematologic toxicity may be greater with zidovudine/lamivudine than with zidovudine alone, although the newborns in these studies also had *in utero* exposure to maternal HIV therapy that may have contributed to the toxicity.

In a French study, more severe anemia and neutropenia were observed in newborns exposed to 6 weeks of zidovudine/lamivudine for prophylaxis plus maternal antepartum zidovudine/lamivudine than in a historical cohort of newborns exposed only to maternal and newborn zidovudine. Anemia was reported in 15% and neutropenia in 18% of newborns exposed to zidovudine/lamivudine, with 2% of newborns requiring blood transfusion and 4% requiring treatment discontinuation for toxicity.[52] Similarly, in a Brazilian study of maternal antepartum and 6-week newborn zidovudine/lamivudine prophylaxis, neonatal hematologic toxicity was common, with anemia seen in 69% and neutropenia in 13% of newborns.[53]

Experience with other NRTI drugs for neonatal prophylaxis is more limited.[54,55] Hematologic and mitochondrial toxicity may be more common with exposure to multiple NRTI drugs than to a single NRTI.[52,56-59]

In rare cases, chronic multiple-dose nevirapine prophylaxis in pregnant women has been associated with

severe and potentially life-threatening rash and hepatic toxicity.[60] These toxicities have not been observed in newborns receiving prophylactic dosing with single-dose nevirapine, the two-drug zidovudine regimen plus three doses of nevirapine in the first week of life in NICHD-HPTN 040/PACTG 1043), or in breastfeeding newborns receiving nevirapine prophylaxis daily for 6 weeks to 18 months to prevent transmission of HIV via breast milk.[5,45-47,49,61]

The Food and Drug Administration (FDA) recently approved infant dosing of raltegravir for term neonates ≥37 weeks gestation at birth and weighing ≥2 kg. Dosing information is not available for preterm or low birthweight infants. Infant raltegravir dosing needs to be increased at 1 week and 4 weeks of age. Raltegravir is metabolized by UGT1A1, the same enzyme responsible for the elimination of bilirubin. UGT enzyme activity is low at birth, and raltegravir elimination is prolonged in neonates. In addition, bilirubin and raltegravir may compete for albumin binding sites, and extremely elevated neonatal plasma raltegravir concentrations could pose a risk of kernicterus.[62] IMPAACT P1110 is a Phase 1, multicenter trial enrolling full-term neonates exposed to HIV and who are at risk of acquiring perinatal HIV-1-infection, with or without *in utero* raltegravir exposure. Daily raltegravir was safe and well tolerated during the first 6 weeks of life. Infants were treated for ≤6 weeks from birth and followed for 24 weeks. There were no drug-related clinical adverse reactions observed and only three laboratory adverse reactions: one case of Grade 4 transient neutropenia in an infant receiving zidovudine-containing regimen; and two cases of bilirubin elevations (one each, Grade 1 and Grade 2) that were considered non-serious and did not require specific therapy[63] (see Pediatric Antiretroviral Drug Information for additional information).

The safety and PK data about daily dosing from P1110 are from raltegravir-naive infants whose mothers did not receive raltegravir; data collection from infants born to mothers who were receiving raltegravir is ongoing. However, the Panel believes that the FDA-approved dosing of raltegravir, delaying the first dose for infants born to mothers who received raltegravir, is reasonable based on current data about clearance of the drug in premature and raltegravir-exposed infants.

Of the protease inhibitors, pediatric drug formulations are available for LPV/r, ritonavir, darunavir, tipranavir, and fosamprenavir, but their use in neonates in the first weeks of life is not recommended given the lack of dosing and safety information. In addition, LPV/r oral solution contains 42.4% alcohol and 15.3% propylene glycol, and enzymes that metabolize these compounds are immature in neonates, particularly preterm newborns. Four premature newborns (two sets of twins) started on LPV/r from birth, developed heart block that resolved after drug discontinuation.[64,65] In studies of adults, both ritonavir and LPV/r cause dose-dependent prolongation of the PR interval, and cases of significant heart block, including complete heart block, have been reported. Elevation of 17-hydroxyprogesterone and dehydroepiandrosterone-sulfate has also been associated with administration of LPV/r in the neonatal period, an association not found with zidovudine. Levels of 17-hydroxyprogesterone were greater in newborns who were also exposed to LPV/r *in utero* than in those exposed only in the neonatal period. Term newborns were asymptomatic but three premature newborns experienced life-threatening symptoms compatible with adrenal insufficiency, including hyponatremia and hyperkalemia with, in one case, cardiogenic shock.[66] On the basis of these and other post-marketing reports of cardiac toxicity (including complete atrioventricular block, bradycardia, and cardiomyopathy), lactic acidosis, acute renal failure, adrenal dysfunction, central nervous system depression, respiratory complications leading to death, and metabolic toxicity,[67] predominantly in preterm neonates, the FDA now recommends that LPV/r oral solution **not be administered** to neonates before a postmenstrual age (first day of the mother's last menstrual period to birth plus the time elapsed after birth) of 42 weeks and a postnatal age of ≥14 days.[68] However, a recent study (ANRS 12174) randomized 1,273 newborns, 615 assigned to LPV/r and 621 assigned to lamivudine, as prophylaxis during breastfeeding in women with CD4 counts above the local threshold for treatment at the time. Newborn study prophylaxis was initiated at 7 days of life and only newborns >2 kg were randomized. Clinical and biological severe adverse events did not differ between groups suggesting that LPV/r is safe in term newborns, 7 days of age and older.[69] At this time, the Panel does not recommend the use of LPV/r before a postmenstrual age of 42 weeks and a postnatal age of ≥14 days.

References

1. Wade NA, Birkhead GS, Warren BL, et al. Abbreviated regimens of zidovudine prophylaxis and perinatal transmission of the human immunodeficiency virus. *N Engl J Med*. 1998;339(20):1409-1414. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9811915.

2. Van Rompay KK, Otsyula MG, Marthas ML, Miller CJ, McChesney MB, Pedersen NC. Immediate zidovudine treatment protects simian immunodeficiency virus-infected newborn macaques against rapid onset of AIDS. *Antimicrob Agents Chemother*. 1995;39(1):125-131. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7695293.

3. Tsai CC, Follis KE, Sabo A, et al. Prevention of SIV infection in macaques by (R)-9-(2-phosphonylmethoxypropyl) adenine. *Science*. 1995;270(5239):1197-1199. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7502044.

4. Bottiger D, Johansson NG, Samuelsson B, et al. Prevention of simian immunodeficiency virus, SIVsm, or HIV-2 infection in cynomolgus monkeys by pre- and postexposure administration of BEA-005. *AIDS*. 1997;11(2):157-162. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9030361.

5. Nielsen-Saines K, Watts DH, Veloso VG, et al. Three postpartum antiretroviral regimens to prevent intrapartum HIV infection. *N Engl J Med*. 2012;366(25):2368-2379. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22716975.

6. Dunn DT, Brandt CD, Krivine A, et al. The sensitivity of HIV-1 DNA polymerase chain reaction in the neonatal period and the relative contributions of intra-uterine and intra-partum transmission. *AIDS*. 1995;9(9):F7-11. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8527070.

7. de Ruiter A, Mercey D, Anderson J, et al. British HIV Association and Children's HIV Association guidelines for the management of HIV infection in pregnant women 2008. *HIV Med.* 2008;9(7):452-502. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18840151.

8. Ferguson W, Goode M, Walsh A, Gavin P, Butler K. Evaluation of 4 weeks' neonatal antiretroviral prophylaxis as a component of a prevention of mother-to-child transmission program in a resource-rich setting. *Pediatr Infect Dis J*. 2011;30(5):408-412. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21266939.

9. Lahoz R, Noguera A, Rovira N, et al. Antiretroviral-related hematologic short-term toxicity in healthy infants: implications of the new neonatal 4-week zidovudine regimen. *Pediatr Infect Dis J*. 2010;29(4):376-379. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19949355.

10. Mofenson LM, Lambert JS, Stiehm ER, et al. Risk factors for perinatal transmission of human immunodeficiency virus type 1 in women treated with zidovudine. Pediatric AIDS Clinical Trials Group Study 185 Team. *N Engl J Med*. 1999;341(6):385-393. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10432323.

11. Garcia PM, Kalish LA, Pitt J, et al. Maternal levels of plasma human immunodeficiency virus type 1 RNA and the risk of perinatal transmission. Women and infants transmission study group. *N Engl J Med*. 1999;341(6):394-402. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10432324.

12. Cooper ER, Charurat M, Mofenson L, et al. Combination antiretroviral strategies for the treatment of pregnant HIV-1-infected women and prevention of perinatal HIV-1 transmission. *J Acquir Immune Defic Syndr*. 2002;29(5):484-494. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11981365.

13. Petra Study Team. Efficacy of three short-course regimens of zidovudine and lamivudine in preventing early and late transmission of HIV-1 from mother to child in Tanzania, South Africa, and Uganda (Petra study): a randomised, double-blind, placebo-controlled trial. *Lancet*. 2002;359(9313):1178-1186. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11955535.

14. Lallemant M, Jourdain G, Le Coeur S, et al. A trial of shortened zidovudine regimens to prevent mother-to-child transmission of human immunodeficiency virus type 1. Perinatal HIV Prevention Trial (Thailand) Investigators. *N Engl J Med*. 2000;343(14):982-991. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11018164.

15. Mandelbrot L, Tubiana R, Le Chenadec J, et al. No perinatal HIV-1 transmission from women with effective antiretroviral therapy starting before conception. *Clin Infect Dis*. 2015. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26197844.

16. Townsend CL, Byrne L, Cortina-Borja M, et al. Earlier initiation of ART and further decline in mother-to-child HIV transmission rates, 2000-2011. *AIDS*. 2014;28(7):1049-1057. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24566097.

17. Mirochnick M, Nielsen-Saines K, Pilotto JH, et al. Nelfinavir and lamivudine pharmacokinetics during the first two weeks of life. *Pediatr Infect Dis J*. 2011;30(9):769-772. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21666540.

18. Haile-Selassie H, Townsend C, Tookey P. Use of neonatal post-exposure prophylaxis for prevention of mother-to-child HIV transmission in the UK and Ireland, 2001-2008. *HIV Med.* 2011;12(7):422-427. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21251184.

19. McKeegan K, Rutstein R, Lowenthal E. Postnatal infant HIV prophylaxis: a survey of U.S. practice. *AIDS Patient Care STDS*. 2011;25(1):1-4. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21162689.

20. Chiappini E, Galli L, Giaquinto C, et al. Use of combination neonatal prophylaxis for the prevention of mother-to-child transmission of HIV infection in European high-risk infants. *AIDS*. 2013;27(6):991-1000. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23211776.

21. Persaud D, Gaye H, et al. Absence of detectable HIV-1 viremia following treatment cessation in an infant. *N Engl J Med*. 2013;369(19):1828-35. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24152233.

22. Butler KM, Gavin P, Coughlan S, et al. Rapid viral rebound after 4 years of suppressive therapy in a seronegative HIV-1 infected infant treated from birth. *Pediatr Infect Dis J*. 2014. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25251719.

23. Bitnun A, Samson L, Chun TW, et al. Early initiation of combination antiretroviral therapy in HIV-1-infected newborns can achieve sustained virologic suppression with low frequency of CD4+ T cells carrying HIV in peripheral blood. *Clin Infect Dis*. 2014;59(7):1012-1019. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24917662.

24. Kakkar FW, Samson L, Vaudry W, et al. Safety of combination antiretroviral prophylaxis in high-risk HIV-exposed newborns: a retrospective review of the Canadian experience. *J Int AIDS Soc*. 2016;19(1):20520. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26880241.

25. Centers for Disease Control and Prevention. Updated guidelines for antiretroviral postexposure prophylaxis after sexual, injection drug use, or other nonoccupational exposure to HIV—United States, 2016. 2016; http://www.cdc.gov/hiv/pdf/programresources/cdc-hiv-npep-guidelines.pdf.

26. Kuhar DT, Henderson DK, Struble KA, et al. Updated US Public Health Service guidelines for the management of occupational exposures to human immunodeficiency virus and recommendations for postexposure prophylaxis. *Infect Control Hosp Epidemiol*. 2013;34(9):875-892. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23917901.

27. Lau E, Brophy J, Samson L, et al. Nevirapine pharmacokinetics and safety in neonates receiving combination antiretroviral therapy for prevention of vertical HIV transmission. *J Acquir Immune Defic Syndr*. 2017;74(5):493-498. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28114187.

28. Cressey TR, Punyawudho B, Le Coeur S, et al. Assessment of nevirapine prophylactic and therapeutic dosing regimens for neonates. *J Acquir Immune Defic Syndr*. 2017;75(5):554-560. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28489732.

29. Clarke DF, Acosta EP, Rizk ML, et al. Raltegravir pharmacokinetics in neonates following maternal dosing. *J Acquir Immune Defic Syndr*. 2014;67(3):310-315. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25162819.

30. Clarke DF, Wong RJ, Wenning L, Stevenson DK, Mirochnick M. Raltegravir *in vitro* effect on bilirubin binding. *Pediatr Infect Dis J*. 2013;32(9):978-980. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23470680.

31. Clarke DF, Penazzato M, Capparelli E, et al. Prevention and treatment of HIV infection in neonates: evidence base for existing WHO dosing recommendations and implementation considerations. *Expert Rev Clin Pharmacol*. 2018;11(1):83-93. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29039686.

32. American Academy of Pediatrics (AAP). Breastfeeding and the use of human milk. 2012. Available at: http://www.Pediatrics.org/cgi/doi/10.1542/peds.2011-3552.

33. Colgrove RC, Pitt J, Chung PH, Welles SL, Japour AJ. Selective vertical transmission of HIV-1 antiretroviral resistance mutations. *AIDS*. 1998;12(17):2281-2288. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9863870.

34. Bauer GR, Colgrove RC, Larussa PS, Pitt J, Welles SL. Antiretroviral resistance in viral isolates from HIV-1-transmitting mothers and their infants. *AIDS*. 2006;20(13):1707-1712. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16931934.

35. Cohan D, Feakins C, Wara D, et al. Perinatal transmission of multidrug-resistant HIV-1 despite viral suppression on an enfuvirtide-based treatment regimen. *AIDS*. 2005;19(9):989-990. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15905684.

36. Desai N, Mathur M. Selective transmission of multidrug resistant HIV to a newborn related to poor maternal adherence. *Sex Transm Infect*. 2003;79(5):419-421. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14573842.

37. De Jose MI, Ramos JT, Alvarez S, Jimenez JL, Munoz-Fernandez MA. Vertical transmission of HIV-1 variants resistant to reverse transcriptase and protease inhibitors. *Arch Intern Med*. 2001;161(22):2738-2739. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11732941.

38. Zeh C, Weidle PJ, Nafisa L, et al. HIV-1 drug resistance emergence among breastfeeding infants born to HIV-infected mothers during a single-arm trial of triple-antiretroviral prophylaxis for prevention of mother-to-child transmission: a secondary analysis. *PLoS Med*. 2011;8(3):e1000430. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21468304.

39. Fogel J, Li Q, Taha TE, et al. Initiation of antiretroviral treatment in women after delivery can induce multiclass drug resistance in breastfeeding HIV-infected infants. *Clin Infect Dis*. 2011;52(8):1069-1076. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21460326.

40. Committee On Pediatric AIDS. Infant feeding and transmission of human immunodeficiency virus in the United States. *Pediatrics*. 2013;131(2):391-396. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23359577.

41. Kuhn L, Reitz C, Abrams EJ. Breastfeeding and AIDS in the developing world. *Curr Opin Pediatr*. 2009;21(1):83-93. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19242244.

42. Van de Perre P, Lepage P, Homsy J, Dabis F. Mother-to-infant transmission of human immunodeficiency virus by breast milk: presumed innocent or presumed guilty? *Clin Infect Dis*. 1992;15(3):502-507. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1445596.

43. Daar ES. Virology and immunology of acute HIV type 1 infection. *AIDS Res Hum Retroviruses*. 1998;14 Suppl 3:S229-234. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9814948.

44. Smith DK, Grohskopf LA, Black RJ, et al. Antiretroviral postexposure prophylaxis after sexual, injection-drug use, or other nonoccupational exposure to HIV in the United States: recommendations from the U.S. Department of Health and Human Services. *MMWR Recomm Rep*. 2005;54(RR-2):1-20. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15660015.

45. Six Week Extended-Dose Nevirapine Study Team, Bedri A, Gudetta B, et al. Extended-dose nevirapine to 6 weeks of age for infants to prevent HIV transmission via breastfeeding in Ethiopia, India, and Uganda: an analysis of three randomised controlled trials. *Lancet*. 2008;372(9635):300-313. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18657709.

46. Kumwenda NI, Hoover DR, Mofenson LM, et al. Extended antiretroviral prophylaxis to reduce breast-milk HIV-1 transmission. *N Engl J Med*. 2008;359(2):119-129. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18525035.

47. Chasela CS, Hudgens MG, Jamieson DJ, et al. Maternal or infant antiretroviral drugs to reduce HIV-1 transmission. *N Engl J Med*. 2010;362(24):2271-2281. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20554982.

48. Kilewo C, Karlsson K, Massawe A, et al. Prevention of mother-to-child transmission of HIV-1 through breast-feeding by treating infants prophylactically with lamivudine in Dar es Salaam, Tanzania: the Mitra Study. *J Acquir Immune Defic Syndr*. 2008;48(3):315-323. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18344879.

49. Taha T, Flynn P, Cababasay M, et al. Comparing maternal triple antiretrovirals (mART) and infant nevirapine (iNVP) prophylaxis for the prevention of mother to child transmission (MTCT) of HIV during breastfeeding (Bf). Presented at: 21st International AIDS Conference; 2016; Durban, SA.

50. Moodley J, Moodley D, Pillay K, et al. Pharmacokinetics and antiretroviral activity of lamivudine alone or when coadministered with zidovudine in human immunodeficiency virus type 1-infected pregnant women and their offspring. *J Infect Dis*. 1998;178(5):1327-1333. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9780252.

51. Moodley D, Moodley J, Coovadia H, et al. A multicenter randomized controlled trial of nevirapine versus a combination of zidovudine and lamivudine to reduce intrapartum and early postpartum mother-to-child transmission of human immunodeficiency virus type 1. *J Infect Dis*. 2003;187(5):725-735. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12599045.

52. Mandelbrot L, Landreau-Mascaro A, Rekacewicz C, et al. Lamivudine-zidovudine combination for prevention of maternal-infant transmission of HIV-1. *JAMA*. 2001;285(16):2083-2093. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11311097.

53. Lambert JS, Nogueira SA, Abreu T, et al. A pilot study to evaluate the safety and feasibility of the administration of AZT/3TC fixed dose combination to HIV infected pregnant women and their infants in Rio de Janeiro, Brazil. *Sex Transm Infect*. 2003;79(6):448-452. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14663118.

54. Gray G, Violari A, McIntyre J, et al. Antiviral activity of nucleoside analogues during short-course monotherapy or dual therapy: its role in preventing HIV infection in infants. *J Acquir Immune Defic Syndr*. 2006;42(2):169-176. Available at:

http://www.ncbi.nlm.nih.gov/pubmed/16639342.

55. Rongkavilit C, van Heeswijk RP, Limpongsanurak S, et al. Dose-escalating study of the safety and pharmacokinetics of nelfinavir in HIV-exposed neonates. *J Acquir Immune Defic Syndr*. 2002;29(5):455-463. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11981361.

56. Torres SM, Walker DM, Carter MM, et al. Mutagenicity of zidovudine, lamivudine, and abacavir following *in vitro* exposure of human lymphoblastoid cells or *in utero* exposure of CD-1 mice to single agents or drug combinations. *Environ Mol Mutagen*. 2007;48(3-4):224-238. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17358033.

57. Le Chenadec J, Mayaux MJ, Guihenneuc-Jouyaux C, Blanche S, Enquete Perinatale Francaise Study G. Perinatal antiretroviral treatment and hematopoiesis in HIV-uninfected infants. *AIDS*. 2003;17(14):2053-2061. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14502008.

58. Pacheco SE, McIntosh K, Lu M, et al. Effect of perinatal antiretroviral drug exposure on hematologic values in HIV-uninfected children: An analysis of the women and infants transmission study. *J Infect Dis*. 2006;194(8):1089-1097. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16991083.

59. Feiterna-Sperling C, Weizsaecker K, Buhrer C, et al. Hematologic effects of maternal antiretroviral therapy and transmission prophylaxis in HIV-1-exposed uninfected newborn infants. *J Acquir Immune Defic Syndr*. 2007;45(1):43-51. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17356471.

60. Hitti J, Frenkel LM, Stek AM, et al. Maternal toxicity with continuous nevirapine in pregnancy: results from PACTG 1022. *J Acquir Immune Defic Syndr*. 2004;36(3):772-776. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15213559.

61. Coovadia HM, Brown ER, Fowler MG, et al. Efficacy and safety of an extended nevirapine regimen in infant children of breastfeeding mothers with HIV-1 infection for prevention of postnatal HIV-1 transmission (HPTN 046): a randomised, double-blind, placebo-controlled trial. *Lancet*. 2012;379(9812):221-228. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22196945.

62. Clarke DF, Wong RJ, Wenning L, Stephenson DK, Mirochnick M. Raltegravir *In vitro* effect on bilirubin binding. *Pediatr Infect Dis J*. 2013. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23470680.

63. Raltegravir [package insert]. Food and Drug Administration. 2017. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/022145s036,203045s013,205786s004lbl.pdf.

64. Lopriore E, Rozendaal L, Gelinck LB, Bokenkamp R, Boelen CC, Walther FJ. Twins with cardiomyopathy and complete heart block born to an HIV-infected mother treated with HAART. *AIDS*. 2007;21(18):2564-2565. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18025905.

65. McArthur MA, Kalu SU, Foulks AR, Aly AM, Jain SK, Patel JA. Twin preterm neonates with cardiac toxicity related to lopinavir/ritonavir therapy. *Pediatr Infect Dis J*. 2009;28(12):1127-1129. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19820426.

66. Simon A, Warszawski J, Kariyawasam D, et al. Association of prenatal and postnatal exposure to lopinavir-ritonavir and adrenal dysfunction among uninfected infants of HIV-infected mothers. *JAMA*. 2011;306(1):70-78. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21730243.

67. Boxwell D, Cao K, Lewis L, Marcus K, Nikhar B. Neonatal toxicity of Kaletra oral solution: LPV, ethanol or prophylene glycol? Presented at: 18th Conference on Retroviruses and Opportunistic Infections. 2011. Boston, MA.

68. Food and Drug Administration. FDA drug safety communication: serious health problems seen in premature babies given kaletra (lopinavir/ritonavir) oral solution. 2011; http://www.fda.gov/Drugs/DrugSafety/ucm246002.htm.

69. Nagot N, Kankasa C, Tumwine JK, et al. Extended pre-exposure prophylaxis with lopinavir-ritonavir versus lamivudine to prevent HIV-1 transmission through breastfeeding up to 50 weeks in infants in Africa (ANRS 12174): a randomised controlled trial. *Lancet*. 2016;387(10018):566-573. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26603917.

Diagnosis of HIV Infection in Infants and Children (Last updated December 7, 2018; last reviewed December 7, 2018)

Panel's Recommendations

- Virologic assays (i.e., HIV RNA and HIV DNA nucleic acid tests [NATs]) that directly detect HIV must be used to diagnose HIV in infants and children aged <18 months with perinatal and postnatal HIV exposure; HIV antibody tests should not be used **(AII)**.
- HIV RNA or HIV DNA NATs are generally equally recommended **(AII)**.
- An assay that detects HIV non-B subtype viruses or Group O infections (e.g., an HIV RNA NAT or a dual-target total DNA/RNA test) is recommended for use in infants and children who were born to mothers with known or suspected non-B subtype virus or Group O infections **(AII)**.
- Virologic diagnostic testing is recommended for all infants with perinatal HIV exposure at the following ages:
  - 14 to 21 days **(AII)**
  - 1 to 2 months **(AII)**
  - 4 to 6 months **(AII)**
- For infants at higher risk of perinatal HIV transmission, additional virologic diagnostic testing is recommended at birth **(AII)** and at 2 to 4 weeks after cessation of antiretroviral prophylaxis **(BII)**.
- A positive virologic test should be confirmed as soon as possible by a repeat virologic test on a second specimen **(AII)**.
- Definitive exclusion of HIV infection in nonbreastfed infants is based on two or more negative virologic tests, with one obtained at age ≥1 month and one at age ≥4 months, or two negative HIV antibody tests from separate specimens obtained at age ≥6 months **(AII)**.
- Some experts confirm the absence of HIV at 12 to 18 months of age in children with prior negative virologic tests by performing an HIV antibody test to document loss of maternal HIV antibodies **(BIII)**.
- Since children aged 18 to 24 months with perinatal HIV exposure occasionally have residual maternal HIV antibodies, definitive exclusion or confirmation of HIV infection in children in this age group who are HIV antibody-positive should be based on an HIV NAT **(AII)**.
- Diagnostic testing in children with nonperinatal exposure only or children with perinatal exposure aged >24 months relies primarily on the use of HIV antibody (or antigen/antibody) tests; when acute HIV infection is suspected, additional testing with an HIV NAT may be necessary to diagnose HIV **(AII)**.

Note: The National Clinician Consultation Center provides consultations on issues related to the management of perinatal HIV infection (1-888-448-8765; 24 hours a day, 7 days a week).

Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*

Rating of Evidence: *I = One or more randomized trials in children† with clinical outcomes and/or validated endpoints; I* = One or more randomized trials in adults with clinical outcomes and/or validated laboratory endpoints with accompanying data in children† from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies in children† with long-term outcomes; II* = One or more well-designed, nonrandomized trials or observational studies in adults with long-term clinical outcomes with accompanying data in children† from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion*

† Studies that include children or children and adolescents, but not studies limited to post-pubertal adolescents

Diagnosis of HIV in Infants and Children

HIV can be definitively diagnosed through use of virologic assays in most non-breastfed infants with perinatal HIV exposure by age 1 month to 2 months, and in virtually all infants with HIV infection by age 4 months to 6 months. Antibody tests, including the newer antigen-antibody combination immunoassays (sometimes referred to as fourth- and fifth-generation tests), do not establish the presence of HIV in infants because of transplacental transfer of maternal HIV antibodies; therefore, a virologic test must be used.[1,2] Positive virologic tests (i.e., nucleic acid tests [NATs]—a class of tests that includes HIV RNA and HIV DNA polymerase chain reaction [PCR] assays, and related RNA qualitative or quantitative assays) indicate likely HIV infection. The first test result should be confirmed as soon as possible by a repeat virologic test on a second specimen, because false-positive results can occur with both RNA and DNA assays.[3] For additional information on HIV and RNA assays and diagnosis of Group M non-subtype B and Group O HIV-1

infections and HIV-2 infections, see the relevant sections below.

Antigen/antibody combination immunoassays which detect HIV-1/2 antibodies as well as HIV-1 p24 antigen are not recommended for diagnosis of HIV in infants. The sensitivity of the antigen component in the first months of life is less than that of an HIV NAT, and antibody tests should not be used for diagnosis in infants and children <18 months of age.[4-6] Children with perinatal HIV exposure who are aged 18 to 24 months occasionally have residual maternal HIV antibodies; definitive confirmation of HIV infection in children in this age group who are HIV antibody-positive should be based on a NAT (see Diagnostic Testing in Children with Perinatal HIV Exposure in Special Situations). Diagnosis in children aged >24 months relies primarily on HIV antibody and antigen/antibody tests (see Diagnostic Testing in Children with Nonperinatal HIV Exposure or Children with Perinatal Exposure Aged >24 Months).[1]

An infant who has a positive HIV antibody test but whose mother's HIV status is unknown (see Maternal HIV Testing and Identification of Perinatal HIV Exposure) should be assumed to have been exposed to HIV. The infant should undergo HIV diagnostic testing as described below[7] and receive antiretroviral (ARV) prophylaxis or empiric HIV therapy as soon as possible. For ARV management of HIV-exposed newborns and newborns with HIV infection (including those who do not yet have confirmed infection), see the Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV section.[8,9]

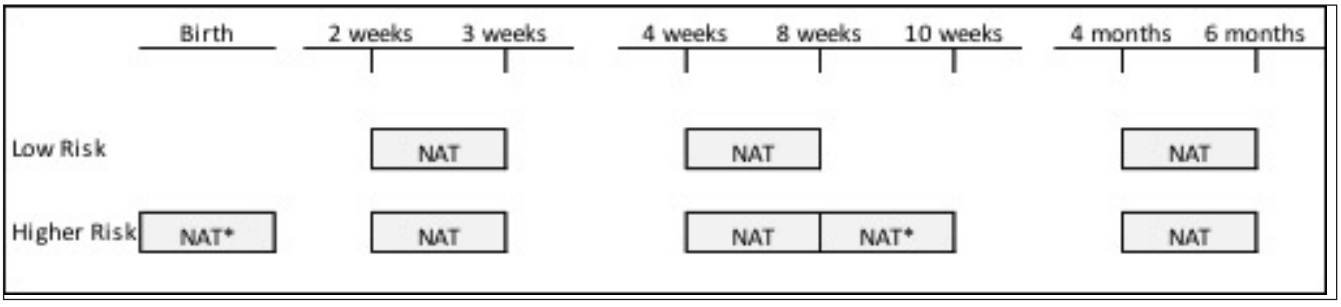
Timing of Diagnostic Testing in Infants with Perinatal HIV Exposure

Confirmation of HIV infection is based on the results of two positive virologic tests from separate blood samples in infants and children younger than 18 months. Figure 1 summarizes the timing of recommended virologic diagnostic testing for infants at low risk of transmission (based on maternal antiretroviral therapy [ART] and viral suppression) with additional time points to be considered for infants at higher risk and those on combination ARV prophylaxis regimens.

Figure 1. Recommended Virologic Testing Schedules for Infants Exposed to HIV by Perinatal HIV Transmission Risk

Low Risk: Infants born to mothers living with HIV who received standard ART during pregnancy and had sustained viral suppression (usually defined as confirmed HIV RNA level below the lower limits of detection of an ultrasensitive assay) and no concerns related to maternal adherence.

Higher Risk: Infants born to mothers living with HIV who did not receive prenatal care, did not receive antepartum or intrapartum ARVs, received intrapartum ARV drugs only, mothers who initiated ART late in pregnancy (during the late second or third trimester), received a diagnosis of acute HIV infection during pregnancy, or had detectable HIV viral loads close to the time of delivery, including those who received combination ARV drugs and did not have sustained viral suppression.



* For higher-risk infants, additional virologic diagnostic testing is recommended at birth and 2 to 4 weeks after cessation of ARV prophylaxis (i.e., at 8–10 weeks of life).

Key to Acronyms: ART = antiretroviral therapy; ARV = antiretroviral; NAT = nucleic acid test

HIV infection can be **presumptively** excluded in nonbreastfed infants with two or more negative virologic

tests (one at age ≥14 days and one at age ≥4 weeks) or one negative virologic test (i.e., negative NAT [RNA or DNA]) at age ≥8 weeks, or one negative HIV antibody test at age ≥6 months.[1,7]

Definitive exclusion of HIV infection in a nonbreastfed infant is based on two or more negative virologic tests (i.e., negative NATs [RNA or DNA]), one at age ≥1 month and one at age ≥4 months, or two negative HIV antibody tests from separate specimens obtained at age ≥6 months.

For both **presumptive** and **definitive** exclusion of HIV infection, a child must have no other laboratory evidence (i.e., no positive virologic test results or low CD4 T lymphocyte [CD4] cell count/percent) or clinical evidence of HIV infection and should not be breastfeeding. Many experts confirm the absence of HIV infection in infants with negative virologic tests by performing an antibody test at age 12 to 18 months to document seroreversion to HIV antibody-negative status.

Pneumocystis jirovecii pneumonia (PCP) prophylaxis is recommended for infants with **indeterminate** HIV infection status starting at age 4 to 6 weeks until they are determined to be **definitively** or **presumptively** without HIV.[10] Thus, PCP prophylaxis can be avoided or discontinued if HIV infection is presumptively excluded (see the Pediatric Opportunistic Infection Guidelines and Initial Postnatal Management of the Neonate Exposed to HIV).

The case definition for **indeterminate** HIV infection status is an HIV-exposed child aged <18 months who was born to a woman living with HIV and who does not meet the criteria for having HIV infection or for having not contracted HIV. This includes infants who do not meet the minimum requirement for **presumptively** uninfected (e.g., having one negative test result at 4 weeks of age).

Virologic Testing at Birth for Newborns at Higher Risk of Perinatal HIV Transmission

Virologic testing at birth should be considered for newborns who are at higher risk of perinatal HIV transmission,[11-16] such as infants born to women with HIV who:

- Did not receive prenatal care
- Did not receive antepartum or intrapartum ARV drugs
- Received intrapartum ARV drugs only
- Initiated ART late in pregnancy (late second or third trimester)
- Received a diagnosis of acute HIV infection during pregnancy
- Had detectable HIV viral load close to the time of delivery
- Received combination ARV drugs and did not have sustained viral suppression

Testing infants who have been exposed to HIV close to the time of birth only identifies 20% to 58% of infants with HIV infection. However, in one study that specifically evaluated infants born to mothers who had not received ARV drugs during pregnancy, and hence were at higher risk of *in utero* infection, birth testing identified 66.4% of infants with HIV infection.[17] Prompt diagnosis of infant HIV infection is critical to allow for discontinuing ARV prophylaxis and instituting early ART (see When to Initiate Therapy in Antiretroviral-Naive Children in the Pediatric ARV Guidelines). Blood samples from the umbilical cord should not be used for diagnostic evaluation because of the potential for contamination with maternal blood. Infants who have a positive virologic test result at or before age 48 hours are considered to have early (i.e., intrauterine) infection, whereas infants who have a negative virologic test result during the first week of life and subsequent positive tests are considered to have late (i.e., intrapartum) infection.[11,12,18]

Virologic Testing at Age 14 to 21 Days

The diagnostic sensitivity of virologic testing increases rapidly by age 2 weeks,[7] and early identification of infection permits discontinuation of neonatal ARV prophylaxis and initiation of ART (see the Infants Younger than 12 Months section and Table 5 in When to Initiate Therapy in Antiretroviral-Naive Children in the Pediatric ARV Guidelines).

Virologic Testing at Age 1 to 2 Months

Testing performed at age 1 month to 2 months is intended to maximize the likelihood of detecting HIV infection in infants.[19,20] Two studies found that the type of maternal or infant prophylaxis used did not affect the sensitivity of diagnostic HIV testing. However, the sensitivity of diagnostic HIV testing was lower during the period of infant ARV prophylaxis than during the subsequent testing interval at 3 months of age, when the infant was no longer receiving prophylaxis. Overall, in both studies, 89% of infants with HIV infection were identified by 4 to 6 weeks of age. Repeat testing was performed at ≥4 to 6 weeks of age during the period of neonatal ARV prophylaxis on infants who had negative test results in the first 7 days of life. This repeat testing determined that 76% of those infants had HIV infection in one study[19] and 68% of those infants had HIV infection in the second study.[17] In both studies, all infants who had negative test results in the first 7 days of life received an HIV diagnosis when the next diagnostic test was performed at 3 months of age.

For infants at higher risk of perinatal HIV transmission, the Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission suggests an additional virologic test 2 to 4 weeks after cessation of ARV prophylaxis (i.e., at 8–10 weeks of age), given the increased risk of infection and concern that ARV prophylaxis, particularly combination ARV prophylaxis, may reduce the sensitivity of testing during prophylaxis.[7,17,19] In these situations, many experts recommend one test at age 4 weeks to 6 weeks to allow prompt recognition of infants with HIV, with an additional test at 8 weeks of life (2 weeks after cessation of prophylaxis at 6 weeks of life) to capture additional cases. For infants at low risk of transmission, a single test obtained at 1 to 2 months of age may be timed to occur 2 to 4 weeks after cessation of ARV prophylaxis.

An infant with two negative virologic test results (one at age ≥14 days and the other at age ≥4 weeks) or one negative test result at age ≥8 weeks can be viewed as presumptively HIV uninfected, assuming the child has not had a positive prior virologic test result, laboratory evidence of CD4 immunosuppression, or clinical evidence indicative of HIV infection.

Virologic Testing at Age 4 to 6 Months

Infants with HIV exposure who have had negative virologic assays at age 14 to 21 days and at age 1 to 2 months, have no clinical evidence of HIV infection, and are not breastfed should be retested at age 4 to 6 months for definitive exclusion of HIV infection.

Antibody Testing at Age 6 Months and Older

Two or more negative results of HIV antibody tests that were performed in nonbreastfed infants at age ≥6 months can also be used to definitively exclude HIV infection in children with no clinical or virologic laboratory-documented evidence of HIV infection.[21,22]

Antibody Testing at Age 12 to 18 Months to Document Seroreversion

Some experts confirm the absence of HIV infection in infants and children with negative virologic test results (when there has not been prior confirmation of two negative antibody test results) by repeat serologic testing between 12 months and 18 months of age to confirm that maternal HIV antibodies transferred *in utero* have cleared.[1] In a study from 2012, the median age at seroreversion was 13.9 months.[23] Although the majority of infants who are without HIV will serorevert by age 15 months to 18 months, there are reports of late seroreversion after 18 months (see below). Factors that might influence the time to seroreversion include maternal disease stage and assay sensitivity.[23-26]

Diagnostic Testing in Children with Perinatal HIV Exposure in Special Situations

Late Seroreversion (≤24 Months of Age)

Nonbreastfed children with perinatal HIV exposure, no other HIV transmission risk, and no clinical or virologic laboratory evidence of HIV infection may have residual HIV antibodies up to age 24 months. These children are called late seroreverters.[23-26] In one study, 14% of children with HIV exposure who

were uninfected seroreverted after age 18 months.[23] These children may have had positive immunoassay results but supplemental antibody test results that indicated indeterminate HIV status (such as Western blot or immunofluorescence assay [IFA]). In such cases, repeat antibody testing at a later date confirmed seroreversion. Due to the possibility of residual HIV antibodies, virologic testing (i.e., with a NAT) is necessary to definitively exclude or confirm HIV infection in children with perinatal HIV exposure, who continue to have a positive HIV antibody (or antigen/antibody) test at age 18 months to 24 months.

Postnatal HIV Infection in Children with Perinatal HIV Exposure and Prior Negative Virologic Test Results for Whom There Are Additional HIV Transmission Risks

In contrast to late seroreverters, in rare situations postnatal HIV infections have been reported in children with HIV exposure who had prior negative HIV virologic tests. This occurs in children who acquire HIV through an additional risk factor after completion of testing (see Diagnostic Testing in Children with Nonperinatal HIV Exposure or Children with Perinatal Exposure Aged >24 Months). If an HIV antibody test is positive at age 18 to 24 months, repeated virologic testing will distinguish late-seroreverting (uninfected) children with residual antibodies from children with antibodies due to underlying HIV infection.

Suspicion of HIV-2 or Non-Subtype B HIV-1 Infections with False-Negative Virologic Test Results

Children with non-subtype B HIV-1 and children with HIV-2 may have false-negative virologic tests but persistent positive immunoassay results and indeterminate HIV-1 Western blot results.[27-29] The diagnostic approach in these situations is discussed below in the sections on Virologic Assays to Diagnose Group M Non-Subtype B and Group O HIV-1 Infections and on Virologic Assays to Diagnose HIV-2 Infections.

Diagnostic Testing in Children with Nonperinatal HIV Exposure or Children with Perinatal HIV Exposure Aged >24 Months

Breastfeeding

Women with HIV should be encouraged to avoid breastfeeding (see Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV). Monitoring of infants born to women with HIV who opt to breastfeed should include immediate HIV diagnostic testing with a NAT and virologic HIV testing at the standard time points (see Figure 1 above). Many experts then recommend testing every 3 months throughout breastfeeding, followed by monitoring at 4 weeks to 6 weeks, 3 months, and 6 months after cessation of breastfeeding. Clinicians caring for a woman with HIV who is considering breastfeeding should consult with an expert and, if necessary, the Perinatal HIV Hotline (888-448-8765). See Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV and Guidance for Counseling and Managing Women Living with HIV in the United States Who Desire to Breastfeed.[30-32]

Premastication

Receipt of solid food that has been premasticated or prewarmed (in the mouth) by a caregiver living with HIV is associated with risk of HIV transmission.[33-38] If this occurs in children with perinatal HIV exposure aged 24 months or younger with prior negative virologic tests, it will be necessary for such children to undergo virologic diagnostic testing, as they may have residual maternal HIV antibodies (see Diagnostic Testing in Children with Perinatal HIV Exposure in Special Situations).

Additional Routes of HIV Transmission

Additional routes of HIV transmission in children include sexual abuse, receipt of contaminated blood products, and needlestick with contaminated needles. In such cases, maternal HIV status may be negative. If the maternal HIV status is unknown, age-appropriate testing should be performed as described for children with perinatal HIV exposure. Acquisition of HIV in older children is possible through accidental

needlestick injuries, sexual transmission, or injection drug use. Medical procedures performed in settings with inadequate infection control practices may pose a potential risk; although tattooing or body piercing presents a potential risk of HIV transmission, no cases of HIV transmission from these activities have been documented.[39]

Diagnostic Testing

Diagnosis of HIV-1 infection in infants and children with nonperinatal HIV exposure only or children with perinatal HIV exposure aged >24 months relies primarily on HIV antibody and antigen/antibody tests.[1,40] Food and Drug Administration (FDA)-approved diagnostic tests include:

- Antigen/antibody combination immunoassays, which detect HIV-1/2 antibodies as well as HIV-1 p24 antigen.
- Recommended for initial testing to screen for established infection with HIV-1 or HIV-2 and for acute HIV-1 infection. However, p24 antigen from HIV-1 non-B strains, HIV-1 non-M strains, and HIV-2 strains may not be detected.[41]
- HIV-1/2 immunoassays (third-generation antibody tests) are alternatives for initial testing.
- HIV-1/HIV-2 antibody differentiation immunoassay, which differentiates HIV-1 antibodies from HIV-2 antibodies is recommended for supplemental testing.
- HIV-1 NAT may be necessary as an additional test to diagnose acute HIV infection.
- HIV-1 Western blot and HIV-1 indirect IFAs (first-generation tests) are alternatives for supplemental testing, but will not detect acute HIV infection.

Diagnosis of HIV-2 in children with nonperinatal exposure or children with perinatal exposure aged >24 months relies on the Centers for Disease Control and Prevention (CDC)/Association of Public Health Laboratories 2014 laboratory testing guidelines, which recommend using an HIV-1/HIV-2 antibody differentiation immunoassay that differentiates HIV-1 antibodies from HIV-2 antibodies for supplemental testing. This is not subject to the same testing ambiguity as when the HIV-1 Western blot is used as a supplemental test; >60% of individuals with HIV-2 are misclassified as having HIV-1 by the HIV-1 Western blot.[1,42] All HIV-2 cases should be reported to the HIV surveillance program of the state or local health department; additional HIV-2 DNA PCR testing can be arranged by a local public health laboratory or the CDC if an HIV-1/HIV-2 antibody differentiation immunoassay is inconclusive. HIV-2 DNA PCR testing may be necessary for definitive diagnosis, though this assay is not commercially available.[43,44]

Virologic Assays to Diagnose HIV in Infants Younger Than 18 Months with Perinatal HIV-1 Exposure

HIV RNA Assays

HIV quantitative RNA assays detect extracellular viral RNA in plasma. Their specificity has been shown to be 100% at birth and at 1, 3, and 6 months of age and is comparable to HIV DNA PCR.[19] Results of quantitative assays that show HIV RNA levels <5,000 copies/mL may not be reproducible, and the test should be repeated before these results are interpreted as documentation of HIV infection in an infant.[45,46] Testing at birth will detect infants who acquire HIV *in utero* and not those who acquire HIV from exposure during or immediately prior to delivery (i.e., in the intrapartum period). Studies have shown that HIV RNA assays identify 25% to 58% of infants with HIV infection from birth through the first week of life, 89% at age 1 month, and 90% to 100% by age 2 months to 3 months (similar to results of HIV DNA PCR for early diagnosis of HIV).[3,7,19,47]

HIV RNA undergoes reverse transcription to double-stranded DNA, which persists intracellularly within an infected cell. HIV DNA PCR assays detect intracellular DNA, and an individual receiving ART will continue to have a positive result even with a suppressed viral load. In contrast, HIV RNA assays are affected by

maternal antenatal treatment or infant combination ARV prophylaxis.[48] In one study, the sensitivity of HIV RNA assays were not associated with the type of maternal ART or infant ARV prophylaxis, but HIV RNA levels at 1 month were significantly lower in infants with HIV infection receiving multidrug prophylaxis (n = 9) compared to levels among infants receiving single-drug zidovudine prophylaxis (n = 47) (median HIV RNA 2.5 $\log_{10}$ copies/mL vs. 5.4 log copies/mL, respectively). In contrast, the median HIV RNA levels were high (median HIV RNA 5.6 log copies/mL) by age 3 months in both groups after stopping prophylaxis.[19] Between 2010 and 2016, a significant decline in baseline viremia was noted in South Africa's Early Infant Diagnosis program, with loss of detectability documented among some infants with HIV. This decline may have reflected the administration of various prophylactic regimens during those years, including Option A, Option B, and Option B+, as recommended by the World Health Organization.[49] Further studies are necessary to evaluate the sensitivity of HIV RNA assays in infants during receipt of three-drug ARV prophylaxis or empiric therapy.

An HIV quantitative RNA assay can be used as a supplemental test for infants who have an initial positive HIV DNA PCR test result. In addition to providing virologic confirmation of infection status, the expense of repeat HIV DNA PCR testing is spared, and an HIV RNA measurement is available to assess baseline viral load. This viral load can also be used to determine HIV genotype and guide initial ARV treatment in an infant with HIV. HIV RNA assays may be more sensitive than HIV DNA PCR for detecting non-subtype B HIV (see Virologic Assays to Diagnose Group M Non-Subtype B and Group O HIV-1 Infections).

The HIV qualitative RNA assay (APTIMA HIV-1 RNA Qualitative Assay) is an alternative diagnostic test that can be used for infant testing. It is the only qualitative RNA test that is approved by the FDA.[18,50-53]

HIV DNA PCR and Related Assays

HIV DNA PCR is a sensitive technique used to detect intracellular HIV viral DNA in peripheral blood mononuclear cells. The specificity of the HIV DNA PCR is 99.8% at birth and 100% at ages 1 month, 3 months, and 6 months. Studies have shown that HIV DNA PCR assays identify 20% to 55% of infants with HIV infection from birth through the first week of life, with the same caveat as for RNA testing—testing at birth only detects *in utero* HIV infection and not infection in those infants who acquire HIV during the intrapartum period. This percentage increases to >90% by 2 weeks to 4 weeks of age and to 100% at ages 3 months and 6 months.[7,18,19,47]

Two studies provided data on diagnostic testing at different time points in infants with confirmed HIV infection, including those who had negative test results at birth (i.e., infants considered to have acquired HIV during the intrapartum period). A randomized, international study of 1,684 infants evaluated the efficacy of three different regimens of neonatal prophylaxis consisting of 6 weeks of zidovudine either alone or with two or three other ARV drugs; none of the infants' mothers had received prenatal ARV drugs. Infant testing was performed at birth, 10 to 14 days, 4 to 6 weeks, and 3 and 6 months (no testing was performed between 6 weeks and 3 months). Ninety-three of 140 infants (66.4%) with HIV infection were identified at birth, and by 4 to 6 weeks of age, 89% of the 140 infants were identified. Of the 47 infants with HIV infection who had negative DNA PCR test results at birth, 68% were identified during the period of neonatal ARV prophylaxis at 4 to 6 weeks; by 3 months, all 47 infants were identified.[17] Data from Thailand showed that, in nonbreastfed infants, receiving a prophylaxis regimen of zidovudine/lamivudine/nevirapine for 6 weeks was associated with a delay in first HIV DNA detection. In this cohort, up to 20% of HIV-exposed infants had their first positive DNA PCR test after 2 months of age, prompting the authors to recommend infant testing at 4 months of age, after neonatal prophylaxis had been discontinued for at least 4 to 6 weeks.[54]

A recent study from Cape Town evaluated the sensitivity of HIV DNA assays within 8 days of life, during and after initiation of infant ART in infants with HIV. The infants had been exposed to a combination of maternal ART *in utero* and early ART for prophylaxis and treatment. The study noted that one infant subsequently had undetectable HIV DNA after 6 days on treatment, another was undetectable after 3 months, and a third was undetectable after 4 months. In seven infants who had virologic suppression (defined as a

continuous downward trend in plasma HIV RNA, with <100 copies/mL after 6 months) total HIV DNA continued to decay over 12 months. The authors suggested that rapid decline of HIV-1 RNA and DNA may complicate definitive diagnosis.[55] A dataset of 38,043 infants from the Western Cape province of South Africa who were tested at a median age of 45 days of life in the setting of intensified vertical HIV transmission prevention regimens, particularly with the Option B+ program, showed that indeterminate PCRs decreased in frequency. These findings should be regarded with a high index of suspicion since many patients had positive results representative of true HIV infections on subsequent samples. These findings point out the need for additional virologic testing for definitive diagnosis.[56] Another group of South African investigators reported similar conclusions in a study of a cohort of 5,743 HIV-exposed neonates from Johannesburg.[57]

Although the AMPLICOR® HIV-1 DNA test has been widely used for diagnosis of infants born to mothers with HIV-1 infection since it was introduced in 1992, it is no longer commercially available in the United States. The sensitivity and specificity of noncommercial HIV-1 DNA tests (using individual laboratory reagents) may differ from the sensitivity and specificity of the FDA-approved commercial test.

The COBAS® AmpliPrep/COBAS® TaqMan® HIV-1 qualitative test (which detects both HIV-1 RNA and proviral DNA in plasma, whole blood, and dried blood spots) may be used for infant diagnosis, but it is not approved by the FDA.[57-59]

Other Issues

Virologic Assays to Diagnose Group M Non-Subtype B and Group O HIV-1 Infections

Although HIV-1 Group M subtype B is the predominant viral subtype found in the United States, multiple subtypes and recombinant forms are found in the United States with a widespread geographic distribution.[60] Recent data from the CDC National HIV Surveillance System showed that the number of foreign-born children with HIV has exceeded the number of U.S.-born children with HIV since 2011, with 65.5% of foreign-born children with HIV being born in sub-Saharan Africa and 14.3% in Eastern Europe.[61] In an evaluation of infants that received a perinatal HIV infection diagnosis in New York state in 2001 and 2002, 16.7% of infants had acquired a non-subtype B strain of HIV, compared with 4.4% of infants born in 1998 and 1999.[62] Among a group of 40 children attending a pediatric HIV clinic in Rhode Island between 1991 and 2012, 14 (35%) acquired HIV with non-B HIV-1 subtypes. All 14 children with non-B subtypes were either born outside the United States or their parents were of foreign origin.[63] In an analysis of 1,277 unique sequences collected in Rhode Island from 2004 to 2011, 8.3% were non-B subtypes (including recombinant forms). Twenty-two percent of non-B subtypes formed transmission clusters, including individuals with perinatally acquired infection.[64] In an analysis of 3,895 HIV-1 sequences collected between July 2011 and June 2012 in the United States, 5.3% were determined to be non-B subtypes (including recombinant forms). Among individual states, the percentage of non-B subtypes ranged from 0% (in 12 states) to 28.6% in South Dakota, with seven states having percentages that were greater than 10%.[65]

Evolving immigration patterns may be contributing to local and regional increases in HIV-1 subtype diversity. Non-subtype B viruses predominate in other parts of the world, such as subtype C in regions of Africa and India and subtype CRF01 in much of Southeast Asia. Group O HIV strains are seen in West-Central Africa.[66] Non-subtype B and Group O strains may also be seen in countries with links to these geographical regions.[67-71] Geographical distribution of HIV groups is available at the HIV Sequence Database.

Currently available real-time HIV RNA PCR assays and the qualitative diagnostic RNA assay have improved sensitivity for detection of non-subtype B HIV infection and the less common Group O strains, compared to older RNA assays that did not detect or appropriately amplify many non-B subtypes and Group O HIV[72-77] (see Clinical and Laboratory Monitoring of Pediatric HIV Infection). Similarly, the COBAS® AmpliPrep/COBAS® TaqMan® HIV-1 qualitative test (a dual-target DNA/RNA test) can identify non-subtype B and Group O infections.[58,59]

Thus, a real-time PCR assay, qualitative RNA assay or a dual-target total DNA/RNA test should be used for infant testing instead of a DNA PCR assay when evaluating an infant born to a mother whose HIV infection is linked to an area endemic for non-subtype B HIV or Group O strains, such as Africa or Southeast Asia. Another indication is when initial testing is negative using a HIV DNA PCR test and non-subtype B or Group O perinatal exposure is suspected. Two negative HIV antibody tests obtained at age ≥6 months provide further evidence to definitively rule out HIV infection. Clinicians should consult with an expert in pediatric HIV infection; state or local public health departments or the CDC may be able to assist in obtaining referrals for diagnostic testing.

Virologic Assays to Diagnose HIV-2 Infections

HIV-2 infection is endemic in Angola; Mozambique; West African countries, including Cape Verde, Ivory Coast, the Gambia, Guinea-Bissau, Mali, Mauritania, Nigeria, Sierra Leone, Benin, Burkina Faso, Ghana, Guinea, Liberia, Niger, Nigeria, Sao Tome, Senegal, and Togo; and parts of India.[78-80] It also occurs in countries such as France and Portugal, which have large numbers of immigrants from these regions.[81,82] HIV-1 and HIV-2 coinfections may also occur, but these are rare outside areas where HIV-2 is endemic. HIV-2 is rare in the United States. Although accurately diagnosing HIV-2 can be difficult, it is clinically important because HIV-2 strains are resistant to several ARV drugs developed to suppress HIV-1.[83-85]

Infant testing with HIV-2-specific DNA PCR tests should be performed at time points similar to those used for HIV-1 testing when evaluating an infant born to a mother with a known or suspected HIV-2 infection. A mother should be suspected of having HIV-2 if her infection is linked to an area endemic for HIV-2 infection or if her HIV test results are suggestive of HIV-2 infection (i.e., the mother has a positive initial HIV 1/2 immunoassay test result, repeatedly indeterminate results on HIV-1 Western blot, and HIV-1 RNA viral loads that are at or below the limit of detection; however, the current recommendation to use an HIV-1/HIV-2 antibody differentiation immunoassay for supplemental testing is not subject to the same testing ambiguity as when the HIV-1 Western blot is used as a supplemental test).[1,86] HIV-2 DNA PCR testing can be arranged by the HIV surveillance program of the state or local health department through their public health laboratory or the CDC, because this assay is not commercially available.[43,44] Clinicians should consult with an expert in pediatric HIV infection when caring for infants with suspected or known exposure to HIV-2.[78,87]

References

1. Centers for Disease Control and Prevention and Association of Public Health Laboratories. Laboratory testing for the diagnosis of HIV infection: updated recommendations. 2014. Available at: http://dx.doi.org/10.15620/cdc.23447.
2. Donovan M, Palumbo P. Diagnosis of HIV: challenges and strategies for HIV prevention and detection among pregnant women and their infants. *Clin Perinatol*. 2010;37(4):751-763, viii. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21078448.
3. Read JS, Committee on Pediatric AIDS, American Academy of Pediatrics. Diagnosis of HIV-1 infection in children younger than 18 months in the United States. *Pediatrics.* 2007;120(6):e1547-1562. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18055670.
4. Tamhane M, Gautney B, Shiu C, et al. Analysis of the optimal cut-point for HIV-p24 antigen testing to diagnose HIV infection in HIV-exposed children from resource-constrained settings. *J Clin Virol*. 2011;50(4):338-341. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21330193.
5. Wessman MJ, Theilgaard Z, Katzenstein TL. Determination of HIV status of infants born to HIV-infected mothers: a review of the diagnostic methods with special focus on the applicability of p24 antigen testing in developing countries. *Scand Journal of Infect Dis*. 2012;44(3):209-215. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22074445.
6. Bhowan K, Sherman GG. Performance of the first fourth-generation rapid human immunodeficiency virus test in children. *Pediatr Infect Dis J*. 2013;32(5):486-488. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23190776.
7. Havens PL, Mofenson LM, American Academy of Pediatrics Committee on Pediatric AIDS. Evaluation and management of the infant exposed to HIV-1 in the United States. *Pediatrics.* 2009;123(1):175-187. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19117880.

8. Ferguson W, Goode M, Walsh A, Gavin P, Butler K. Evaluation of 4 weeks' neonatal antiretroviral prophylaxis as a component of a prevention of mother-to-child transmission program in a resource-rich setting. *Pediatr Infect Dis J*. 2011;30(5):408-412. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21266939.

9. Sollai S, Noguera-Julian A, Galli L, et al. Strategies for the prevention of mother to child transmission in Western countries: an update. *Pediatr Infect Dis J*. 2015;34(5 Suppl 1):S14-30. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25894973.

10. Panel on Opportunistic Infections in HIV-Exposed and HIV-Infected Children. Guidelines for the prevention and treatment of opportunistic infections in HIV-exposed and HIV-infected children. 2018. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/oi_guidelines_Pediatrics.pdf.

11. Lilian RR, Kalk E, Technau KG, Sherman GG. Birth diagnosis of HIV infection on infants to reduce infant mortality and monitor for elimination of mother-to-child transmission. *Pediatr Infect Dis J*. 2013. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23574775.

12. Jourdain G, Mary JY, Coeur SL, et al. Risk factors for *in utero* or intrapartum mother-to-child transmission of human immunodeficiency virus type 1 in Thailand. *J Infect Dis*. 2007;196(11):1629-1636. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18008246.

13. Tubiana R, Le Chenadec J, Rouzioux C, et al. Factors associated with mother-to-child transmission of HIV-1 despite a maternal viral load <500 copies/mL at delivery: a case-control study nested in the French perinatal cohort (EPF-ANRS CO1). *Clin Infect Dis*. 2010;50(4):585-596. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20070234.

14. Katz IT, Shapiro DE, Tuomala R. Factors associated with lack of viral suppression at delivery. *Ann Intern Med*. 2015;162(12):874-875. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26075762.

15. Momplaisir FM, Brady KA, Fekete T, Thompson DR, Diez Roux A, Yehia BR. Time of HIV diagnosis and engagement in prenatal care impact virologic outcomes of pregnant women with HIV. *PLoS One*. 2015;10(7):e0132262. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26132142.

16. Mandelbrot L, Tubiana R, Le Chenadec J, et al. No perinatal HIV-1 transmission from women with effective antiretroviral therapy starting before conception. *Clin Infect Dis*. 2015;61(11):1715-1725. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26197844.

17. Nielsen-Saines K, Watts DH, Veloso VG, et al. Three postpartum antiretroviral regimens to prevent intrapartum HIV infection. *N Engl J Med*. 2012;366(25):2368-2379. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22716975.

18. Lilian RR, Kalk E, Bhowan K, et al. Early diagnosis of *in utero* and intrapartum HIV infection in infants prior to 6 weeks of age. *J Clin Microbiol*. 2012;50(7):2373-2377. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22518871.

19. Burgard M, Blanche S, Jasseron C, et al. Performance of HIV-1 DNA or HIV-1 RNA tests for early diagnosis of perinatal HIV-1 infection during anti-retroviral prophylaxis. *J Pediatr*. 2012;160(1):60-66 e61. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21868029.

20. Lilian RR, Johnson LF, Moolla H, Sherman GG. A mathematical model evaluating the timing of early diagnostic testing in HIV-exposed infants in South Africa. *J Acquir Immune Defic Syndr*. 2014;67(3):341-348. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25118910.

21. Kuhn L, Schramm DB, Shiau S, et al. Young age at start of antiretroviral therapy and negative HIV antibody results in HIV-infected children when suppressed. *AIDS*. 2015;29(9):1053-1060. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25870988.

22. Payne H, Mkhize N, Otwombe K, et al. Reactivity of routine HIV antibody tests in children who initiated antiretroviral therapy in early infancy as part of the children with HIV early antiretroviral therapy (CHER) trial: a retrospective analysis. *Lancet Infect Dis*. 2015;15(7):803-809. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26043884.

23. Gutierrez M, Ludwig DA, Khan SS, et al. Has highly active antiretroviral therapy increased the time to seroreversion in HIV exposed but uninfected children? *Clin Infect Dis*. 2012;55(9):1255-1261. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22851494.

24. Gulia J, Kumwenda N, Li Q, Taha TE. HIV seroreversion time in HIV-1-uninfected children born to HIV-1-infected mothers in Malawi. *J Acquir Immune Defic Syndr*. 2007;46(3):332-337. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17786126.

25. Alcantara KC, Pereira GA, Albuquerque M, Stefani MM. Seroreversion in children born to HIV-positive and AIDS mothers from Central West Brazil. *Trans R Soc Trop Med Hyg*. 2009;103(6):620-626. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19339030.

26. Sohn AH, Thanh TC, Thinh le Q, et al. Failure of human immunodeficiency virus enzyme immunoassay to rule out infection among polymerase chain reaction-negative Vietnamese infants at 12 months of age. *Pediatr Infect Dis J*. 2009;28(4):273-276. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19289981.

27. Kline NE, Schwarzwald H, Kline MW. False negative DNA polymerase chain reaction in an infant with subtype C human immunodeficiency virus 1 infection. *Pediatr Infect Dis J*. 2002;21(9):885-886. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12380591.

28. Zaman MM, Recco RA, Haag R. Infection with non-B subtype HIV type 1 complicates management of established infection in adult patients and diagnosis of infection in newborn infants. *Clin Infect Dis*. 2002;34(3):417-418. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11774090.

29. Obaro SK, Losikoff P, Harwell J, Pugatch D. Failure of serial human immunodeficiency virus type 1 DNA polymerase chain reactions to identify human immunodeficiency virus type 1 clade A/G. *Pediatr Infect Dis J*. 2005;24(2):183-184. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15702052.

30. Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission. Recommendations for the use of antiretroviral drugs in pregnant women with HIV infection and interventions to reduce perinatal HIV transmission in the United States. 2018. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/PerinatalGL.pdf.

31. Committee on Pediatric AIDS. Infant feeding and transmission of human immunodeficiency virus in the United States. *Pediatrics*. 2013;131(2):391-396. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23359577.

32. King CC, Kourtis AP, Persaud D, et al. Delayed HIV detection among infants exposed to postnatal antiretroviral prophylaxis during breastfeeding. *AIDS*. 2015;29(15):1953-1961. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26153671.

33. Centers for Disease Control and Prevention. Premastication of food by caregivers of HIV-exposed children—nine U.S. sites, 2009-2010. *MMWR Morb Mortal Wkly Rep*. 2011;60(9):273-275. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21389930.

34. Gaur AH, Freimanis-Hance L, Dominguez K, et al. Knowledge and practice of prechewing/prewarming food by HIV-infected women. *Pediatrics*. 2011;127(5):e1206-1211. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21482608.

35. Hafeez S, Salami O, Alvarado M, Maldonado M, Purswani M, Hagmann S. Infant feeding practice of premastication: an anonymous survey among human immunodeficiency virus-infected mothers. *Arch Pediatr Adolesc Med*. 2011;165(1):92-93. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21199989.

36. Maritz ER, Kidd M, Cotton MF. Premasticating food for weaning African infants: a possible vehicle for transmission of HIV. *Pediatrics*. 2011;128(3):e579-590. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21873699.

37. Ivy W, 3rd, Dominguez KL, Rakhmanina NY, et al. Premastication as a route of pediatric HIV transmission: case-control and cross-sectional investigations. *J Acquir Immune Defic Syndr*. 2012;59(2):207-212. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22027873.

38. Gaur AH, Cohen RA, Read JS, et al. Prechewing and prewarming food for HIV-exposed children: a prospective cohort experience from Latin America. *AIDS Patient Care STDS*. 2013;27(3):142-145. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23477456.

39. Centers for Disease Control and Prevention. HIV transmission. 2018. Available at: https://www.cdc.gov/hiv/basics/transmission.html.

40. Alexander TS. Human immunodeficiency virus diagnostic testing: 30 years of evolution. *Clin Vaccine Immunol*. 2016;23(4):249-253. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26936099.

41. Ly TD, Plantier JC, Leballais L, Gonzalo S, Lemee V, Laperche S. The variable sensitivity of HIV Ag/Ab combination assays in the detection of p24Ag according to genotype could compromise the diagnosis of early HIV infection. *J Clin Virol*. 2012;55(2):121-127. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22795598.

42. Centers for Disease Control and Prevention. HIV-2 infection surveillance—United States, 1987–2009. *MMWR Morb Mortal Wkly Rep*. 2011;60(29):985-988. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21796096.

43. Shanmugam V, Switzer WM, Nkengasong JN, et al. Lower HIV-2 plasma viral loads may explain differences between the natural histories of HIV-1 and HIV-2 infections. *J Acquir Immune Defic Syndr*. 2000;24(3):257-263. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10969350.

44. Damond F, Benard A, Balotta C, et al. An international collaboration to standardize HIV-2 viral load assays: results from the 2009 ACHI(E)V(2E) quality control study. *J Clin Microbiol*. 2011;49(10):3491-3497. Available at: http://

www.ncbi.nlm.nih.gov/pubmed/21813718.

45. Lilian RR, Bhowan K, Sherman GG. Early diagnosis of human immunodeficiency virus-1 infection in infants with the NucliSens EasyQ assay on dried blood spots. *J Clin Virol*: the official publication of the Pan American Society for Clinical Virology. 2010;48(1):40-43. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20211580.

46. Patel JA, Anderson EJ, Dong J. False positive ultrasensitive HIV bDNA viral load results in diagnosis of perinatal HIV-infection in the era of low transmission. *Laboratory Medicine*. 2009;40(10):611-614. Available at: http://labmed.oxfordjournals.org/content/40/10/611.

47. American Academy of Pediatrics Committee on Pediatric AIDS. HIV testing and prophylaxis to prevent mother-to-child transmission in the United States. *Pediatrics*. 2008;122(5):1127-1134. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18977995.

48. Saitoh A, Hsia K, Fenton T, et al. Persistence of human immunodeficiency virus (HIV) type 1 DNA in peripheral blood despite prolonged suppression of plasma HIV-1 RNA in children. *J Infect Dis*. 2002;185(10):1409-1416. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11992275.

49. Mazanderani AH, Moyo F, Kufa T, Sherman GG. Brief report: declining baseline viremia and escalating discordant HIV-1 confirmatory results within South Africa's early infant diagnosis program, 2010-2016. *J Acquir Immune Defic Syndr*. 2018;77(2):212-216. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29084045.

50. Food and Drug Administration. APTIMA HIV-1 RNA qualitative assay. 2006. Available at: http://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/BloodDonorScreening/InfectiousDisease/ucm149922.htm.

51. Pierce VM, Neide B, Hodinka RL. Evaluation of the gen-probe aptima HIV-1 RNA qualitative assay as an alternative to Western blot analysis for confirmation of HIV infection. *J Clin Microbiol*. 2011;49(4):1642-1645. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21346052.

52. Fiscus SA, McMillion T, Nelson JA, Miller WC. Validation of the gen-probe aptima qualitative HIV-1 RNA assay for diagnosis of human immunodeficiency virus infection in infants. *J Clin Microbiol*. 2013;51(12):4137-4140. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24088864.

53. Nelson JA, Hawkins JT, Schanz M, et al. Comparison of the gen-probe aptima HIV-1 and abbott HIV-1 qualitative assays with the roche amplicor HIV-1 DNA assay for early infant diagnosis using dried blood spots. *J Clin Virol*. 2014;60(4):418-421. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24929752.

54. Puthankit T, Rojanwiwat T. Delayed HIV DNA PCR detection among infants received combination ART prophylaxis. Presented at: Conference on Retroviruses and Opportunistic Infections. 2017. Seattle, WA.

55. Veldsman KA, Maritz J, Isaacs S, et al. Rapid decline of HIV-1 DNA and RNA in infants starting very early antiretroviral therapy may pose a diagnostic challenge. *AIDS*. 2018;32(5):629-634. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29334551.

56. Maritz J, Maharaj JN, Cotton MF, Preiser W. Interpretation of indeterminate HIV-1 PCR results are influenced by changing vertical transmission prevention regimens. *J Clin Virol*. 2017;95:86-89. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28898704.

57. Technau KG, Mazanderani AH, Kuhn L, et al. Prevalence and outcomes of HIV-1 diagnostic challenges during universal birth testing - an urban South African observational cohort. *J Int AIDS Soc*. 2017;20(Suppl 6):21761. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28872276.

58. Templer SP, Seiverth B, Baum P, Stevens W, Seguin-Devaux C, Carmona S. Improved sensitivity of a dual-target HIV-1 qualitative test for plasma and dried blood spots. *J Clin Microbiol*. 2016;54(7):1877-1882. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27194686.

59. Mossoro-Kpinde CD, Jenabian MA, Gody JC, et al. Evaluation of the upgraded version 2.0 of the Roche COBAS((R)) AmpliPrep/COBAS((R)) TaqMan HIV-1 qualitative assay in Central African Children. *Open AIDS J*. 2016;10:158-163. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27857825.

60. Pyne MT, Hackett J, Jr., Holzmayer V, Hillyard DR. Large-scale analysis of the prevalence and geographic distribution of HIV-1 non-B variants in the United States. *J Clin Microbiol*. 2013;51(8):2662-2669. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23761148.

61. Nesheim SR, Linley L, Gray KM, et al. Country of Birth of Children With Diagnosed HIV Infection in the United States, 2008-2014. *J Acquir Immune Defic Syndr*. 2018;77(1):23-30. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29040167.

62. Karchava M, Pulver W, Smith L, et al. Prevalence of drug-resistance mutations and non-subtype B strains among HIV-infected infants from New York State. *J Acquir Immune Defic Syndr*. 2006;42(5):614-619. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16868498.

63. Rogo T, DeLong AK, Chan P, Kantor R. Antiretroviral treatment failure, drug resistance, and subtype diversity in the only pediatric HIV clinic in Rhode Island. *Clin Infect Dis*. 2015;60(9):1426-1435. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25637585.

64. Chan PA, Reitsma MB, DeLong A, et al. Phylogenetic and geospatial evaluation of HIV-1 subtype diversity at the largest HIV center in Rhode Island. *Infect Genet Evol*. 2014;28:358-366. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24721515.

65. Germer JJ, Wu P, Soderberg JD, Mandrekar JN, Yao JD. HIV-1 subtype diversity among clinical specimens submitted for routine antiviral drug resistance testing in the United States. *Diagn Microbiol Infect Dis*. 2015;83(3):257-260. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26302855.

66. Bush S, Tebit DM. HIV-1 group O origin, evolution, pathogenesis, and treatment: unraveling the complexity of an outlier 25 years later. *AIDS Rev*. 2015;17(3):147-158. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26450803.

67. Auwanit W, Isarangkura-Na-Ayuthaya P, Kasornpikul D, Ikuta K, Sawanpanyalert P, Kameoka M. Detection of drug resistance-associated and background mutations in human immunodeficiency virus type 1 CRF01_AE protease and reverse transcriptase derived from drug treatment-naive patients residing in central Thailand. *AIDS Res Hum Retroviruses*. 2009;25(6):625-631. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19500016.

68. Deshpande A, Jauvin V, Pinson P, Jeannot AC, Fleury HJ. Phylogenetic analysis of HIV-1 reverse transcriptase sequences from 382 patients recruited in JJ Hospital of Mumbai, India, between 2002 and 2008. *AIDS Res Hum Retroviruses*. 2009;25(6):633-635. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19534630.

69. Chaix ML, Seng R, Frange P, et al. Increasing HIV-1 non-B subtype primary infections in patients in France and effect of HIV subtypes on virological and immunological responses to combined antiretroviral therapy. *Clin Infect Dis*. 2013;56(6):880-887. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23223603.

70. Hemelaar J, Gouws E, Ghys PD, Osmanov S, WHO-UNAIDS Network for HIV Isolation Characterisation. Global trends in molecular epidemiology of HIV-1 during 2000–2007. *AIDS*. 2011;25(5):679-689. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21297424.

71. Dauwe K, Mortier V, Schauvliege M, et al. Characteristics and spread to the native population of HIV-1 non-B subtypes in two European countries with high migration rate. *BMC Infect Dis*. 2015;15:524. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26572861.

72. Church D, Gregson D, Lloyd T, et al. Comparison of the RealTime HIV-1, COBAS TaqMan 48 v1.0, Easy Q v1.2, and Versant v3.0 assays for determination of HIV-1 viral loads in a cohort of Canadian patients with diverse HIV subtype infections. *J Clin Microbiol*. 2011;49(1):118-124. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21084515.

73. Cobb BR, Vaks JE, Do T, Vilchez RA. Evolution in the sensitivity of quantitative HIV-1 viral load tests. *J Clin Virol*. 2011;52 Suppl 1:S77-82. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22036041.

74. Katsoulidou A, Rokka C, Issaris C, et al. Comparative evaluation of the performance of the abbott realtime HIV-1 assay for measurement of HIV-1 plasma viral load on genetically diverse samples from Greece. *Virol J*. 2011;8:10. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21219667.

75. Gueudin M, Leoz M, Lemee V, et al. A new real-time quantitative PCR for diagnosis and monitoring of HIV-1 group O infection. *J Clin Microbiol*. 2012;50(3):831-836. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22170927.

76. Xu S, Song A, Nie J, et al. Comparison between the automated Roche Cobas AmpliPrep/Cobas TaqMan HIV-1 test version 2.0 assay and its version 1 and Nuclisens HIV-1 EasyQ version 2.0 assays when measuring diverse HIV-1 genotypes in China. *J Clin Virol*. 2012;53(1):33-37. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22051503.

77. Muenchhoff M, Madurai S, Hempenstall AJ, et al. Evaluation of the NucliSens EasyQ v2.0 assay in comparison with the Roche Amplicor v1.5 and the Roche CAP/CTM HIV-1 Test v2.0 in quantification of C-clade HIV-1 in plasma. *PLoS One*. 2014;9(8):e103983. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25157919.

78. Torian LV, Eavey JJ, Punsalang AP, et al. HIV type 2 in New York City, 2000-2008. *Clin Infect Dis*. 2010;51(11):1334-1342. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21039219.

79. Campbell-Yesufu OT, Gandhi RT. Update on human immunodeficiency virus (HIV)-2 infection. *Clin Infect Dis*. 2011;52(6):780-787. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21367732.

80. Prince PD, Matser A, van Tienen C, Whittle HC, Schim van der Loeff MF. Mortality rates in people dually infected with

HIV-1/2 and those infected with either HIV-1 or HIV-2: a systematic review and meta-analysis. *AIDS*. 2014;28(4):549-558. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23921613.

81. Barin F, Cazein F, Lot F, et al. Prevalence of HIV-2 and HIV-1 group O infections among new HIV diagnoses in France: 2003-2006. *AIDS*. 2007;21(17):2351-2353. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18090288.

82. Thiebaut R, Matheron S, Taieb A, et al. Long-term nonprogressors and elite controllers in the ANRS CO5 HIV-2 cohort. *AIDS*. 2011;25(6):865-867. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21358376.

83. Menendez-Arias L, Alvarez M. Antiretroviral therapy and drug resistance in human immunodeficiency virus type 2 infection. *Antiviral Res*. 2014;102:70-86. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24345729.

84. Tchounga BK, Inwoley A, Coffie PA, et al. Re-testing and misclassification of HIV-2 and HIV-1&2 dually reactive patients among the HIV-2 cohort of the West African database to evaluate AIDS collaboration. *J Int AIDS Soc*. 2014;17:19064. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25128907.

85. Balestre E, Ekouevi DK, Tchounga B, et al. Immunologic response in treatment-naive HIV-2-infected patients: the IeDEA West Africa cohort. *J Int AIDS Soc*. 2016;19(1):20044. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26861115.

86. Linley L, Ethridge SF, Oraka E, et al. Evaluation of supplemental testing with the multispot HIV-1/HIV-2 rapid test and APTIMA HIV-1 RNA qualitative assay to resolve specimens with indeterminate or negative HIV-1 Western blots. *J Clin Virol*. 2013;58 Suppl 1:e108-112. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24342469.

87. Burgard M, Jasseron C, Matheron S, et al. Mother-to-child transmission of HIV-2 infection from 1986 to 2007 in the ANRS French Perinatal Cohort EPF-CO1. *Clin Infect Dis*. 2010;51(7):833-843. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20804413.

Initial Postnatal Management of the Neonate Exposed to HIV (Last updated December 7, 2018; last reviewed December 7, 2018)

Panel's Recommendations

- A complete blood count and differential should be performed on newborns as a baseline evaluation **(BIII)**.
- If hematologic abnormalities are identified in infants receiving prophylaxis, decisions on whether to continue infant antiretroviral (ARV) prophylaxis need to be individualized. Consultation with an expert in pediatric HIV infection is advised if early discontinuation of prophylaxis is considered **(CIII)**.
- Decisions about the timing of subsequent monitoring of hematologic parameters in infants depend on the infant's baseline hematologic values, gestational age at birth, clinical condition, infant receipt of zidovudine, other ARV drugs, and concomitant medications; and maternal antepartum therapy **(CIII)**.
- Hemoglobin and neutrophil counts should be remeasured 4 weeks after initiation of prophylaxis for infants who receive combination zidovudine/lamivudine-containing ARV prophylaxis regimens **(AI)**.
- Routine measurement of serum lactate is not recommended. However, measurement of the enzyme can be considered if an infant develops severe clinical symptoms of unknown etiology (particularly neurologic symptoms) **(CIII)**.
- Virologic tests are required to diagnose HIV infection in infants aged <18 months (see Diagnosis of HIV Infection in Infants and Children) **(AII)**.
- To prevent *Pneumocystis jirovecii* pneumonia (PCP), all infants born to women with HIV should begin PCP prophylaxis at ages 4 to 6 weeks, after completing their ARV prophylaxis regimen, unless there is adequate test information to presumptively exclude HIV infection (see the Pediatric Opportunistic Infections Guidelines) **(AII)**.
- Health care providers should routinely inquire about breastfeeding and premastication and advise caregivers on safe feeding options **(AII)**.

Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*

Rating of Evidence: *I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

Postnatal Management of the Neonate Exposed to HIV

Following birth, infants exposed to HIV should have a detailed physical examination, and a thorough maternal history should be obtained. Women with HIV may have coinfections with other pathogens that can be transmitted from mother to child, such as cytomegalovirus, Zika virus, herpes simplex virus, hepatitis B, hepatitis C, syphilis, toxoplasmosis, or tuberculosis. Infants born to mothers with such coinfections should undergo appropriate evaluation as indicated to exclude the possibility of transmission of additional infectious agents. The routine primary immunization schedule for children should be followed for HIV-exposed infants born to women with HIV. Modifications in the schedule may be required for infants with known HIV infection (see the Pediatric Opportunistic Infections Guidelines for more information).

Infants should be monitored for toxicities associated with the antiretroviral (ARV) drugs that they were exposed to *in utero*, or are receiving for the prevention of perinatal HIV transmission (see Antiretroviral Management of the Newborns with Perinatal HIV Exposure and Perinatal HIV). Comprehensive care also includes appropriate HIV diagnostic testing and infant feeding support to assist mothers to abstain from breastfeeding. No evidence is available to enable the Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission to assess whether any changes in routine bathing practices, or timing of circumcision, are indicated for newborns with perinatal HIV exposure.

Hematologic Toxicity

A complete blood count and differential should be performed before starting newborns exposed to HIV on antiretroviral (ARV) drug prophylaxis or empiric HIV therapy (see Antiretroviral Management of the Newborns with Perinatal HIV Exposure and Perinatal HIV). Decisions about the timing of hematologic

monitoring of infants after birth depend on several factors, including the infant's baseline hematologic values, gestational age at birth, and clinical condition; the infant ARV drugs and concomitant medications being administered; and the maternal antepartum ARV drug regimen. Anemia is the primary complication seen in neonates who received a 6-week postnatal prophylaxis regimen with zidovudine. In PACTG 076, infants in the zidovudine group had lower hemoglobin levels at birth than those in the placebo group, with the maximal difference between the groups (1 g/dL) occurring at age 3 weeks.[1] The lowest mean value for hemoglobin levels (10 g/dL) occurred at age 6 weeks in the zidovudine group. By age 12 weeks, hemoglobin values in both groups were similar. No significant differences in other laboratory parameters were observed between groups. Hematologic safety data on administration of zidovudine 4 mg/kg twice daily in infants are limited. Some experts remeasure hemoglobin and neutrophil counts routinely after 4 weeks of zidovudine prophylaxis and/or when diagnostic HIV polymerase chain reaction (PCR) tests are obtained.

Older studies previously showed that the association seen with *in utero* exposure to maternal ARVs and anemia and/or neutropenia in infants was greater with combination ARV drug regimens than with zidovudine alone.[2-4] In PACTG 316, where 77% of mothers received antenatal combination therapy, significant Grade 3 or higher anemia was noted in 13% and neutropenia in 12% of infants, respectively. Some experts recommend more intensive monitoring of hematologic tests at birth and when diagnostic HIV PCR tests are obtained in infants exposed to combination ARV drug regimens *in utero* or during the neonatal period.

Data are limited on infants receiving zidovudine in combination with other ARV drugs for prophylaxis. However, higher rates of hematologic toxicity have been observed in infants receiving zidovudine/lamivudine and other combination prophylactic regimens than in those receiving zidovudine alone or zidovudine plus nevirapine.[5-7] Hemoglobin levels and neutrophil counts, therefore, should be remeasured 4 weeks after initiation of prophylaxis and/or at the time that diagnostic HIV PCR testing is done in infants who receive combination zidovudine/lamivudine-containing ARV prophylaxis regimens.[8]

If hematologic abnormalities are found, decisions on whether to continue infant ARV prophylaxis need to be individualized. Considerations include the extent of the abnormality, whether related symptoms are present, duration of infant prophylaxis, and risk of HIV infection (as assessed by maternal history of ARV prophylaxis, maternal viral load near delivery, and mode of delivery). Compared with the 6-week zidovudine regimen, a 4-week zidovudine regimen has been reported to result in earlier recovery from anemia in HIV-exposed but otherwise healthy infants.[9] A 4-week (instead of a 6-week) zidovudine neonatal chemoprophylaxis regimen is recommended when a mother has received standard antiretroviral therapy (ART) during pregnancy with consistent viral suppression and no concerns related to maternal adherence; the shorter regimen will mitigate the risk of anemia in infants born to such women and thus at low risk of acquiring HIV (see Antiretroviral Management of Newborns).[10,11]

Hyperlactatemia

Hyperlactatemia has been reported in infants with *in utero* exposure to ARV drugs, but it appears to be transient and, in most cases, asymptomatic.[12,13] Routine measurement of serum lactate to assess for potential mitochondrial toxicity is not recommended in asymptomatic neonates because the clinical relevance of hyperlactatemia is unknown and the value of lactate levels as a predictive measure of toxicity appears poor.[12,13] Serum lactate measurement should be considered, however, for infants who develop severe clinical symptoms of unknown etiology, particularly neurologic symptoms. ARV prophylaxis should be discontinued in infants with symptoms and if serum lactate levels are significantly abnormal (i.e., >5 mmol/L), with an expert in pediatric HIV infection consulted regarding alternate prophylaxis.

Prophylaxis Against Pneumocystis jirovecii *Pneumonia*

To prevent *Pneumocystis jirovecii* pneumonia, all infants born to women with HIV should begin trimethoprim-sulfamethoxazole (TMP-SMX) prophylaxis at age 4 to 6 weeks, after completion of the infant ARV prophylaxis regimen, unless there is adequate virologic test information to presumptively exclude HIV infection (see the Pediatric Opportunistic Infections Guidelines).[14]

HIV Testing of the Infant

All infants perinatally exposed to HIV require virologic HIV testing to diagnose or exclude HIV infection. For a detailed discussion, including types of tests and recommended HIV testing schedule, see Diagnosis of HIV Infection in Infants and Children.

Infant Feeding Practices and Risk of HIV Transmission

In the United States, where safe infant feeding alternatives are available, it is recommended that women with HIV not breastfeed their infants.[15] Maternal receipt of ART is likely to reduce free virus in breast milk, but the presence of cell-associated virus (intracellular HIV DNA) remains unaffected and may continue to pose a transmission risk.[16] However, clinicians should be aware that some women may face considerable social, familial, and personal pressures to breastfeed despite this recommendation. (see Guidance for Counseling and Managing Women Living with HIV in the United States Who Desire to Breastfeed). It is important to address possible barriers to formula feeding beginning as early as possible in the antenatal period.

Some HIV transmission events in later infancy are thought to have resulted from infants being fed solid food that has been premasticated (prechewed or prewarmed) by caregivers with HIV. Phylogenetic comparisons of virus from cases and suspected sources and supporting clinical history and investigations identified the practice of feeding premasticated foods to infants as a potential risk factor for HIV transmission. Health care providers should routinely inquire about premastication, instruct caregivers living with HIV against this feeding practice, and advise on safer feeding options.[17,18]

References

1. Connor EM, Sperling RS, Gelber R, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. Pediatric AIDS clinical trials group protocol 076 study group. *N Engl J Med*. 1994;331(18):1173-1180. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7935654.

2. Feiterna-Sperling C, Weizsaecker K, Buhrer C, et al. Hematologic effects of maternal antiretroviral therapy and transmission prophylaxis in HIV-1-exposed uninfected newborn infants. *J Acquir Immune Defic Syndr*. 2007;45(1):43-51. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17356471.

3. El Beitune P, Duarte G. Antiretroviral agents during pregnancy: consequences on hematologic parameters in HIV-exposed, uninfected newborn infant. *Eur J Obstet Gynecol Reprod Biol*. 2006;128(1-2):59-63. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16876310.

4. Dryden-Peterson S, Shapiro RL, Hughes MD, et al. Increased risk of severe infant anemia after exposure to maternal HAART, Botswana. *J Acquir Immune Defic Syndr*. 2011;56(5):428-436. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21266910.

5. Nielsen-Saines K, Watts DH, Veloso VG, et al. Three postpartum antiretroviral regimens to prevent intrapartum HIV infection. *N Engl J Med*. 2012;366(25):2368-2379. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22716975.

6. Smith C, Forster JE, Levin MJ, et al. Serious adverse events are uncommon with combination neonatal antiretroviral prophylaxis: a retrospective case review. *PLoS One*. 2015;10(5):e0127062. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26000984.

7. Kakkar FW, Samson L, Vaudry W, et al. Safety of combination antiretroviral prophylaxis in high-risk HIV-exposed newborns: a retrospective review of the Canadian experience. *J Int AIDS Soc*. 2016;19(1):20520. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26880241.

8. Mandelbrot L, Landreau-Mascaro A, Rekacewicz C, et al. Lamivudine-zidovudine combination for prevention of maternal-infant transmission of HIV-1. *JAMA*. 2001;285(16):2083-2093. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11311097.

9. Lahoz R, Noguera A, Rovira N, et al. Antiretroviral-related hematologic short-term toxicity in healthy infants: implications of the new neonatal 4-week zidovudine regimen. *Pediatr Infect Dis J*. 2010;29(4):376-379. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19949355.

10. de Ruiter A, Taylor GP, Clayden P, et al. British HIV association guidelines for the management of HIV infection in pregnant women 2012 (2014 interim review). *HIV Med*. 2014;15 Suppl 4:1-77. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25604045.

11. Ferguson W, Goode M, Walsh A, Gavin P, Butler K. Evaluation of 4 weeks' neonatal antiretroviral prophylaxis as a component of a prevention of mother-to-child transmission program in a resource-rich setting. *Pediatr Infect Dis J*. 2011;30(5):408-412. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21266939.

12. Ekouevi DK, Toure R, Becquet R, et al. Serum lactate levels in infants exposed peripartum to antiretroviral agents to prevent mother-to-child transmission of HIV: Agence Nationale de Recherches Sur le SIDA et les Hepatites Virales 1209 study, Abidjan, Ivory Coast. *Pediatrics*. 2006;118(4):e1071-1077. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16950945.

13. Noguera A, Fortuny C, Munoz-Almagro C, et al. Hyperlactatemia in human immunodeficiency virus-uninfected infants who are exposed to antiretrovirals. *Pediatrics*. 2004;114(5):e598-603. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15492359.

14. Mofenson LM, Brady MT, Danner SP, et al. Guidelines for the Prevention and Treatment of Opportunistic Infections among HIV-exposed and HIV-infected children: recommendations from CDC, the National Institutes of Health, the *HIV Med*icine Association of the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the American Academy of Pediatrics. *MMWR Recomm Rep*. 2009;58(RR-11):1-166. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19730409.

15. Committee on Pediatric AIDS. Infant feeding and transmission of human immunodeficiency virus in the United States. *Pediatrics*. 2013;131(2):391-396. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23359577.

16. Gaillard P, Fowler MG, Dabis F, et al. Use of antiretroviral drugs to prevent HIV-1 transmission through breast-feeding: from animal studies to randomized clinical trials. *J Acquir Immune Defic Syndr*. 2004;35(2):178-187. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14722452.

17. Ivy W, 3rd, Dominguez KL, Rakhmanina NY, et al. Premastication as a route of pediatric HIV transmission: case-control and cross-sectional investigations. *J Acquir Immune Defic Syndr*. 2012;59(2):207-212. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22027873.

18. Gaur AH, Dominguez KL, Kalish ML, et al. Practice of feeding premasticated food to infants: a potential risk factor for HIV transmission. *Pediatrics*. 2009;124(2):658-666. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19620190.

Long-Term Follow-Up of Infants Exposed to Antiretroviral Drugs (Last updated December 7, 2018; last reviewed December 7, 2018)

Panel's Recommendation
• Children with *in utero* or neonatal exposure to antiretroviral (ARV) drugs who develop significant organ system abnormalities of unknown etiology, particularly of the nervous system or heart, should be evaluated for potential mitochondrial dysfunction **(CIII)**. • It is important that the long-term medical record of a child without HIV includes information about *in utero* and neonatal ARV exposure **(BIII)**.
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*

Beginning in the 1990s, evolving long-term monitoring studies, outcomes studies, and other types of surveillance and research have been conducted to assess whether *in utero* exposure to antiretroviral (ARV) drugs may pose later risks to children's health. These include studies of children without HIV born to women with HIV infection, e.g., the Pediatric AIDS Clinical Trial Group (PACTG) Late Outcomes Study, and the Surveillance Monitoring for ART Toxicities (SMARTT) from the Pediatric HIV/AIDS Cohort Study (PHACS). Participation of children and their parents in these types of observational studies provides an essential contribution to the research needed to monitor and identify long-term health outcomes from *in utero* HIV and ARV exposure. Available evidence does not permit definitive conclusions about whether exposure to ARV agents *in utero* might affect the long-term risk of malignancy, cardiometabolic, or neuropsychological outcomes in children; however, the balance of evidence accumulated during the past 2 decades, particularly related to zidovudine exposure, is reassuring. Potential toxicities require further, long-term investigation, especially as individual antenatal ARV drugs and ARV drug combinations continue to evolve. Initial data from follow-up of PACTG 076 infants through age 6 years did not indicate any differences in immunologic, neurologic, or growth parameters between infants who were exposed to the zidovudine regimen and those who received placebo, and no malignancies were noted.[1,2] However, concerns remain that exposure to ARV drugs may have long-term effects on mitochondrial and immunologic function. Ongoing studies within the PHACS and other cohorts of children who are HIV-exposed but uninfected may help to identify the long-term risks of ARV drug exposure in infancy.

Potential Mitochondrial Toxicity

Nucleoside reverse transcriptase inhibitor (NRTI) drugs induce some degree of mitochondrial dysfunction reflecting varying affinity for mitochondrial gamma DNA polymerase. This affinity can interfere with mitochondrial replication, resulting in mitochondrial DNA (mtDNA) depletion and dysfunction.[3-5] Aberrant histological morphology of mitochondria, mtDNA mutations, alterations in mtDNA levels in cord blood mononuclear cells, and even aneuploidy in cord blood cells have all been described in both non-human primates and neonates exposed *in utero* to NRTI drugs.[6-11] Reported increased and decreased alterations in mtDNA levels add further complexity to interpretation of their clinical significance; in addition, the data may be confounded by stage of maternal HIV infection, differences in laboratory assays and cell lines used and duration of elevation.[8,10,12-15] One study has reported that respiratory chain mitochondrial function is subtly and transiently perturbed, with an increased incidence of abnormal newborn metabolic screen results for products of intermediary metabolism (elevated amino acids and acylcarnitines) in infants who are HIV exposed but uninfected compared with infants without HIV exposure.[16] The degrees to which these theoretical concerns and documented mitochondrial abnormalities are clinically relevant are unknown, but they are significantly outweighed by the robust, proven efficacy of maternal and infant ARV prophylaxis in preventing perinatal HIV transmission.[8,17]

Evidence of clinically apparent effects of mitochondrial toxicity are also conflicting. A low rate of hyperlactatemia (3.4%) is documented among infants who are HIV-exposed but uninfected born to U.S. women receiving antiretroviral therapy (ART).[18] However, earlier studies from the French Perinatal Study Group cohort noted a significantly increased incidence of clinical effects possibly reflecting mitochondrial dysfunction including seizures, cognitive and motor delays, abnormal neuroimaging, hyperlactatemia, cardiac dysfunction,

and two deaths, with abnormal mitochondrial histology noted among some infants without HIV born to women with HIV (who received or did not receive ARV drugs during pregnancy: 12/2,644 vs. 0/1,748, respectively, $P = 0.002$).[19,20] Further clinical studies from the United States and Europe have not duplicated these reported findings from the French Studies.[21-27] In a report from a long-term follow-up study in the United States (PACTG 219/219C), 20 children with possible symptoms of mitochondrial dysfunction were identified among a cohort of 1,037 infants who were HIV-exposed but uninfected.[26] Definitive diagnosis was not possible because none of the children had biopsies for mitochondrial function; however, 3 of the 20 children had no exposure to ARV drugs. In the other 17 children, there was an association between symptoms and first exposure to zidovudine/lamivudine limited to the third trimester, but overall exposure to NRTI drugs was not associated with symptoms. Some small alterations in mtDNA and oxidative phosphorylation enzyme activities were documented in stored specimens from these children, but the clinical significance of these observations remains unknown.[28,29]

Given the above data, mitochondrial dysfunction should be considered in children without HIV, but with perinatal exposure to ARV drugs who present with severe clinical findings of unknown etiology, particularly neurologic findings. It is important that the long-term medical record of a child without HIV includes information about ARV exposure in the event that the child develops unusual symptoms later in life, or if adverse late effects of HIV or ARV exposure in children without HIV are identified in the future.[8,30,31]

Potential Cancer Risk and Exposure to Nucleoside Reverse Transcriptase Inhibitor Drugs

Although older studies have not found an association between *in utero* ARV exposure and malignances, follow-up was limited to early childhood.[1,2,27] Animal studies have reported potential transplacental genotoxicity of nucleoside analogue therapy in monkeys, and micro-nucleated erythrocytes have been identified among infants with *in utero* nucleoside analogue exposure.[32,33] In an initial report from the French Perinatal Cohort in 2008, which included cross-check with the French National Cancer Registry, the incidence of cancer among 9,127 children who were HIV-exposed but uninfected (median age 5.4 years) was not significantly different from that expected for the general population; however, the relative risk of cancer for children was higher with exposure to a didanosine/lamivudine combination than to zidovudine monotherapy.[34] An updated report from the French Perinatal Cohort described 21 cancers in 15,163 children without HIV (median age 9.9 years) exposed *in utero* to HIV and ≥1 NRTI drug.[35] Among the NRTIs studied, didanosine (which **is no longer recommended**) was potentially associated with risk of cancer. In a study in the United States, there were 4 cancer diagnoses among 3,087 children exposed to HIV; cancer incidence in children who were HIV exposed but not exposed to ARV prophylaxis was not significantly different than incidence in children exposed to any ARV prophylaxis, and the number of cancer cases did not differ significantly from cases expected based on national reference rates.[36] Continued follow-up of children who are HIV- and ARV-exposed but uninfected is needed to evaluate the potential risk of cancer as these children age into adulthood.

Potential Immunologic Dysfunction

The potential impact of HIV exposure on the immune system of an infant without HIV is unclear. One study reported lower CD4 T lymphocyte (CD4) cell counts in HIV-exposed but uninfected infants born to mothers whose viral load at delivery was >1,000 copies/mL than in HIV-exposed but uninfected infants whose mothers had a viral load <50 copies/mL at delivery.[37] Other data suggest that exposure to HIV *in utero* may be associated with alterations in CD4 and CD8 cell-mediated immune responses in infants to vaccines and non-specific antigens in infants.[38] More recent data indicate immune activation and proinflammatory responses are greater in infants who are HIV exposed than in infants who are HIV unexposed.[39-43]

Potential Increased Morbidity and Mortality

The French Perinatal Cohort Group has reported an increased risk of serious bacterial infections with encapsulated organisms in infants HIV-exposed born to mothers with low CD4 numbers near the time of delivery.[44]

Data from Botswana also show higher rates of morbidity and mortality in infants and children HIV-exposed but uninfected than in infants HIV-unexposed.[45-47] A meta-analysis assessing all-cause mortality in infants and children HIV-exposed but uninfected consistently observed increased risk in this group compared to HIV-

unexposed infants.[48] Further study is needed regarding the reproducibility of these data, and whether there is an immunological basis for the increased susceptibility of infants and children HIV exposed but uninfected to infectious diseases.[49]

Conclusion

Ongoing evaluation of the early and late effects of *in utero* exposure to ARV drugs and infant feeding approaches include the Pediatric HIV/AIDS Cohort Study Surveillance Monitoring of Antiretroviral Toxicity study, natural history studies, and HIV/AIDS surveillance conducted by state health departments and the Centers for Disease Control and Prevention. Because much of the available follow-up data to date relate to *in utero* exposure to antenatal zidovudine or other NRTIs alone, and most pregnant women with HIV currently receive ART regimens, it is critical that studies to evaluate potential adverse effects of *in utero* drug exposure continue to be supported. HIV surveillance databases from states that require HIV reporting provide an opportunity to collect population-based information concerning *in utero* exposure to ARV drugs. To the extent permitted by federal law and regulations, data from these confidential registries can be compared with information from birth defect and cancer registries to identify potential adverse outcomes.

References

1. Culnane M, Fowler M, Lee SS, et al. Lack of long-term effects of *in utero* exposure to zidovudine among uninfected children born to HIV-infected women. Pediatric AIDS clinical trials group protocol 219/076 teams. *JAMA*. 1999;281(2):151-157. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9917118.

2. Hanson IC, Antonelli TA, Sperling RS, et al. Lack of tumors in infants with perinatal HIV-1 exposure and fetal/neonatal exposure to zidovudine. *J Acquir Immune Defic Syndr Hum Retrovirol*. 1999;20(5):463-467. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10225228.

3. Brinkman K, Ter Hofstede HJ, Burger DM, et al. Adverse effects of reverse transcriptase inhibitors: mitochondrial toxicity as common pathway. *AIDS*. 1998;12(14):1735-1744. Available at: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9792373&dopt=Abstract.

4. Birkus G, Hitchcock MJ, Cihlar T. Assessment of mitochondrial toxicity in human cells treated with tenofovir: comparison with other nucleoside reverse transcriptase inhibitors. *Antimicrob Agents Chemother*. 2002;46(3):716-723. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11850253.

5. Saitoh A, Haas RH, Naviaux RK, Salva NG, Wong JK, Spector SA. Impact of nucleoside reverse transcriptase inhibitors on mitochondrial DNA and RNA in human skeletal muscle cells. *Antimicrob Agents Chemother*. 2008;52(8):2825-2830. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18541728.

6. Divi RL, Leonard SL, Kuo MM, et al. Transplacentally exposed human and monkey newborn infants show similar evidence of nucleoside reverse transcriptase inhibitor-induced mitochondrial toxicity. *Environ Mol Mutagen*. 2007;48(3-4):201-209. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16538687.

7. Poirier MC, Divi RL, Al-Harthi L, et al. Long-term mitochondrial toxicity in HIV-uninfected infants born to HIV-infected mothers. *J Acquir Immune Defic Syndr*. 2003;33(2):175-183. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12794551.

8. Jao J, Abrams EJ. Metabolic complications of *in utero* maternal HIV and antiretroviral exposure in HIV-exposed Infants. *Pediatr Infect Dis J*. 2014;33(7):734-740. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24378947.

9. Martin F, Taylor GP. The safety of highly active antiretroviral therapy for the HIV-positive pregnant mother and her baby: is 'the more the merrier'? *J Antimicrob Chemother*. 2009;64(5):895-900. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19706669.

10. Jao J, Powis KM, Kirmse B, et al. Lower mitochondrial DNA and altered mitochondrial fuel metabolism in hiv-exposed uninfected infants in cameroon. *AIDS*. 2017;31(18):2475-2481. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28926411.

11. Budd MA, Calli K, Samson L, et al. Blood mitochondrial DNA content in HIV-exposed uninfected children with Autism Spectrum Disorder. *Viruses*. 2018;10(2). Available at: https://www.ncbi.nlm.nih.gov/pubmed/29439467.

12. Aldrovandi GM, Chu C, Shearer WT, et al. Antiretroviral exposure and lymphocyte mtDNA content among uninfected infants of HIV-1-infected women. *Pediatrics*. 2009;124(6):e1189-1197. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19933732.

13. Cote HC, Raboud J, Bitnun A, et al. Perinatal exposure to antiretroviral therapy is associated with increased blood mitochondrial DNA levels and decreased mitochondrial gene expression in infants. *J Infect Dis*. 2008;198(6):851-859. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18684095.

14. Gingelmaier A, Grubert TA, Kost BP, et al. Mitochondrial toxicity in HIV type-1-exposed pregnancies in the era of highly active antiretroviral therapy. *Antivir Ther*. 2009;14(3):331-338. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19474467.

15. Ajaykumar A, Zhu M, Soudeyns H, et al. HEU blood MTDNA content remains elevated from birth into early life (0-3 years). Abstract 879. Presented at: Conference on Retroviruses and Opportunistic Infections. 2018. Boston, Massachusetts. Available at: http://www.croiconference.org/sessions/heu-blood-mtdna-content-remains-elevated-birth-early-life-0-3-years-0.

16. Kirmse B, Hobbs CV, Peter I, et al. Abnormal newborn screens and acylcarnitines in HIV-exposed and ARV-exposed infants. *Pediatr Infect Dis J*. 2013;32(2):146-150. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22935866.

17. Newell ML, Bunders MJ. Safety of antiretroviral drugs in pregnancy and breastfeeding for mother and child. *Curr Opin HIV AIDS*. 2013;8(5):504-510. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23743789.

18. Crain MJ, Williams PL, Griner R, et al. Point-of-care capillary blood lactate measurements in human immunodeficiency virus-uninfected children with *in utero* exposure to human immunodeficiency virus and antiretroviral medications. *Pediatr Infect Dis J*. 2011;30(12):1069-1074. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22051859.

19. Blanche S, Tardieu M, Rustin P, et al. Persistent mitochondrial dysfunction and perinatal exposure to antiretroviral nucleoside analogues. *Lancet*. 1999;354(9184):1084-1089. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10509500.

20. Barret B, Tardieu M, Rustin P, et al. Persistent mitochondrial dysfunction in HIV-1-exposed but uninfected infants: clinical screening in a large prospective cohort. *AIDS*. 2003;17(12):1769-1785. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12891063.

21. Sperling RS, Shapiro DE, McSherry GD, et al. Safety of the maternal-infant zidovudine regimen utilized in the pediatric AIDS clinical trial group 076 study. *AIDS*. 1998;12(14):1805-1813. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9792381.

22. The Perinatal Safety Review Working Group. Nucleoside exposure in the children of HIV-infected women receiving antiretroviral drugs: absence of clear evidence for mitochondrial disease in children who died before 5 years of age in five United States cohorts. *J Acquir Immune Defic Syndr*. 2000;25(3):261-268. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11115957.

23. Lipshultz SE, Easley KA, Orav EJ, et al. Absence of cardiac toxicity of zidovudine in infants. Pediatric pulmonary and cardiac complications of vertically transmitted HIV infection study group. *N Engl J Med*. 2000;343(11):759-766. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10984563.

24. European Collaborative Study. Exposure to antiretroviral therapy *in utero* or early life: the health of uninfected children born to HIV-infected women. *J Acquir Immune Defic Syndr*. 2003;32(4):380-387. Available at: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12640195&dopt=Abstract.

25. Alimenti A, Forbes JC, Oberlander TF, et al. A prospective controlled study of neurodevelopment in HIV-uninfected children exposed to combination antiretroviral drugs in pregnancy. *Pediatrics*. 2006;118(4):e1139-1145. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16940166.

26. Brogly SB, Ylitalo N, Mofenson LM, et al. *In utero* nucleoside reverse transcriptase inhibitor exposure and signs of possible mitochondrial dysfunction in HIV-uninfected children. *AIDS*. 2007;21(8):929-938. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17457086.

27. Hankin C, Lyall H, Peckham C, Tookey P. Monitoring death and cancer in children born to HIV-infected women in England and Wales: use of HIV surveillance and national routine data. *AIDS*. 2007;21(7):867-869. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17415042.

28. Brogly SB, DiMauro S, Van Dyke RB, et al. Short communication: transplacental nucleoside analogue exposure and mitochondrial parameters in HIV-uninfected children. *AIDS Res Hum Retroviruses*. 2011;27(7):777-783. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21142587.

29. Brogly SB, Foca M, Deville JG, et al. Potential confounding of the association between exposure to nucleoside analogues and mitochondrial dysfunction in HIV-uninfected and indeterminate infants. *J Acquir Immune Defic Syndr*. 2010;53(1):154-157. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20035168.

30. Mofenson LM, Watts DH. Safety of pediatric HIV elimination: the growing population of HIV- and antiretroviral-exposed but uninfected infants. *PLoS Med*. 2014;11(4):e1001636. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24781352.

31. Hazra R, Siberry GK, Mofenson LM. Growing up with HIV: children, adolescents, and young adults with perinatally

acquired HIV infection. *Ann Rev Med*. 2010;61:169-185. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19622036.

32. Olivero OA, Fernandez JJ, Antiochos BB, Wagner JL, St Claire ME, Poirier MC. Transplacental genotoxicity of combined antiretroviral nucleoside analogue therapy in Erythrocebus patas monkeys. *J Acquir Immune Defic Syndr*. 2002;29(4):323-329. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11917235.

33. Witt KL, Cunningham CK, Patterson KB, et al. Elevated frequencies of micronucleated erythrocytes in infants exposed to zidovudine *in utero* and postpartum to prevent mother-to-child transmission of HIV. *Environ Mol Mutagen*. 2007;48(3-4):322-329. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17358032.

34. Benhammou V, Warszawski J, Bellec S, et al. Incidence of cancer in children perinatally exposed to nucleoside reverse transcriptase inhibitors. *AIDS*. 2008;22(16):2165-2177. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18832880.

35. Hleyhel M, Goujon S, Delteil C, et al. Risk of cancer in children exposed to didanosine *in utero*. *AIDS*. 2016;30(8):1245-1256. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26854809.

36. Ivy W, 3rd, Nesheim SR, Paul SM, et al. Cancer among children with perinatal exposure to HIV and antiretroviral medications--New Jersey, 1995-2010. *J Acquir Immune Defic Syndr*. 2015;70(1):62-66. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26017660.

37. Kakkar F, Lamarre V, Ducruet T, et al. Impact of maternal HIV-1 viremia on lymphocyte subsets among HIV-exposed uninfected infants: protective mechanism or immunodeficiency. *BMC Infect Dis*. 2014;14:236. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24885498.

38. Kidzeru EB, Hesseling AC, Passmore JA, et al. *In-utero* exposure to maternal HIV infection alters T-cell immune responses to vaccination in HIV-uninfected infants. *AIDS*. 2014;28(10):1421-1430. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24785950.

39. Schoeman JC, Moutloatse GP, Harms AC, et al. Fetal metabolic stress disrupts immune homeostasis and induces proinflammatory responses in human immunodeficiency virus type 1- and combination antiretroviral therapy-exposed infants. *J Infect Dis*. 2017;216(4):436-446. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28633455.

40. Evans C, Chasekwa B, Rukobo S, et al. Inflammation, CMV and the growth hormone axis in HIV-exposed uninfected infants. Abstract 873. Presented at: Conference on Retroviruses and Opportunistic Infections. 2018. Boston, Massachusetts. Available at: http://www.croiconference.org/sessions/inflammation-cmv-and-growth-hormone-axis-hiv-exposed-uninfected-infants.

41. Mussi-Pinhata MM, Weinberg A, Yu Q, et al. Increased inflammation and monocyte activation in HIV-exposed uninfected infants. Presented at: Conference Retroviruses and Opportunistic Infections. 2018. Boston, Massachusetts. Available at: http://www.croiconference.org/sessions/increased-inflammation-and-monocyte-activation-hiv-exposed-uninfected-infants-0.

42. Broncano PG, Kgole SW, Masasa G, et al. Innate immune activation among HIV-1 exposed uninfected infants from Botwswana. Abstract 881. Presented at: Conference on Retroviruses Opportunistic Infections. 2018. Boston, Massachusetts. Available at: http://www.croiconference.org/sessions/innate-immune-activation-among-hiv-1-exposed-uninfected-infants-botswana.

43. Mitchell C, Dominguez S, George V, et al. Microbial translocation, immune activation, and gut dysbiosis in HIV-exposed infants. Abstract 882. Presented at: Conferences on Retroviruses and Opportunistic Infections. 2018. Boston, Massachusetts. Available at: http://www.croiconference.org/sessions/microbial-translocation-immune-activation-and-gut-dysbiosis-hiv-exposed-infants-0.

44. Taron-Brocard C, Le Chenadec J, Faye A, et al. Increased risk of serious bacterial infections due to maternal immunosuppression in HIV-exposed uninfected infants in a European country. *Clin Infect Dis*. 2014;59(9):1332-1345. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25053719.

45. Zash R, Leidner J, Souda S, et al. HIV-exposed children account for more than half of 24-month mortality in Botswana. Presented at: The 23rd Conference on Retroviruses and Opportunistic Infections. 2016. Boston, MA.

46. Dryden-Peterson S, Ramos T, Shapiro R, Lockman S. Maternal ART and hospitalization or death among HIV-exposed uninfected infants. Presented at: The 23rd Conference on Retroviruses and Opportunistic Infections. 2016. Seattle, WA.

47. Ajibola G, Mayondi G, Leidner J, et al. Higher mortality in HIV-exposed/uninfected vs. HIV-unexposed infants, Botswana. Presented at: The 23rd Conference on Retroviruses and Opportunistic Infections. 2016. Seattle, WA.

48. Brennan AT, Bonawitz R, Gill CJ, et al. A meta-analysis assessing all-cause mortality in HIV-exposed uninfected compared with HIV-unexposed uninfected infants and children. *AIDS*. 2016;30(15):2351-2360. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27456985.

49. Ruck C, Reikie BA, Marchant A, Kollmann TR, Kakkar F. Linking susceptibility to infectious diseases to immune system abnormalities among HIV-exposed uninfected infants. *Front Immunol*. 2016;7:310. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27594857.

Appendix A: Review of Clinical Trials of Antiretroviral Interventions to Prevent Perinatal HIV Transmission (Last updated December 7, 2018; last reviewed December 7, 2018)

One of the major achievements in HIV research was the demonstration by the PACTG 076 clinical trial that administering zidovudine to pregnant women and their infants could reduce the risk of perinatal transmission by nearly 70%.[1] Following the results of PACTG 076, researchers began to explore the development of shorter, less expensive prophylactic regimens that are more applicable in resource-constrained settings. In addition, multiple studies have tried to determine the optimal regimens for reducing the risk of postnatal transmission during breastfeeding. More recently, in the context of recommendations for universal antiretroviral therapy (ART), studies have also explored the efficacy of universal ART during pregnancy and breastfeeding. This Appendix provides a table summarizing the results of major studies of antiretroviral (ARV) interventions used to prevent perinatal transmission (see Supplemental Table 1) and a brief discussion of lessons learned. In many cases, a direct comparison of results from these trials is not possible because the studies involved diverse patient populations from different geographic locations, with differing viral subtypes and infant feeding practices. However, some generalizations are relevant to understanding the use of ARV drugs for prevention of perinatal transmission in both resource-limited and resource-rich countries. Furthermore, these studies have provided critical information elucidating the risks, timing, and mechanisms of perinatal transmission.

ART is more effective antenatally in reducing perinatal transmission than a single-drug prophylactic regimen.

ARV drugs are highly effective at preventing perinatal transmission, even in women living with advanced HIV.[2,3] Efficacy has been demonstrated for a number of short-course ARV regimens, including zidovudine alone, zidovudine plus lamivudine, single-dose nevirapine, and single-dose nevirapine combined with either short-course zidovudine or zidovudine/lamivudine.[4-13] In general, combination regimens are more effective than single-drug regimens in reducing the risk of perinatal transmission. In addition, administering ARV drugs during the antepartum, intrapartum, and postpartum periods is a more effective approach for preventing perinatal transmission than administering ARV drugs during only the antepartum and intrapartum periods or the intrapartum and postpartum periods.[5,14,15]

Almost all trials in resource-limited countries have included oral intrapartum prophylaxis, with varying durations of maternal antenatal and/or infant (and sometimes maternal) postpartum prophylaxis. Regimens with antenatal components, including those starting as late as 36 weeks' gestation, can reduce the risk of perinatal transmission, even when these regimens are lacking an infant prophylaxis component.[10-12] However, longer-duration antenatal zidovudine prophylaxis that begins at 28 weeks' gestation is more effective than shorter-duration zidovudine prophylaxis that begins at 35 weeks' gestation.[13] The Perinatal HIV Prevention Trial (PHPT)-5 trial demonstrated that women who received <8 weeks of prophylaxis during pregnancy had a significantly greater risk of perinatal transmission than women who received longer durations of prophylaxis.[16] The European National Study of HIV in Pregnancy and Childhood demonstrated that each additional week of an antenatal, triple-drug regimen corresponded to a 10% reduction in risk of transmission.[17] More prolonged infant post-exposure prophylaxis does not appear to substitute for longer-duration maternal ARV prophylaxis.[13]

The Promoting Maternal and Infant Survival Everywhere (PROMISE) study was a large randomized clinical trial that demonstrated the superiority of ART over zidovudine-based prophylaxis for prevention of *in utero* transmission in women with CD4 T lymphocyte (CD4) cell counts >350 cells/mm^3.[18] Pregnant women were randomized to one of three study arms:

- Zidovudine plus single-dose nevirapine at delivery plus postpartum tenofovir disoproxil fumarate (TDF)/emtricitabine tail
- Zidovudine plus lamivudine plus lopinavir/ritonavir (LPV/r)
- TDF plus emtricitabine plus LPV/r

The rate of perinatal transmission through 1 week of life was significantly lower among women receiving ART

(0.5%, 9 infections among 1,710 infants) than among those randomized to receive zidovudine plus single-dose nevirapine plus postpartum TDF/emtricitabine tail (1.8%, 25 infections among 1,386 infants).

Regimens that do not include maternal ARV therapy during pregnancy have been evaluated because some women may lack antenatal care and present for prenatal care for the first time when they go into labor. Regimens that include only intrapartum and postpartum drug administration also have been shown to be effective in reducing the risk of perinatal transmission.[4-6] However, without continued infant post-exposure prophylaxis, intrapartum pre-exposure prophylaxis alone with nucleoside reverse transcriptase inhibitor drugs (zidovudine/lamivudine) is not effective in reducing the risk of transmission.[5] The South African Intrapartum Nevirapine Trial (SAINT) trial demonstrated that intrapartum/postpartum zidovudine/lamivudine and single-dose intrapartum/newborn nevirapine are similar in efficacy and safety.[6]

Combination infant ARV prophylaxis is recommended in the United States for infants at high risk for HIV acquisition.

Delayed maternal HIV diagnosis or delayed presentation for pregnancy care may result in missing the opportunity to provide maternal ARV drugs during pregnancy or labor. In the absence of maternal therapy, the standard infant prophylaxis regimen of 6 weeks of zidovudine was effective in reducing the risk of HIV transmission compared with no prophylaxis, based on epidemiological data in resource-rich countries.[19] A trial in Malawi in breastfeeding infants demonstrated that adding 1 week of zidovudine therapy to infant single-dose nevirapine reduced risk of transmission by 36% compared with infant single-dose nevirapine alone.[7]

To define the optimal infant prophylaxis regimen in the absence of maternal antepartum ARV drug administration in a formula-fed population of infants such as in the United States, the NICHD-HPTN 040/P1043 (NCT00099359) clinical trial compared three infant ARV regimens in formula-fed infants born to mothers who did not receive ARV drugs during the current pregnancy:

- Standard 6 weeks of zidovudine alone
- 6 weeks of zidovudine plus three doses of nevirapine given in the first week of life (first dose given within 48 hours of birth, second dose given 48 hours after first dose, third dose given 96 hours after second dose)
- 6 weeks of zidovudine plus lamivudine and nelfinavir given from birth through age 2 weeks.[20]

The study demonstrated that both the dual- and triple-combination regimens reduced the risk of intrapartum transmission by approximately 50% compared with infant prophylaxis with zidovudine alone, although there was more hematologic toxicity with the triple regimen (see Supplemental Table 1). Based on these data, combination ARV prophylaxis is now recommended in the United States for infants born to women who are at increased risk for transmission (see Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV).

Single-dose intrapartum nevirapine is not recommended for women in the United States who are receiving standard recommended antenatal ARV prophylaxis.

PACTG 316 (a clinical trial conducted in the United States, Europe, Brazil, and the Bahamas) demonstrated that adding single-dose nevirapine to combination antenatal ARV prophylaxis for non-breastfeeding women with very low viral loads at the time of delivery did not offer significant benefit.[21] Thus, adding single-dose intrapartum nevirapine is not recommended for women in the United States who are receiving standard recommended antenatal ARV prophylaxis (see Intrapartum Antiretroviral Therapy/Prophylaxis).

Breastfeeding by women with HIV infection is not recommended in the United States.

Breastfeeding by women living with HIV (including those receiving ARV drugs) **is not recommended** in the United States, where replacement feeding is affordable, feasible, acceptable, sustainable, and safe, and the risk of infant mortality due to diarrheal and respiratory infections is low.[22]

Clinical trials in resource-limited settings have demonstrated that both infant prophylaxis (daily infant nevirapine, lamivudine, and LPV/r) during breastfeeding and maternal triple-drug prophylaxis during breastfeeding decrease the risk of postnatal infection (see Supplemental Table 1).[2,23-31] The PROMISE trial

was a large, randomized clinical trial that demonstrated that daily infant nevirapine and maternal ART have similar safety and efficacy for prevention of perinatal transmission during breastfeeding in women with CD4 cell counts ≥350 cells/mm^3.[18,32] At 6 to 14 days postpartum, the study randomized participants to receive either infant nevirapine or maternal ART until 18 months after delivery or breastfeeding cessation. The rates of perinatal transmission were similar (0.58%, 5 infections among 1,211 infants receiving nevirapine vs. 0.57%, 7 infections among 1,219 infants whose mothers received ART), both strategies were safe, and infant HIV-1–free survival was high across both arms (97.7% with infant nevirapine vs. 97.1% with maternal ART at 24 months).

Hypothetically, maternal triple-drug prophylaxis may be less effective than infant prophylaxis if the maternal regimen is first started postpartum or late in pregnancy, because it takes several weeks to months to achieve full viral suppression in breast milk.[27,33] Importantly, although prophylaxis significantly lowers the risk of postnatal infection, neither infant nor maternal postpartum ARV prophylaxis eliminates the risk of HIV transmission through breast milk. Therefore, breastfeeding is not recommended for women living in the United States (including those receiving combination ARV drug regimens).[22] Finally, both infant nevirapine prophylaxis and maternal ART during breastfeeding may be associated with the development of ARV drug resistance in infants who acquire HIV despite prophylaxis; multiclass drug resistance has been described in breastfeeding infants with HIV despite maternal triple-drug prophylaxis.[34-38]

Supplemental Table 1. Results of Major Studies on Antiretroviral Interventions to Prevent Perinatal HIV Transmission (page 1 of 7)

Study Name; Location(s); Mode of Infant Feeding	Antiretroviral Drugs	Antepartum and Intrapartum Interventions	Postpartum Interventions	Perinatal Transmission Rate and Efficacy
PACTG 076; United States, France;[1] Formula feeding	ZDV vs. placebo	Long (from 14 weeks) IV IP	Long (6 weeks); infant only	Perinatal transmission at 18 months was 8.3% in ZDV arm vs. 25.5% in placebo arm (68% efficacy).
CDC Short-Course ZDV Trial; Thailand;[12] Formula feeding	ZDV vs. placebo	Short (from 36 weeks) Oral IP	None	Perinatal transmission at 6 months was 9.4% in ZDV arm vs. 18.9% in placebo arm (50% efficacy).
DITRAME (ANRS 049a) Trial; Ivory Coast, Burkina Faso;[11,39] Breastfeeding	ZDV vs. placebo	Short (from 36 weeks) Oral IP	Short (1 week); mother only	Perinatal transmission at 6 months was 18.0% in ZDV arm vs. 27.5% in placebo arm (38% efficacy). Perinatal transmission at 15 months was 21.5% in ZDV arm vs. 30.6% in placebo arm (30% efficacy). Perinatal transmission was 22.5% in ZDV arm vs. 30.2% in placebo arm in pooled analysis at 24 months (26% efficacy).
CDC Short-Course ZDV Trial; Ivory Coast;[10,11] Breastfeeding	ZDV vs. placebo	Short (from 36 weeks) Oral IP	None	Perinatal transmission at 3 months was 16.5% in ZDV arm vs. 26.1% in placebo arm (37% efficacy). Perinatal transmission was 22.5% in ZDV arm vs. 30.2% in placebo arm in pooled analysis at 24 months (26% efficacy).
PETRA Trial; South Africa, Tanzania, Uganda;[5] Breastfeeding and formula feeding	AP/IP/PP ZDV plus 3TC vs. IP/PP ZDV plus 3TC vs. IP-only ZDV plus 3TC vs. Placebo	Short (from 36 weeks) Oral IP	Short (1 week); mother and infant	Perinatal transmission at 6 weeks was 5.7% for AP/IP/PP ZDV plus 3TC, 8.9% for IP/PP ZDV plus 3TC, 14.2% for IP-only ZDV plus 3TC, and 15.3% for placebo (efficacy compared with placebo: 63%, 42%, and 0%, respectively). Perinatal transmission at 18 months was 14.9% for AP/IP/PP ZDV plus 3TC, 18.1% for IP/PP ZDV plus 3TC, 20.0% for IP-only ZDV plus 3TC, and 22.2% for placebo (efficacy compared with placebo: 34%, 18%, and 0%, respectively).

Supplemental Table 1. Results of Major Studies on Antiretroviral Interventions to Prevent Perinatal HIV Transmission (page 2 of 7)

Study Name; Location(s); Mode of Infant Feeding	Antiretroviral Drugs	Antepartum and Intrapartum Interventions	Postpartum Interventions	Perinatal Transmission Rate and Efficacy
HIVNET 012 Trial; Uganda;[4] Breastfeeding	SD NVP vs. ZDV	No AP ARV drugs Oral IP: • SD NVP vs. oral ZDV	SD NVP within 72 hours of birth; infant only vs. ZDV for 1 week; infant only	Perinatal transmission at 6–8 weeks was 11.8% in NVP arm vs. 20.0% in ZDV arm (42% efficacy) and 15.7% in NVP arm vs. 25.8% in ZDV arm at 18 months (41% efficacy).
SAINT Trial; South Africa;[6] Breastfeeding and formula feeding	SD NVP vs. ZDV plus 3TC	No AP ARV drugs Oral IP: • SD NVP vs. ZDV plus 3TC	SD NVP within 48 hours of birth; mother and infant vs. ZDV plus 3TC for 1 week; mother and infant	Perinatal transmission at 8 weeks was 12.3% in SD NVP arm vs. 9.3% in ZDV plus 3TC arm (difference not statistically significant, $P = 0.11$).
PHPT-1; Thailand;[13] Formula feeding	4 ZDV regimens with different durations of AP and infant PP administration; no placebo	Long (from 28 weeks) or short (from 36 weeks) Oral IP	Long (6 weeks) or short (3 days); infant only	Perinatal transmission rate was 10.5% in the short-short arm. This arm was stopped at interim analysis. Perinatal transmission at 6 months was 6.5% in long-long arm vs. 4.7% in long-short arm and 8.6% in short-long arm (no statistical difference). *In utero* transmission was significantly higher with short vs. long maternal therapy regimens (5.1% vs. 1.6%).
PACTG 316 Trial; Bahamas, Belgium, Brazil, France, Germany, Italy, Spain, Sweden, Switzerland, United Kingdom, United States;[21] Formula feeding	SD NVP vs. placebo among women already receiving ZDV alone (23%) or ZDV plus other ARV drugs (77% combination therapy)	Nonstudy ARV regimen Oral IP: • Placebo vs. SD NVP plus IV ZDV	Placebo vs. SD NVP within 72 hours of birth plus nonstudy ARV drugs (ZDV); infant only	77% of women received dual- or triple-combination ARV regimens during pregnancy. Trial stopped early because of very low perinatal transmission in both arms: 1.4% in SD NVP arm vs. 1.6% in placebo arm (53% of perinatal transmission was *in utero*).
PHPT-2; Thailand;[40] Formula feeding	ZDV alone vs. ZDV plus maternal and infant SD NVP vs. ZDV plus maternal SD NVP	ZDV from 28 weeks Oral IP: • ZDV alone, *or* • ZDV plus SD NVP	ZDV for 1 week with or without SD NVP; infant only	ZDV-alone arm was stopped because the rate of perinatal transmission was higher in this arm than in the ZDV/NVP arm (6.3% vs. 1.1%, respectively). In arms in which the mother received SD NVP, the perinatal transmission rate did not differ significantly whether the infant received SD NVP or not (2.0% vs. 2.8%, respectively).
DITRAME Plus (ANRS 1201.0) Trial; Ivory Coast;[15] Breastfeeding and formula feeding	Open label, ZDV plus SD NVP	ZDV from 36 weeks Oral IP: • ZDV plus SD NVP	SD NVP plus ZDV for 1 week; infant only	Perinatal transmission at 6 weeks was 6.5% (95% CI, 3.9% to 9.1%); perinatal transmission for historical control group receiving short ZDV (98% of whom were breastfed) was 12.8%.
DITRAME Plus (ANRS 1201.1) Trial; Ivory Coast;[15] Breastfeeding and formula feeding	Open label, ZDV plus 3TC plus SD NVP	ZDV plus 3TC from 32 weeks (stopped at 3 days PP) Oral IP: • ZDV plus 3TC plus SD NVP	SD NVP plus ZDV for 1 week; infant only	Perinatal transmission at 6 weeks was 4.7% (95% CI, 2.4% to 7.0%); perinatal transmission for historical control group receiving short ZDV (98% of whom were breastfed) was 12.8%.

Supplemental Table 1. Results of Major Studies on Antiretroviral Interventions to Prevent Perinatal HIV Transmission (page 3 of 7)

Study Name; Location(s); Mode of Infant Feeding	Antiretroviral Drugs	Antepartum and Intrapartum Interventions	Postpartum Interventions	Perinatal Transmission Rate and Efficacy
NVAZ Trial; Malawi;[7] Breastfeeding	Neonatal SD NVP vs. SD NVP plus ZDV	No AP or IP ARV drugs	SD NVP with or without ZDV for 1 week; infant only	Perinatal transmission at 6–8 weeks was 15.3% in SD NVP plus ZDV arm vs. 20.9% in SD NVP-only arm. Perinatal transmission rates at 6–8 weeks among infants without HIV at birth were 7.7% and 12.1%, respectively (36% efficacy).
Postnatal NVP plus ZDV Trial; Malawi;[8] Breastfeeding	Neonatal SD NVP vs. SD NVP plus ZDV	No AP ARV Oral IP: • SD NVP	SD NVP with or without ZDV for 1 week; infant only	Perinatal transmission at 6–8 weeks was 16.3% in NVP plus ZDV arm vs. 14.1% in SD NVP-only arm (difference not statistically significant). Perinatal transmission rates at 6–8 weeks among infants without HIV at birth were 6.5% and 16.9%, respectively.
Post-Exposure Infant Prophylaxis; South Africa;[9] Breastfeeding and formula feeding	Neonatal SD NVP vs. ZDV for 6 weeks	No AP or IP ARV drugs	SD NVP vs. ZDV for 6 weeks	For formula-fed infants only, perinatal transmission at 6 weeks was 14.3% in SD NVP arm vs. 14.1% in ZDV arm (not significant, $P = 0.30$). For breastfed infants only, perinatal transmission was 12.2% in SD NVP arm vs. 19.6% in ZDV arm ($P = 0.03$).
Mashi; Botswana;[41,42] Breastfeeding and formula feeding	Initial: • Short-course ZDV with/without maternal and infant SD NVP and with/without breastfeeding Revised: • Short-course ZDV plus infant SD NVP with/without maternal SD NVP and with/without breastfeeding; women with CD4 counts <200 cells/mm^3 received combination therapy.	First Randomization: • ZDV from 34 weeks Oral IP: • ZDV plus either SD NVP or placebo	Second Randomization: • Breastfeeding plus ZDV (infant) 6 months plus SD NVP; infant only, vs. • Formula feeding plus ZDV (infant) 4 weeks plus SD NVP; infant only	Initial Design: • In formula-feeding arm, perinatal transmission at 1 month was 2.4% in maternal and infant SD NVP arm vs. 8.3% in placebo arm ($P = 0.05$). • In breastfeeding plus infant ZDV arm, perinatal transmission at 1 month was 8.4% in SD NVP arm vs. 4.1% in placebo arm (difference not statistically significant). Revised Design: • Perinatal transmission at 1 month was 4.3% in maternal plus infant SD NVP arm vs. 3.7% in maternal placebo plus infant SD NVP arm (no significant difference; no interaction with mode of infant feeding). Perinatal transmission at 7 months was 9.1% in breastfeeding plus ZDV arm vs. 5.6% in formula-feeding arm; mortality at 7 months was 4.9% in breastfeeding plus ZDV arm vs. 9.3% in formula-feeding arm; HIV-free survival at 18 months was 15.6% in the breastfeeding plus ZDV arm vs. 14.2% in the formula-feeding arm.
SWEN; Uganda, Ethiopia, India;[24] Breastfeeding	SD NVP vs. NVP for 6 weeks	No AP ARV drugs Oral IP: • SD NVP	Infant SD NVP vs. NVP for 6 weeks	Postnatal Infection in Infants Without HIV at Birth: • Perinatal transmission at 6 weeks was 5.3% in SD NVP arm vs. 2.5% in extended NVP arm (risk ratio 0.54, $P = 0.009$). • Perinatal transmission at 6 months was 9.0% in SD NVP arm vs. 6.9% in extended NVP arm (risk ratio 0.80, $P = 0.16$). HIV-free survival was significantly lower in extended NVP arm at both 6 weeks and 6 months of age.

Supplemental Table 1. Results of Major Studies on Antiretroviral Interventions to Prevent Perinatal HIV Transmission (page 4 of 7)

Study Name; Location(s); Mode of Infant Feeding	Antiretroviral Drugs	Antepartum and Intrapartum Interventions	Postpartum Interventions	Perinatal Transmission Rate and Efficacy
PEPI-Malawi Trial; Malawi;[23] Breastfeeding	SD NVP plus ZDV for 1 week (control) vs. 2 extended infant regimens (NVP or NVP/ZDV) for 14 weeks	No AP ARV drugs Oral IP: • SD NVP (if mother presents in time)	Infant SD NVP plus ZDV for 1 week (control) vs. Control plus NVP for 14 weeks vs. Control plus NVP/ZDV for 14 weeks	Postnatal Infection in Infants Without HIV at Birth: • Perinatal transmission at 6 weeks was 5.1% in control arm vs. 1.7% in extended NVP arm (67% efficacy) and 1.6% in extended NVP/ZDV arm (69% efficacy). • Perinatal transmission at 9 months was 10.6% in control arm vs. 5.2% in extended NVP arm (51% efficacy) and 6.4% in extended NVP/ZDV arm (40% efficacy). No significant difference in perinatal transmission between the extended prophylaxis arms; however, more hematologic toxicity with NVP/ZDV.
MITRA; Tanzania;[26] Breastfeeding	Infant 3TC for 6 months (observational)	ZDV/3TC from 36 weeks through labor	Maternal ZDV/3TC for 1 week; infant 3TC for 6 months	Perinatal transmission at 6 months was 4.9% (postnatal perinatal transmission between 6 weeks and 6 months was 1.2%).
Kisumu Breastfeeding Study; Kenya;[29] Breastfeeding	Maternal triple-drug prophylaxis (observational)	ZDV/3TC/NVP (NFV if CD4 count >250 cells/mm^3) from 34 weeks through labor	Maternal ZDV/3TC/NVP (NFV if CD4 count >250 cells/mm^3) for 6 months, infant SD NVP	Perinatal transmission at 6 months was 5.0% (postnatal perinatal transmission between 7 days and 6 months was 2.6%).
MITRA-PLUS; Tanzania;[25] Breastfeeding	Maternal triple-drug prophylaxis (observational)	ZDV/3TC/NVP (NFV if CD4 count >200 cells/mm^3) from 34 weeks through labor	Maternal ZDV/3TC/NVP (NFV if CD4 count >200 cells/mm^3) for 6 months, infant ZDV/3TC for 1 week	Perinatal transmission at 6 months was 5.0% (postnatal perinatal transmission between 6 weeks and 6 months was 0.9%), not significantly different from 6-month infant prophylaxis in MITRA.
Kesho Bora; Multi-African;[28] Breastfeeding primarily	AP ZDV/SD NVP with no postnatal prophylaxis vs. Maternal triple-drug prophylaxis in women with CD4 counts 200–500 cells/mm^3	Arm 1: • ZDV/3TC/LPV/r Arm 2: • ZDV plus SD NVP From 28 weeks through labor	Arm 1: • Maternal ZDV/3TC/LPV/r for 6 months, infant SD NVP plus ZDV for 1 week Arm 2: • Maternal ZDV/3TC for 1 week (no further postnatal prophylaxis), infant SD NVP plus ZDV for 1 week (no further postnatal prophylaxis)	Perinatal transmission at birth was 1.8% with maternal triple-drug prophylaxis (Arm 1) vs. 2.5% with ZDV/SD NVP (Arm 2), not significantly different. In women with CD4 counts 350–500 cells/mm^3, perinatal transmission at birth was 1.7% in both arms. Perinatal transmission at 12 months was 5.4% with maternal triple-drug prophylaxis (Arm 1) vs. 9.5% with ZDV/SD NVP (with no further postnatal prophylaxis after 1 week) (Arm 2) (P = 0.029).
Mma Bana; Botswana;[2] Breastfeeding	Compared 2 maternal triple-drug prophylaxis regimens in women with CD4 counts >200 cells/mm^3	Arm 1: • ZDV/3TC/ABC Arm 2: • ZDV/3TC/LPV/r From 26 weeks through labor	Arm 1: • Maternal ZDV/3TC/ABC for 6 months, infant SD NVP plus ZDV for 4 weeks Arm 2: • Maternal ZDV/3TC/LPV/r for 6 months, infant SD NVP plus ZDV for 4 weeks	Perinatal transmission at 6 months overall was 1.3%: 2.1% in ZDV/3TC/ABC Arm 1 vs. 0.4% in ZDV/3TC/LPV/r Arm 2 (P = 0.53).

Supplemental Table 1. Results of Major Studies on Antiretroviral Interventions to Prevent Perinatal HIV Transmission (page 5 of 7)

Study Name; Location(s); Mode of Infant Feeding	Antiretroviral Drugs	Antepartum and Intrapartum Interventions	Postpartum Interventions	Perinatal Transmission Rate and Efficacy
BAN; Malawi;[27,43] Breastfeeding	Postpartum maternal triple-drug prophylaxis vs. infant NVP in women with CD4 counts ≥250 cells/mm^3	No AP drugs IP Regimens *Arm 1 (Control):* • ZDV/3TC plus SD NVP *Arm 2:* • ZDV/3TC plus SD NVP *Arm 3:* • ZDV/3TC plus SD NVP	Arm 1 (Control): • Maternal ZDV/3TC for 1 week; infant SD NVP plus ZDV/3TC for 1 week Arm 2: • Control as above, then maternal ZDV/3TC/LPV/r for 6 months Arm 3: • Control as above, then infant NVP for 6 months	Postnatal Infection in Infants Without HIV at 2 Weeks: • Perinatal transmission at 28 weeks was 5.7% in control Arm 1, 2.9% in maternal triple-drug prophylaxis Arm 2 (P = 0.009 vs. control), and 1.7% in infant NVP Arm 3 (P < 0.001 vs. control). • Perinatal transmission at 48 weeks was 7.0% in control Arm 1, 4.0% in maternal triple-drug prophylaxis Arm 2 (P = 0.0273 vs. control), and 4% in infant NVP Arm 3 (P = 0.0027 vs. control). No significant difference between maternal triple-drug prophylaxis (Arm 2) and infant NVP (Arm 3) (P = 0.12 at 28 weeks and P = 0.426 at 48 weeks).
HPTN 046; South Africa, Tanzania, Uganda, Zimbabwe;[38,44] Breastfeeding	Postpartum prophylaxis to prevent breast milk transmission of HIV with 6 weeks of infant NVP vs. 6 months of infant NVP	AP drugs allowed if required for maternal health	All infants received daily NVP from birth through age 6 weeks. Arm 1: • Daily infant NVP from 6 weeks through 6 months Arm 2: • Daily infant placebo from 6 weeks through 6 months	In infants without HIV at age 6 weeks, the 6-month infant HIV infection rate was 1.1% (0.3% to 1.8%) in the extended NVP arm vs. 2.4% (1.3% to 3.6%) in the placebo arm (P = 0.048). 18-month postnatal infection rates were 2.2% (1.1% to 3.3%) in the extended NVP arm vs. 3.1% (1.9% to 4.4%) in the placebo arm (P = 0.28). HIV infection and mortality rates did not differ between arms at any age through 18 months. At infant randomization at age 6 weeks, 29% of mothers in each arm were receiving a triple-drug ARV regimen for the treatment of HIV. For mothers receiving triple-drug ARV regimens at the time of randomization, in infants without HIV at age 6 weeks, the 6-month infant HIV infection rate was 0.2% and not statistically different from the rates seen in the extended NVP arm (0.5%) and placebo arm (0%). For mothers with CD4 counts >350 cells/mm^3 who were not receiving triple-drug ARV regimens, in infants without HIV at age 6 weeks, the 6-month infant HIV infection rate was 0.7% (0% to 1.5%) in the extended NVP arm vs. 2.8% (1.3% to 4.4%) in the placebo arm (P = 0.014).

Supplemental Table 1. Results of Major Studies on Antiretroviral Interventions to Prevent Perinatal HIV Transmission (page 6 of 7)

Study Name; Location(s); Mode of Infant Feeding	Antiretroviral Drugs	Antepartum and Intrapartum Interventions	Postpartum Interventions	Perinatal Transmission Rate and Efficacy
NICHD-HPTN 040/ PACTG 1043 Trial; Brazil, Argentina, South Africa, United States;[45] Formula feeding	Infant prophylaxis with 6 weeks of ZDV vs. 6 weeks of infant ZDV plus 3 doses of NVP in first week of life vs. 6 weeks of infant ZDV plus 2 weeks 3TC/NFV	No AP drugs If mother presented early enough, IV ZDV during labor through delivery	Arm 1 (Control): • Infant ZDV for 6 weeks Arm 2: • Control as above plus NVP, with first dose within 48 hours of birth, second dose 48 hours later, and third dose 96 hours after second dose Arm 3: • Control as above, plus 3TC and NFV from birth through age 2 weeks	IP HIV transmission among infants with negative HIV test at birth: 4.8% (3.2% to 7.1%) with ZDV (Arm 1) vs. 2.2% (1.2% to 3.9%) with ZDV plus NVP (Arm 2) (P = 0.046 compared with Arm 1) vs. 2.4% (1.4% to 4.3%) with ZDV plus 3TC/NFV (Arm 3) (P = 0.046 compared with Arm 1). Overall HIV transmission rates, including *in utero* infection: 11.0% (8.7% to 14.0%) with ZDV (Arm 1) vs. 7.1% (5.2% to 9.6%) with ZDV plus NVP (Arm 2) (P = 0.035 compared with Arm 1) vs. 7.4% (5.4% to 9.9%) with ZDV plus 3TC/NFV (Arm 3) (P = 0.035 compared with Arm 1). Grade 3 or 4 neutropenia more frequent in ZDV/3TC/NFV Arm 3 (70 infants) than in ZDV-alone Arm 1 (33 infants) or ZDV/NVP Arm 2 (32 infants) (P < 0.001).
ANRS 12174 Trial; Burkina Faso, South Africa, Uganda, Zambia;[30,31] Breastfeeding	Compared 2 infant ARV prophylaxis regimens during breastfeeding; infants tested PCR-negative at birth and were born to mothers with CD4 counts >350 cells/mm^3	As per standard of care	Arm 1: • Daily infant LPV/r from 1 week through 50 weeks of age Arm 2: • Daily infant 3TC from 1 week through 50 weeks of age	Postnatal Infection in Infants Without HIV at Birth: • Postnatal transmission at age 50 weeks was 1.4% (0.70–2.76) in Arm 1 vs. 1.5% (0.80–2.91) in Arm 2 (P = 0.83). • HIV-free survival was 96.5% (84.6–97.7) in Arm 1 vs. 96.3% (94.4–97.5) in Arm 2 (P = 0.85).
PROMOTE; Uganda;[46] Breastfeeding	Compared 2 triple-ARV regimens; no CD4 restriction	Arm 1: • ZDV/3TC/LPV/r Arm 2: • ZDV/3TC/EFV • ARVs started at 12–28 weeks' gestation and continued through labor	Randomized regimen continued postpartum through 1 year of breastfeeding	HIV-free survival was 92.9% in the LPV/r arm vs. 97.2% in the EFV arm (P = 0.10). Only 2 of 374 liveborn infants acquired infection, both in the LPV/r arm.
PROMISE; India, Malawi, South Africa, Tanzania, Uganda, Zambia, Zimbabwe;[18] Breastfeeding and formula feeding (antepartum component)	Compared ZDV prophylaxis and 2 ART regimens during pregnancy among women at >14 weeks' gestation and with CD4 counts ≥350 cells/mm^3	Arm 1: • ZDV during pregnancy plus SD NVP plus TDF plus FTC at delivery Arm 2: • ZDV plus 3TC plus LPV/r Arm 3: • TDF plus FTC plus LPV/r	Arm 1: • TDF/FTC tail continued for 6–14 days postpartum Arms 2 and 3: • ART regimen continued for 6–14 days postpartum Infants received once-daily NVP for 6 weeks.	Infant HIV Infection Rates by Age 14 Days *Arm 1:* • 1.8% (25/1,386) *Arm 2:* • 0.5% (7/1,385) *Arm 3:* • 0.6% (2/325) Combined ART arms vs. ZDV arm difference in perinatal transmission risk: -1.3% (95% CI, -2.1% to -0.4%)

Supplemental Table 1. Results of Major Studies on Antiretroviral Interventions to Prevent Perinatal HIV Transmission (page 7 of 7)

Study Name; Location(s); Mode of Infant Feeding	Antiretroviral Drugs	Antepartum and Intrapartum Interventions	Postpartum Interventions	Perinatal Transmission Rate and Efficacy
PROMISE; India, Malawi, South Africa, Tanzania, Uganda, Zambia, Zimbabwe;[18] Breastfeeding (postpartum component)	Compared infant NVP and maternal ART during breastfeeding among infants born to women with CD4 counts ≥350 cells/mm^3	This was a postpartum study. intervention only. Eligible women included women enrolled in PROMISE antepartum (see above) and women who received no ARV drugs during pregnancy.	Arm 1: • Mothers received TDF plus FTC plus LPV/r Arm 2: • Once-daily infant NVP Regimens were continued until 42 days after last breastmilk exposure or age 18 months, whichever came first.	Infant Infection Rates: *Arm 1:* • 0.57% (7/1,219) *Arm 2:* • 0.58% (7/1,211) Rates of Infant HIV-1–Free Survival at 24 Months *Arm 1:* • 97.1% *Arm 2:* • 97.7%

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; AP = antepartum; ARV = antiretroviral; ART = antiretroviral therapy; CD4 = CD4 T lymphocyte; CDC = Centers for Disease Control and Prevention; CI = confidence interval; EFV = efavirenz; FTC = emtricitabine; IP = intrapartum; IV = intravenous; LPV/r = lopinavir/ritonavir; NFV = nelfinavir; NVP = nevirapine; PCR = polymerase chain reaction; PP = postpartum; SD = single-dose; TDF = tenofovir disoproxil fumarate; ZDV = zidovudine

References

1. Connor EM, Sperling RS, Gelber R, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. *N Engl J Med*. 1994;331(18):1173-1180. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7935654.

2. 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.

3. Kesho Bora Study Group. Eighteen-month follow-up of HIV-1-infected mothers and their children enrolled in the kesho bora study observational cohorts. *J Acquir Immune Defic Syndr*. 2010;54(5):533-541. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20543706.

4. Jackson JB, Musoke P, Fleming T, et al. Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: 18-month follow-up of the HIVNET 012 randomised trial. *Lancet*. 2003;362(9387):859-868. Available at: http://www.ncbi.nlm.nih.gov/pubmed/13678973.

5. Petra Study Team. Efficacy of three short-course regimens of zidovudine and lamivudine in preventing early and late transmission of HIV-1 from mother to child in Tanzania, South Africa, and Uganda (Petra study): a randomised, double-blind, placebo-controlled trial. *Lancet*. 2002;359(9313):1178-1186. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11955535.

6. Moodley D, Moodley J, Coovadia H, et al. A multicenter randomized controlled trial of nevirapine versus a combination of zidovudine and lamivudine to reduce intrapartum and early postpartum mother-to-child transmission of human immunodeficiency virus type 1. *J Infect Dis*. 2003;187(5):725-735. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12599045.

7. Taha TE, Kumwenda NI, Gibbons A, et al. Short postexposure prophylaxis in newborn babies to reduce mother-to-child transmission of HIV-1: NVAZ randomised clinical trial. *Lancet*. 2003;362(9391):1171-1177. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14568737.

8. Taha TE, Kumwenda NI, Hoover DR, et al. Nevirapine and zidovudine at birth to reduce perinatal transmission of HIV in an African setting: a randomized controlled trial. *JAMA*. 2004;292(2):202-209. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15249569.

9. Gray GE, Urban M, Chersich MF, et al. A randomized trial of two postexposure prophylaxis regimens to reduce mother-to-child HIV-1 transmission in infants of untreated mothers. *AIDS*. 2005;19(12):1289-1297. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16052084.

10. Wiktor SZ, Ekpini E, Karon JM, et al. Short-course oral zidovudine for prevention of mother-to-child transmission of HIV-1 in Abidjan, Cote d'Ivoire: a randomised trial. *Lancet*. 1999;353(9155):781-785. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10459958.

11. Leroy V, Karon JM, Alioum A, et al. Twenty-four month efficacy of a maternal short-course zidovudine regimen to prevent mother-to-child transmission of HIV-1 in West Africa. *AIDS*. 2002;16(4):631-641. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11873008.

12. Shaffer N, Chuachoowong R, Mock PA, et al. Short-course zidovudine for perinatal HIV-1 transmission in Bangkok, Thailand: a randomised controlled trial. Bangkok collaborative perinatal HIV transmission study group. *Lancet*. 1999;353(9155):773-780. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10459957.

13. Lallemant M, Jourdain G, Le Coeur S, et al. A trial of shortened zidovudine regimens to prevent mother-to-child transmission of human immunodeficiency virus type 1. Perinatal HIV prevention trial (Thailand) investigators. *N Engl J Med*. 2000;343(14):982-991. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11018164.

14. Leroy V, Sakarovitch C, Cortina-Borja M, et al. Is there a difference in the efficacy of peripartum antiretroviral regimens in reducing mother-to-child transmission of HIV in Africa? *AIDS*. 2005;19(16):1865-1875. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16227795.

15. Dabis F, Bequet L, Ekouevi DK, et al. Field efficacy of zidovudine, lamivudine and single-dose nevirapine to prevent peripartum HIV transmission. *AIDS*. 2005;19(3):309-318. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15718842.

16. Lallemant M, Le Coeur S, Sirirungsi W, et al. Randomized noninferiority trial of two maternal single-dose nevirapine-sparing regimens to prevent perinatal HIV in Thailand. *AIDS*. 2015;29(18):2497-2507. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26372485.

17. Townsend CL, Cortina-Borja M, Peckham CS, de Ruiter A, Lyall H, Tookey PA. Low rates of mother-to-child transmission of HIV following effective pregnancy interventions in the United Kingdom and Ireland, 2000-2006. *AIDS*. 2008;22(8):973-981. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18453857.

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. Wade NA, Birkhead GS, Warren BL, et al. Abbreviated regimens of zidovudine prophylaxis and perinatal transmission of the human immunodeficiency virus. *N Engl J Med*. 1998;339(20):1409-1414. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9811915.

20. Nielsen-Saines K, Watts DH, Veloso VG, et al. Three postpartum antiretroviral regimens to prevent intrapartum HIV infection. *N Engl J Med*. 2012;366(25):2368-2379. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22716975.

21. Dorenbaum A, Cunningham CK, Gelber RD, et al. Two-dose intrapartum/newborn nevirapine and standard antiretroviral therapy to reduce perinatal HIV transmission: a randomized trial. *JAMA*. 2002;288(2):189-198. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12095383.

22. Committee on Pediatric AIDS. Infant feeding and transmission of human immunodeficiency virus in the United States. *Pediatrics*. 2013;131(2):391-396. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23359577.

23. Kumwenda NI, Hoover DR, Mofenson LM, et al. Extended antiretroviral prophylaxis to reduce breast-milk HIV-1 transmission. *N Engl J Med*. 2008;359(2):119-129. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18525035.

24. Six Week Extended-Dose Nevirapine Study Team, Bedri A, Gudetta B, et al. Extended-dose nevirapine to 6 weeks of age for infants to prevent HIV transmission via breastfeeding in Ethiopia, India, and Uganda: an analysis of three randomised controlled trials. *Lancet*. 2008;372(9635):300-313. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18657709.

25. Kilewo C, Karlsson K, Ngarina M, et al. Prevention of mother-to-child transmission of HIV-1 through breastfeeding by treating mothers with triple antiretroviral therapy in Dar es Salaam, Tanzania: the mitra plus study. *J Acquir Immune Defic Syndr*. 2009;52(3):406-416. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19730269.

26. Kilewo C, Karlsson K, Massawe A, et al. Prevention of mother-to-child transmission of HIV-1 through breast-feeding by treating infants prophylactically with lamivudine in Dar es Salaam, Tanzania: the mitra study. *J Acquir Immune Defic Syndr*. 2008;48(3):315-323. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18344879.

27. Chasela CS, Hudgens MG, Jamieson DJ, et al. Maternal or infant antiretroviral drugs to reduce HIV-1 transmission. *N Engl J Med*. 2010;362(24):2271-2281. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20554982.

28. Kesho Bora Study Group, de Vincenzi I. Triple antiretroviral compared with zidovudine and single-dose nevirapine prophylaxis during pregnancy and breastfeeding for prevention of mother-to-child transmission of HIV-1 (kesho bora study): a randomised controlled trial. *Lancet Infect Dis*. 2011;11(3):171-180. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21237718.

29. Thomas TK, Masaba R, Borkowf CB, et al. Triple-antiretroviral prophylaxis to prevent mother-to-child HIV transmission through breastfeeding--the Kisumu Breastfeeding Study, Kenya: a clinical trial. *PLoS Med*. 2011;8(3):e1001015. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21468300.

30. Kankasa C, Nagot N, Meda N. Infant lopinavir/r versus 3TC to prevent postnatal HIV-1 transmission: the ANRS 12174 trial. Presented at: 21st Conference on Retroviruses and Opportunistic Infections. 2014. Boston, MA.

31. Nagot N, Kankasa C, Tumwine JK, et al. Extended pre-exposure prophylaxis with lopinavir-ritonavir versus lamivudine to prevent HIV-1 transmission through breastfeeding up to 50 weeks in infants in Africa (ANRS 12174): a randomised controlled trial. *Lancet*. 2016;387(10018):566-573. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26603917.

32. Flynn PM, Taha TE, Cababasay M, et al. Prevention of HIV-1 transmission through breastfeeding: efficacy and safety of maternal antiretroviral therapy versus infant nevirapine prophylaxis for duration of breastfeeding in HIV-1-infected women with high CD4 cell count (IMPAACT PROMISE): a randomized, open-label, clinical trial. *J Acquir Immune Defic Syndr*. 2018;77(4):383-392. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29239901.

33. Mofenson LM. Protecting the next generation--eliminating perinatal HIV-1 infection. *N Engl J Med*. 2010;362(24):2316-2318. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20554987.

34. Moorthy A, Gupta A, Bhosale R, et al. Nevirapine resistance and breast-milk HIV transmission: effects of single and extended-dose nevirapine prophylaxis in subtype C HIV-infected infants. *PLoS One*. 2009;4(1):e4096. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19119321.

35. Lidstrom J, Guay L, Musoke P, et al. Multi-class drug resistance arises frequently in HIV-infected breastfeeding infants whose mothers initiate HAART postpartum. Presented at: 17th Conference on Retroviruses and Opportunistic Infections. 2010. San Francisco, CA.

36. Zeh C, Weidle PJ, Nafisa L, et al. HIV-1 drug resistance emergence among breastfeeding infants born to HIV-infected mothers during a single-arm trial of triple-antiretroviral prophylaxis for prevention of mother-to-child transmission: a secondary analysis. *PLoS Med*. 2011;8(3):e1000430. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21468304.

37. Fogel J, Li Q, Taha TE, et al. Initiation of antiretroviral treatment in women after delivery can induce multiclass drug resistance in breastfeeding HIV-infected infants. *Clin Infect Dis*. 2011;52(8):1069-1076. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21460326.

38. Coovadia HM, Brown ER, Fowler MG, et al. Efficacy and safety of an extended nevirapine regimen in infant children of breastfeeding mothers with HIV-1 infection for prevention of postnatal HIV-1 transmission (HPTN 046): a randomised, double-blind, placebo-controlled trial. *Lancet*. 2012;379(9812):221-228. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22196945.

39. Dabis F, Msellati P, Meda N, et al. 6-month efficacy, tolerance, and acceptability of a short regimen of oral zidovudine to reduce vertical transmission of HIV in breastfed children in Cote d'Ivoire and Burkina Faso: a double-blind placebo-controlled multicentre trial. DITRAME Study Group. DIminution de la transmission mere-enfant. *Lancet*. 1999;353(9155):786-792. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10459959.

40. Lallemant M, Jourdain G, Le Coeur S, et al. Single-dose perinatal nevirapine plus standard zidovudine to prevent mother-to-child transmission of HIV-1 in Thailand. *N Engl J Med*. 2004;351(3):217-228. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15247338.

41. Shapiro RL, Thior I, Gilbert PB, et al. Maternal single-dose nevirapine versus placebo as part of an antiretroviral strategy to prevent mother-to-child HIV transmission in Botswana. *AIDS*. 2006;20(9):1281-1288. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16816557.

42. Thior I, Lockman S, Smeaton LM, et al. Breastfeeding plus infant zidovudine prophylaxis for 6 months vs formula feeding plus infant zidovudine for 1 month to reduce mother-to-child HIV transmission in Botswana: a randomized trial: the Mashi Study. *JAMA*. 2006;296(7):794-805. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16905785.

43. Jamieson DJ, Chasela CS, Hudgens MG, et al. Maternal and infant antiretroviral regimens to prevent postnatal HIV-1 transmission: 48-week follow-up of the BAN randomised controlled trial. *Lancet*. 2012. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22541418.

44. Fowler MG, Coovadia H, Herron CM, et al. Efficacy and safety of an extended nevirapine regimen in infants of breastfeeding mothers with HIV-1 infection for prevention of HIV-1 transmission (HPTN 046): 18-month results of a randomized, double-blind, placebo-controlled trial. *J Acquir Immune Defic Syndr*. 2014;65(3):366-374. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24189151.

45. Nielsen-Saines K, et al. Tenofovir disoproxil fumarate (TDF) pharmacokinetics (PK) with daily dosing in the first week of life (HPTN 057). Abstract no. TUAB0201. Presented at: 19th International AIDS Conference. 2012. Washington, DC.

46. Cohan D, Natureeba P, Koss CA, et al. Efficacy and safety of lopinavir/ritonavir versus efavirenz-based antiretroviral therapy in HIV-infected pregnant Ugandan women. *AIDS*. 2015;29(2):183-191. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25426808.

Appendix B: Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy

Table 10. Antiretroviral Drug Use in Pregnant Women with HIV: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy[a] (page 1 of 21)

Note: When using FDCs, refer to other sections in Appendix B and Table 10 for information about the dosing and safety of individual drug components of the FDC during pregnancy.

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations	Use in Pregnancy	Last Reviewed
NRTIs NRTIs are recommended for use as part of combination regimens, usually including 2 NRTIs with either an NNRTI or 1 or more PIs. Use of single or dual NRTIs alone is not recommended for treatment of HIV infection. See text for discussion of potential maternal and infant mitochondrial toxicity.				
Abacavir (ABC) *Ziagen* (ABC/3TC) *Epzicom* (ABC/DTG/3TC) *Triumeq* (ABC/3TC/ZDV) *Trizivir* **Note:** Generic available for some formulations.	ABC (Ziagen)[d] *Tablet:* • 300 mg *Solution:* • 20 mg/mL ABC/3TC (Epzicom):[d] • ABC 600 mg plus 3TC 300 mg tablet ABC/DTG/3TC (Triumeq): • ABC 600 mg plus 3TC 300 mg plus DTG 50 mg tablet ABC/3TC/ZDV (Trizivir):[d] • ABC 300 mg plus 3TC 150 mg plus ZDV 300 mg tablet	Standard Adult Doses *ABC (Ziagen):* • ABC 300 mg twice daily or ABC 600 mg once daily, without regard to food *ABC/3TC (Epzicom):* • 1 tablet once daily without regard to food *ABC/DTG/3TC (Triumeq):* • 1 tablet daily without regard to food *ABC/3TC/ZDV (Trizivir):* • 1 tablet twice daily without regard to food Dosing in Pregnancy: • No change in dose indicated. PK in Pregnancy: • PK not significantly altered in pregnancy. • For guidance about use of combination products in pregnancy, please see the specific sections on other components (i.e., 3TC, ZDV, DTG).	High placental transfer to fetus.[b] No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects). HSRs occur in approximately 5% to 8% of nonpregnant individuals. A small percentage of reactions are fatal, and these fatal reactions are usually associated with re-challenge. Rate of reactions during pregnancy is unknown. Testing for HLA-B*5701 identifies patients at risk of reactions and should be done and documented as negative before starting ABC. Patients should be educated regarding symptoms of HSR.	December 7, 2018
Didanosine (ddI) *Videx* *Videx EC* **Note:** Generic available for some formulations	ddI (Videx) *Buffered Tablets (Non-EC):* • No longer available *Solution:* • 10 mg/mL oral solution Videx EC (EC Beadlets) Capsules: • 125 mg • 200 mg • 250 mg • 400 mg Delayed-Release Capsules:[d] • 200 mg • 250 mg • 400 mg	Standard Adult Doses *Body Weight ≥60 kg:* • ddI 400 mg once daily *With TDF:* • ddI 250 mg once daily; take 1/2 hour before or 2 hours after a meal. *Body Weight <60 kg:* • ddI 250 mg once daily *With TDF:* • ddI 200 mg once daily; take 1/2 hour before or 2 hours after a meal. **Note:** Preferred dosing with oral solution is twice daily (total daily dose divided into 2 doses). Take 1/2 hour before or 2 hours after a meal. Dosing in Pregnancy: • No change in dose indicated.	ddI **is not recommended** for pregnant women. Low-moderate placental transfer to fetus.[b] ddI **should not be used** with d4T. Lactic acidosis, sometimes fatal, has been reported in pregnant women receiving ddI and d4T together.	December 7, 2018

Table 10. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy[a] (page 2 of 21)

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations	Use in Pregnancy	Last Reviewed
Didanosine, continued		PK in Pregnancy: • PK is not significantly altered in pregnancy.		
Emtricitabine (FTC) *Emtriva* (FTC/EFV/TDF) *Atripla* (FTC/BIC/TAF) *Biktarvy* (FTC/RPV/TDF) *Complera* (FTC/TAF) *Descovy* (FTC/EVG/COBI/TAF) *Genvoya* (FTC/RPV/TAF) *Odefsey* (FTC/EVG/COBI/TDF) *Stribild* (FTC/DRV/COBI/TAF) *Symtuza* (FTC/TDF) *Truvada*	FTC (Emtriva) *Capsule:* • 200 mg *Oral Solution:* • 10 mg/mL FTC/EFV/TDF (Atripla): • FTC 200 mg plus EFV 600 mg plus TDF 300 mg tablet FTC/BIC/TAF (Biktarvy): • FTC 200 mg plus BIC 50 mg plus TAF 25 mg tablet FTC/RPV/TDF (Complera): • FTC 200 mg plus RPV 25 mg plus TDF 300 mg tablet FTC/TAF (Descovy): • FTC 200 mg plus TAF 25 mg tablet FTC/EVG/COBI/TAF (Genvoya): • FTC 200 mg plus EVG 150 mg plus COBI 150 mg plus TAF 10 mg tablet FTC/RPV/TAF (Odefsey): • FTC 200 mg plus RPV 25 mg plus TAF 25 mg tablet FTC/EVG/COBI/TDF (Stribild): • FTC 200 mg plus EVG 150 mg plus COBI 150 mg plus TDF 300 mg tablet FTC/DRV/COBI/TAF (Symtuza): • FTC 200 mg plus DRV 800 mg plus COBI 150 mg plus TAF 10 mg tablet FTC/TDF (Truvada): • FTC 200 mg plus TDF 300 mg tablet	Standard Adult Doses *FTC (Emtriva)* *Capsule:* • EVG 200 mg once daily without regard to food *Oral Solution:* • EVG 240 mg (24 mL) once daily without regard to food *FTC/EFV/TDF (Atripla):* • 1 tablet once daily at or before bedtime • Take on an empty stomach to reduce side effects. *FFTC/BIC/TAF (Biktarvy):* • 1 tablet once daily with or without food *FTC/RPV/TDF (Complera):* • 1 tablet once daily with food *FTC/TAF (Descovy):* • 1 tablet once daily with or without food *FTC/EVG/COBI/TAF (Genvoya):* • 1 tablet once daily with food *FTC/RPV/TAF (Odefsey):* • 1 tablet once daily with food *FTC/EVG/COBI/TDF (Stribild):* • 1 tablet once daily with food *FTC/DRV/COBI/TAF (Symtuza):* • 1 tablet once daily with food *FTC/TDF (Truvada):* • 1 tablet once daily without regard to food Dosing in Pregnancy: • No change in FTC dose indicated. PK in Pregnancy: • PK of FTC is not significantly altered in pregnancy. • For guidance about use of combination products in pregnancy, please see the specific sections on other components (i.e., TDF, TAF, EFV, RPV, DRV, EVG, BIC, COBI)	High placental transfer to fetus.[b] No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects). If patient is HBV-coinfected, it is possible that a HBV flare may occur if the drug is stopped; see HIV/Hepatitis B Virus Coinfection.	December 7, 2018

Table 10. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy[a] (page 3 of 21)

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations	Use in Pregnancy	Last Reviewed
Lamivudine (3TC) *Epivir* (3TC/TDF) *Cimduo* (3TC/ZDV) *Combivir* (3TC/DOR/TDF) *Delstrigo* (3TC/ABC) *Epzicom* (3TC/EFV/TDF) *Symfi* (3TC/EFV/TDF) *Symfi Lo* (3TC/TDF) *Temixys* (3TC/ABC/DTG) *Triumeq* (3TC/ABC/ZDV) *Trizivir* **Note:** Generic available for some formulations	3TC (Epivir)[d] *Tablets:* • 150 mg • 300 mg *Oral Solution:* • 10 mg/mL 3TC/TDF (Cimduo): • 3TC 300 mg plus TDF 300 mg tablet 3TC/ZDV (Combivir):[d] • 3TC 150 mg plus ZDV 300 mg tablet 3TC/DOR/TDF (Delstrigo): • 3TC 300 mg plus DOR 100 mg plus TDF 300 mg tablet 3TC/ABC (Epzicom):[d] • 3TC 300 mg plus ABC 600 mg tablet 3TC/EFV/TDF (Symfi): • 3TC 300 mg plus EFV 600 mg plus TDF 300 mg tablet 3TC/EFV/TDF (Symfi Lo): • 3TC 300 mg plus EFV 400 mg plus TDF 300 mg tablet 3TC/TDF (Temixys): • 3TC 300 mg plus TDF 300 mg tablet 3TC/ABC/DTG (Triumeq): • 3TC 300 mg plus ABC 600 mg plus DTG 50 mg tablet 3TC/ABC/ZDV (Trizivir):[d] • 3TC 150 mg plus ABC 300 mg plus ZDV 300 mg tablet	Standard Adult Doses *3TC (Epivir):* • 3TC 150 mg twice daily or 300 mg once daily, without regard to food *3TC/TDF (Cimduo):* • 1 tablet once daily without regard to food *3TC/ZDV (Combivir):* • 1 tablet twice daily without regard to food *3TC/DOR/TDF (Delstrigo):* • 1 tablet once daily without regard to food *3TC/ABC (Epzicom):* • 1 tablet once daily without regard to food *3TC/EFV/TDF (Symfi or Symfi Lo):* • 1 tablet once daily on an empty stomach and preferably at bedtime *3TC/ABC/DTG (Triumeq):* • 1 tablet once daily without regard to food *3TC/TDF (Temixys):* • 1 tablet once daily without regard to food *3TC/ABC/ZDV (Trizivir):* • 1 tablet twice daily without regard to food PK in Pregnancy: • PK not significantly altered in pregnancy. Dosing in Pregnancy: • No change in dose indicated. • For guidance about use of combination products in pregnancy, please see the specific sections on other components (i.e., ABC, DOR, DTG, EFV, TDF, ZDV).	High placental transfer to fetus.[b] No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects). If patient has HIV/HBV coinfection, it is possible that an HBV flare may occur if the drug is stopped; see HIV/Hepatitis B Virus Coinfection. **Note:** 3TC products developed specifically for treatment of HBV (e.g., Epivir-HBV) contain a lower dose of 3TC that **is not appropriate** for treatment of HIV.	December 7, 2018

Table 10. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy[a] (page 4 of 21)

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations	Use in Pregnancy	Last Reviewed
Stavudine (d4T) *Zerit* **Note:** Generic products are available for all formulations.	d4T (Zerit) *Capsules:* • 15 mg • 20 mg • 30 mg • 40 mg *Oral Solution:* • 1 mg/mL following reconstitution **Note:** Extended-release capsule formulation (Zerit XR) has been discontinued by the manufacturer.	Standard Adult Doses[e] *Body Weight ≥60 kg:* • 40 mg twice daily without regard to meals *Body Weight <60 kg:* • 30 mg twice daily without regard to meals Dosing in Pregnancy: • No change in dose indicated. PK in Pregnancy: • PK not significantly altered in pregnancy.	d4T **is not recommended** for pregnant women. High placental transfer.[b] No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects). Lactic acidosis, sometimes fatal, has been reported in pregn aant women receiving ddI and d4T together.	December 7, 2018
Tenofovir Alafenamide (TAF) *Vemlidy* (TAF/BIC/FTC) *Biktarvy* (TAF/FTC) *Descovy* (TAF/EVG/COBI/FTC) *Genvoya* (TAF/FTC/RPV) *Odefsey* (TAF/DRV/COBI/FTC) *Symtuza* **Note:** Generic available for some formulations.	TAF (Vemlidy)[d] *Tablet:* • 25 mg TAF/BIC/FTC (Biktarvy): • TAF 25 mg plus BIC 50 mg plus FTC 200 mg tablet TAF/FTC (Descovy): • TAF 25 mg plus FTC 200 mg tablet TAF/EVG/COBI/FTC (Genvoya): • TAF 10 mg plus EVG 150 mg plus COBI 150 mg plus FTC 200 mg tablet TAF/FTC/RPV (Odefsey): • TAF 25 mg plus FTC 200 mg plus RPV 25 mg tablet TAF/DRV/COBI/FTC (Symtuza): • TAF 10 mg plus DRV 800 mg plus COBI 150 mg plus FTC 200 mg tablet	Standard Adult Dose *TAF (Vemlidy):* • 1 tablet once daily with food *TAF/BIC/FTC (Biktarvy):* • 1 tablet once daily with or without food *TAF/FTC (Descovy):* • 1 tablet once daily with or without food • Same dose (TAF 25 mg) can be used with or without pharmaco-enhancers. *TAF/EVG/COBI/FTC (Genvoya):* • 1 tablet once daily with food *TAF/FTC/RPV (Odefsey):* • 1 tablet once daily with food *TAF/DRV/COBI/FTC (Symtuza):* • 1 tablet once daily with food PK in Pregnancy: • Plasma PK not significantly altered in pregnancy.	Low placental transfer to fetus.[b] Insufficient data to assess for teratogenicity in humans. No evidence of teratogenicity in rats. Renal function should be monitored because of potential for renal toxicity.	December 7, 2018

Table 10. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy[a] (page 5 of 21)

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations	Use in Pregnancy	Last Reviewed
Tenofovir Alafenamide, continued		Dosing in Pregnancy: • No change in dose indicated. • For guidance about use of combination products in pregnancy, please see the specific sections on other components (i.e., BIC, COBI. DRV, EVG, FTC, RPV).		
Tenofovir Disoproxil Fumarate (TDF) *Viread* (TDF/EFV/FTC) *Atripla* (TDF/3TC) *Cimduo* (TDF/FTC/RPV) *Complera* (TDF/DOR/3TC) *Delstrigo* (TDF/EVG/COBI/FTC) *Stribild* (TDF/EFV/3TC) *Symfi* (TDF/EFV/3TC) *Symfi Lo* (TDF/3TC) *Temixys* (TDF/FTC) *Truvada* **Note:** Generic available for some formulations	TDF (Viread) *Tablet:*[d] • 300 mg *Powder:* • 40 mg/1 g oral powder TDF/EFV/FTC (Atripla): • TDF 300 mg plus EFV 600 mg plus FTC 200 mg tablet TDF/3TC (Cimduo): • TDF 300 mg plus 3TC 300 mg tablet TDF/FTC/RPV (Complera): • TDF 300 mg plus FTC 200 mg plus RPV 25 mg tablet TDF/DOR/3TC (Delstrigo): • TDF 300 mg plus DOR 100 mg plus 3TC 300 mg tablet TDF/EVG/COBI /FTC (Stribild): • TDF 300 mg plus EVG 150 mg plus COBI 150 mg plus FTC 200 mg tablet TDF/EFV/3TC (Symfi): • TDF 300 mg plus EFV 600 mg plus 3TC 300 mg tablet TDF/EFV/3TC (Symfi Lo): • TDF 300 mg plus EFV 400 mg plus 3TC 300 mg tablet	Standard Adult Doses *TDF (Viread)* *Tablet:* • TDF 300 mg once daily without regard to food *Powder:* • TDF 8 mg/kg (up to a maximum of TDF 300 mg). Take with food. *TDF/EFV/FTC (Atripla):* • 1 tablet once daily at or before bedtime. Take on an empty stomach to reduce side effects. *TDF/3TC (Cimduo):* • 1 tablet once daily without regard to food *TDF/FTC/RPV (Complera):* • 1 tablet once daily with food *TDF/DOR/3TC (Delstrigo):* • 1 tablet once daily without regard to food. *TDF/EVG/COBI/FTC (Stribild):* • 1 tablet once daily with food *TDF/EFV/3TC (Symfi or Symfi Lo):* • 1 tablet once daily on an empty stomach and preferably at bedtime *TDF/3TC (Temixys):* • 1 tablet once daily without regard to food	High placental transfer to fetus.[b] No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects). Studies in monkeys (at doses approximately 2-fold higher than those for human therapeutic use) show decreased fetal growth and reduction in fetal bone porosity within 2 months of starting maternal therapy. Human studies demonstrate no consistent link to low birth weight, but data are conflicting about potential effects on growth outcomes later in infancy. If patient is HBV coinfected, it is possible that an HBV flare may occur if TDF is stopped; see HIV/Hepatitis B Virus Coinfection. Renal function should be monitored because of potential for renal toxicity.	December 7, 2018

Table 10. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy[a] (page 6 of 21)

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations	Use in Pregnancy	Last Reviewed
Tenofovir Disoproxil Fumarate, continued	TDF/3TC (Temixys): • TDF 300 mg plus 3TC 300 mg tablet TDF/FTC (Truvada): • TDF 300 mg plus FTC 200 mg tablet	*TDF/FTC (Truvada):* • 1 tablet once daily without regard to food PK in Pregnancy: • AUC is lower in third trimester than postpartum, but trough levels are adequate. Dosing in Pregnancy: • No change in dose is indicated. • For guidance about use of combination products in pregnancy, please see the specific sections on other components (i.e., 3TC, COBI, DOR, EFV, EVG, FTC, RPV)		
Zidovudine (ZDV) *Retrovir* (ZDV/3TC) *Combivir* (ZDV/ABC/3TC) *Trizivir* **Note:** Generic available for all formulations.	ZDV (Retrovir) *Capsule:* • 100 mg *Tablet:* • 300 mg *Oral Solution:* • 10 mg/mL *Intravenous Solution:* • 10 mg/mL ZDV/3TC (Combivir): • ZDV 300 mg plus 3TC 150 mg tablet ZDV/ABC/3TC (Trizivir): • ZDV 300 mg plus 3TC 150 mg plus ABC 300 mg tablet	Standard Adult Dose *ZDV (Retrovir):* • ZDV 300 mg BID or ZDV 200 mg TID without regard to food *Active Labor:* • ZDV 2 mg/kg IV loading dose, followed by ZDV 1 mg/kg/hour continuous infusion from beginning of active labor until delivery *Combivir:* • 1 tablet twice daily without regard to food *Trizivir:* • 1 tablet twice daily without regard to food Dosing in Pregnancy: • No change in dose is indicated. PK in Pregnancy: • PK is not significantly altered in pregnancy. • For guidance about use of combination products in pregnancy, please see the specific sections on other components (i.e., ABC, 3TC)	High placental transfer to fetus.[b] No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects).	December 7, 2018

Table 10. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy[a] (page 7 of 21)

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations	Use in Pregnancy	Last Reviewed
NNRTI NNRTIs are recommended for use in combination regimens with 2 NRTI drugs. Hypersensitivity reactions, including hepatic toxicity and rash, more common in women; unclear if increased in pregnancy.				
Doravirine (DOR) *Pifeltro* (DOR/3TC/TDF) *Delstrigo*	DOR (Pifeltro): • 100 mg tablet DOR/3TC/TDF (Delstrigo): • DOR 100 mg plus 3TC 300 mg plus TDF 300 mg tablet	Standard Adult Dose *DOR (Pifeltro):* • 100 mg once daily with or without food *DOR/3TC/TDF (Delstrigo):* • 1 tablet once daily with or without food PK in Pregnancy: • No PK studies in human pregnancy. Dosing in Pregnancy: • Insufficient data to make dosing recommendation. • For guidance about use of combination products in pregnancy, please see the specific sections on other components (i.e., 3TC, TDF)	No human data are available on placental transfer of DOR, but animal studies suggest that DOR crosses the placenta. Insufficient data to assess for teratogenicity in humans. No evidence of teratogenicity in rats or rabbits.	December 7, 2018
Efavirenz (EFV) *Sustiva* (EFV/FTC/TDF) *Atripla* (EFV/3TC/TDF) *Symfi* (EFV/3TC/TDF) *Symfi Lo* **Note:** Generic available for some formulations.	EFV (Sustiva)[d] *Capsules:* • 50 mg • 200 mg *Tablet:* • 600 mg EFV/FTC/TDF (Atripla): • EFV 600 mg plus FTC 200 mg tablet TDF 300 mg plus EFV/3TC/TDF (Symfi): • EFV 600 mg plus 3TC 300 mg plus TDF 300 mg tablet EFV/3TC/TDF (Symfi Lo): • EFV 400 mg plus 3TC 300 mg plus TDF 300 mg tablet	Standard Adult Doses *EFV (Sustiva):* • EFV 600 mg once daily at or before bedtime, on an empty stomach to reduce side effects *EFV/FTC/TDF (Atripla):* • 1 tablet once daily at or before bedtime, on an empty stomach to reduce side effects *EFV/3TC/TDF (Symfi or Symfi Lo):* • 1 tablet once daily on an empty stomach and preferably at bedtime PK in Pregnancy: • AUC is decreased during the third trimester compared with postpartum, but nearly all third-trimester participants exceeded target exposure. Dosing in Pregnancy: • No change in dose is indicated.	Moderate placental transfer to fetus.[b] The FDA advises women to avoid becoming pregnant while taking EFV and advises health care providers to avoid administration during the first trimester of pregnancy, as fetal harm may occur. Although the limited data on first-trimester EFV exposure cannot rule out a 2-fold or 3-fold increased incidence of a rare outcome such as NTDs, the available data from a meta-analysis of >2,000 births suggest that there is no large increase in the risk of neural tube defects with first-trimester exposure (e.g., a 10-fold increase to a rate of 1%). As a result, the current Perinatal Guidelines do not restrict the use of EFV in pregnant women or in women who are planning to become pregnant. This is consistent with both the British HIV Association and WHO guidelines for use of ARV drugs in pregnancy.	December 7, 2018

Table 10. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy[a] (page 8 of 21)

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations	Use in Pregnancy	Last Reviewed
Efavirenz, continued		• For guidance about use of combination products in pregnancy, please see the specific sections on other components (i.e., 3TC, FTC, TDF)	EFV should be continued in pregnant women who are on a virologically suppressive, EFV-based regimen, because ARV drug changes during pregnancy may be associated with loss of viral control and an increased risk of perinatal transmission (see Pregnant Women Living with HIV Who are Currently Receiving Antiretroviral Therapy).	
Etravirine (ETR) *Intelence*	ETR (Intelence) *Tablets:* • 25 mg • 100 mg • 200 mg For patients unable to swallow tablets whole, the tablets may be dispersed in a glass of water.	Standard Adult Dose *ETR (Intelence):* • 200 mg twice daily with food PK in Pregnancy: • PK data in pregnancy (n = 26) suggest that etravirine exposure during pregnancy increases 1.2-fold to 1.6-fold. Dosing in Pregnancy: • No change in dose indicated.	Variable placental transfer, usually in the moderate to high categories, ranging from 0.19–4.25 (data from 19 mother-infant pairs).[b] Insufficient data to assess for teratogenicity in humans. No evidence of teratogenicity in rats or rabbits.	December 7, 2018
Nevirapine (NVP) *Viramune Viramune XR (Extended Release)* **Note:** Generic available for some formulations	NVP (Viramune) *Tablets:* • 200 mg[d] *Oral Suspension:* • 50 mg/5 mL Viramune XR Tablets: • 100 mg • 400 mg[d]	Standard Adult Dose: • 200 mg once-daily Viramune (immediate release) for 14 days (lead-in period); thereafter, 200 mg twice daily or 400 mg (Viramune XR tablet) once daily, without regard to food. • Repeat lead-in period if therapy is discontinued for >7 days. • In patients who develop mild-to-moderate rash without constitutional symptoms during lead-in period, continue lead-in dosing until rash resolves, but administer for ≤28 days total. PK in Pregnancy: • PK of immediate release tablets is not significantly altered in pregnancy.	High placental transfer to fetus.[b] No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects and 2-fold increase in cardiovascular and genitourinary defects. Increased risk of symptomatic, often rash-associated, and potentially fatal liver toxicity among women with CD4 cell counts ≥250/mm^3 when first initiating therapy; pregnancy does not appear to increase risk. NVP should be initiated in pregnant women with CD4 cell counts ≥250 cells/mm^3 only when benefit clearly outweighs risk because of potential increased risk of	December 7, 2018

Table 10. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy[a] (page 9 of 21)

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations	Use in Pregnancy	Last Reviewed
Nevirapine, continued		• No data are available on extended release formulations in pregnancy. Dosing in Pregnancy: • No change in dose indicated.	life-threatening hepatotoxicity in women with high CD4 cell counts. Elevated transaminase levels at baseline may increase the risk of NVP toxicity. Women who become pregnant while taking NVP-containing regimens and who are tolerating their regimens well can continue therapy, regardless of CD4 cell count.	
Rilpivirine (RPV) *Edurant* (RPV/FTC/TDF) *Complera* (RPV/DTG) *Juluca* (RPV/FTC/TAF) *Odefsey*	RPV (Edurant) *Tablets:* • 25 mg RPV/FTC/TDF (Complera): • RPV 25 mg plus FTC 200 mg plus TDF 300 mg tablet RPV/DTG (Juluca): • RPV 25 mg plus DTG 50 mg tablet RPV/FTC/TAF (Odefsey): • RPV 25 mg plus FTC 200 mg plus TAF 25 mg tablet	Standard Adult Dose *RPV (Edurant):* • RPV 25 mg once daily with food *RPV/FTC/TDF (Complera):* • 1 tablet once daily with food *RPV/DTG (Juluca):* • 1 tablet once daily with food *RPV/FTC/TAF (Odefsey):* • 1 tablet once daily with food PK in Pregnancy: • RPV PK highly variable during pregnancy. RPV AUC and trough concentration reduced 20% to 50% lower in pregnancy than postpartum. While most pregnant women exceeded target exposure, those with detectable viral loads had lower RPV troughs. Dosing in Pregnancy: • While RPV plasma concentration is reduced during pregnancy, higher-than-standard doses have not been studied. Insufficient data are available to recommend a dosing change in pregnancy. With standard dosing, viral loads should be monitored more frequently. • For guidance about use of combination products in pregnancy, please see the specific sections on other components (i.e., DTG, FTC, TAF, TDF).	Moderate to high placental transfer to fetus.[b] No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects). 2-drug regimens (e.g., RPV/DTG FDC) **are not recommended** in pregnancy.	December 7, 2018

Table 10. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy[a] (page 10 of 21)

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations	Use in Pregnancy	Last Reviewed
PIs PIs are recommended for use in combination regimens with 2 NRTI drugs. Hyperglycemia, new onset or exacerbation of diabetes mellitus, and diabetic ketoacidosis reported with PI use; unclear if pregnancy increases risk. Conflicting data regarding preterm delivery in women receiving PIs (see Combination Antiretroviral Drug Regimens and Pregnancy Outcomes).				
Atazanavir (ATV) *Reyataz* **Note:** Generic available for some formulations. **Note:** ATV must be combined with low-dose RTV boosting in pregnancy. (ATV/COBI) *Evotaz*	ATV (Reyataz) *Capsules*: • 100 mg (generic product only) • 150 mg[d] • 200 mg[d] • 300 mg[d] *Oral Powder:* • 50 mg packet ATV/COBI (Evotaz): • ATV 300 mg plus COBI 150 mg tablet	Standard Adult Doses *ARV-Naive Patients* *Without RTV Boosting:* • ATV 400 mg once daily with food; ATV without RTV boosting **is not recommended** when used with TDF, H2-receptor antagonists, PPIs, or during pregnancy. *With RTV Boosting:* • ATV 300 mg plus RTV 100 mg once daily with food • When combined with EFV in ARV-naive patients: ATV 400 mg plus RTV 100 mg once daily with food *ARV-Experienced Patients:* • ATV 300 mg plus RTV 100 mg once daily with food • Do not use with PPIs or EFV *If Combined with an H2-Receptor Antagonist:* ATV 300 mg plus RTV 100 mg once daily with food *If Combined with an H2-Receptor Antagonist and TDF:* • ATV 400 mg plus RTV 100 mg once daily with food Powder Formulation: • Oral powder is taken with RTV once daily with food at the same recommended adult dose as the capsules. ATV/COBI (Evotaz): • 1 tablet once daily with food PK in Pregnancy *ATV (Reyataz):* • ATV concentrations reduced during pregnancy; further reduced when given concomitantly with TDF or H2-receptor antagonist. *ATV/COBI (Evotaz):* • No PK studies in human pregnancy. • For guidance about use of combination products in pregnancy, please see the specific sections on other components (i.e., COBI).	Low placental transfer to fetus.[b] No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects). Must be given as low-dose RTV-boosted regimen in pregnancy. Effect of *in utero* ATV exposure on infant indirect bilirubin levels is unclear. Nonpathologic elevations of neonatal hyperbilirubinemia have been observed in some, but not all, clinical trials to date. Oral powder (but *not* capsules) contains phenylalanine, which can be harmful to patients with phenylketonuria. ATV/COBI **is not recommended** for use in pregnancy. For women who become pregnant while taking ATV/COBI, consider switching to a more effective, recommended regimen. If an ATV/COBI regimen is continued, doses should be administered with food; viral load should be monitored frequently.	December 7, 2018

Table 10. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy[a] (page 11 of 21)

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations	Use in Pregnancy	Last Reviewed
Atazanavir, continued		Dosing in Pregnancy *ATV (Reyataz):* • Use of unboosted ATV **is not recommended** during pregnancy. • Use of ATV **is not recommended** for ARV-experienced pregnant women taking TDF *and* an H2-receptor antagonist. • Use of an increased dose (ATV 400 mg plus RTV 100 mg once daily with food) during the second and third trimesters results in plasma ATV concentrations equivalent to those seen in nonpregnant adults on standard dosing. Although some experts recommend increased ATV dosing in all women during the second and third trimesters, the package insert recommends increased ATV dosing only for ARV-experienced pregnant women in the second and third trimesters who are also receiving either TDF or an H2-receptor antagonist. *ATV/COBI (Evotaz):* • Insufficient data to make dosing recommendation in pregnancy (see Cobicistat section).		
Darunavir (DRV) *Prezista* **Note:** Must be combined with low-dose RTV or COBI boosting. (DRV/COBI) *Prezcobix* (DRV/COBI/FTC/TAF) *Symtuza*	DRV (Prezista): *Tablet:* • 75 mg • 150 mg • 600 mg • 800 mg *Oral Suspension:* • 100 mg/mL DRV/COBI (Prezcobix): • DRV 800 mg plus COBI 150 mg tablet DRV/COBI/FTC/TAF (Symtuza): • DRV 800 mg plus COBI 150 mg plus FTC 200 mg plus TAF 10 mg tablet	**Standard Adult Doses** ARV-Naive Patients: • DRV 800 mg plus RTV 100 mg once daily with food • DRV 800 mg plus COBI 150 mg once daily with food ARV-Experienced Patients: *If Patient Has No DRV Resistance Mutations:* • DRV 800 mg plus RTV 100 mg once daily with food • DRV 800 mg plus COBI 150 mg once daily with food *If Any DRV Resistance Mutations Are Present:* • DRV 600 mg plus RTV 100 mg twice daily with food *DRV/COBI (Prezcobix):* • 1 tablet once daily with food *DRV/COBI/FTC/TAF (Symtuza):* • 1 tablet once daily with food Dosing in Pregnancy: • The Panel **does not recommend** once-daily dosing with DRV/r during pregnancy or the use of DRV/c during pregnancy. Twice-daily DRV/r dosing (DRV 600 mg plus RTV 100 mg with food) is	Low placental transfer to fetus.[b] No evidence of teratogenicity in mice, rats, or rabbits. No evidence of human teratogenicity. Must be boosted with low-dose RTV. The Panel **does not recommend** once-daily dosing with DRV/COBI during pregnancy or the use of DRV/COBI during pregnancy. If a DRV/c regimen is continued during pregnancy, viral load should be monitored frequently.	December 7, 2018

Table 10. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy[a] (page 12 of 21)

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations	Use in Pregnancy	Last Reviewed
Darunavir, continued		recommended for all pregnant women. Increased twice-daily DRV dose (DRV 800 mg plus RTV 100 mg with food) during pregnancy does not result in an increase in darunavir exposure and **is not recommended**. PK in Pregnancy: • Decreased exposure in pregnancy with use of DRV/r. • For guidance about use of combination products in pregnancy, please see the specific sections on other components (i.e., COBI, FTC, TAF)		
Fosamprenavir (FPV) *Lexiva (a prodrug of amprenavir)* **Note:** Must be combined with low-dose RTV boosting in pregnancy.	FPV (Lexiva) *Tablets:* • 700 mg *Oral Suspension:* • 50 mg/mL	Standard Adult Doses *FPV (Lexiva)* *ARV-Naive Patients:* • FPV 1400 mg twice daily without food, *or* • FPV 1400 mg plus RTV 100 or 200 mg once daily without food, *or* • FPV 700 mg plus RTV 100 mg twice daily without food *PI-Experienced Patients:* • Once-daily dosing **is not recommended** • FPV 700 mg plus RTV 100 mg twice daily without food *Coadministered with EFV:* • FPV 700 mg plus RTV 100 mg twice daily without food; *or* • FPV 1400 mg plus RTV 300 mg once daily without food PK in Pregnancy: • With RTV boosting, AUC is reduced during the third trimester. However, exposure is greater during the third trimester with boosting than in nonpregnant adults without boosting, and trough concentrations achieved during the third trimester were adequate for patients without PI resistance mutations. Dosing in Pregnancy: • Use of unboosted FPV or once-daily FPV with RTV boosting **is not recommended** during pregnancy. No change is indicated in standard boosted twice-daily dose (FPV 700 mg plus RTV 100 mg twice daily without food).	FPV **should not** be used during pregnancy. Low placental transfer to fetus.[b] Insufficient data to assess for teratogenicity in humans. Increased fetal loss in rabbits, but no increase in defects in rats and rabbits.	December 7, 2018

Table 10. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy[a] (page 13 of 21)

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations	Use in Pregnancy	Last Reviewed
Indinavir (IDV) *Crixivan* **Note:** Must be combined with low-dose RTV boosting in pregnancy	IDV (Crixivan) *Capsules:* • 200 mg • 400 mg	Standard Adult Dose *Without RTV Boosting:* • IDV 800 mg every 8 hours, taken 1 hour before or 2 hours after meals; may be taken with skim milk or a low-fat meal. *With RTV Boosting:* • IDV 800 mg plus RTV 100 mg twice daily without regard to meals PK in Pregnancy: • IDV exposure markedly reduced when administered without RTV boosting during pregnancy. IDV exposure is low with IDV 400 mg/RTV 100 mg dosing during pregnancy; no PK data available on alternative boosted dosing regimens in pregnancy. Dosing in Pregnancy: • Use of unboosted IDV **is not recommended** during pregnancy.	Minimal placental transfer to fetus.[b] No evidence of human teratogenicity in cases reported to the Antiretroviral Pregnancy Registry (can rule out 2-fold increase in overall birth defects). Must be given as low-dose, RTV-boosted regimen in pregnancy. Theoretical concern regarding increased indirect bilirubin levels, which may exacerbate physiologic hyperbilirubinemia in neonates. Minimal placental passage mitigates this concern. Given the available alternative ARVs, IDV **is not recommended** for treatment of pregnant women in the United States.	December 7, 2018
Lopinavir/ Ritonavir (LPV/r) *Kaletra*	LPV/r (Kaletra) *Tablets (Coformulated):* • LPV/r 200 mg/50 mg • LPV/r 100 mg/25 mg *Oral Solution:* • LPV/r 400 mg/100 mg/5 mL	Standard Adult Dose: • LPV/r 400 mg/100 mg twice daily, *or* • LPV/r 800 mg/200 mg once daily *Tablets:* • Take without regard to food. *Oral Solution:* • Take with food. With EFV or NVP (PI-Naive or PI-Experienced Patients): • LPV/r 500 mg/125 mg tablets twice daily without regard to meals (use a combination of 2 LPV 200-mg plus RTV 50-mg tablets and 1 LPV 100-mg plus RTV 25-mg tablet), *or* • LPV/r 520 mg/130 mg oral solution (6.5 mL) twice daily with food	Low placental transfer to fetus.[b] No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects). Oral solution contains 42% alcohol and 15% propylene glycol and is not recommended for use in pregnancy. Once-daily LPV/r dosing **is not recommended** during pregnancy.	December 7, 2018

Table 10. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy[a] (page 14 of 21)

Generic Name (Abbreviation) *Trade Name*	**Formulation**	**Dosing Recommendations**	**Use in Pregnancy**	**Last Reviewed**
Lopinavir/ Ritonavir, continued		PK in Pregnancy: • With twice-daily dosing, LPV exposure is reduced in pregnant women receiving standard adult doses; increasing the dose by 50% results in exposure equivalent to that seen in nonpregnant adults receiving standard doses. • No PK data are available for once-daily dosing in pregnancy. Dosing in Pregnancy: • Once-daily dosing **is not recommended** during pregnancy. • Some experts recommend that an increased dose (i.e., LPV/r 600 mg/150 mg twice daily without regard to meals or LPV/r 500 mg/125 mg twice daily without regard to meals) should be used in the second and third trimesters, especially in PI-experienced pregnant women and women who start treatment during pregnancy with a baseline viral load >50 copies/mL. If standard dosing is used, monitor virologic response and, if available, LPV drug levels.		
Nelfinavir (NFV) *Viracept*	NFV (Viracept): *Tablets:* • 250 mg • 625 mg (tablets can be dissolved in a small amount of water) *Powder for Oral Suspension:* • 50 mg/g	Standard Adult Dose: • NFV 1250 mg twice daily, *or* • NFV 750 mg 3 times daily with food PK in Pregnancy: • Lower NFV exposure was observed during the third trimester than postpartum in women receiving NFV 1250 mg twice daily; however, adequate drug levels are generally achieved during pregnancy, although levels are variable in late pregnancy. Dosing in Pregnancy: • NFV 750 mg 3 times daily with food **is not recommended** during pregnancy. No change in standard dose (NFV 1250 mg twice daily with food) indicated.	NFV **should not** be used during pregnancy. Minimal to low placental transfer to fetus.[b] No evidence of human teratogenicity; can rule out 1.5-fold increase in overall birth defects and 2-fold increase in risk of cardiovascular and genitourinary birth defects. Contains aspartame; should not be used in individuals with phenylketonuria.	December 7, 2018

Table 10. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy[a] (page 15 of 21)

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations	Use in Pregnancy	Last Reviewed
Saquinavir (SQV) *Invirase* **Note:** Must be combined with low-dose RTV for PK boosting	SQV (Invirase) *Tablet:* • 500 mg *Capsule:* • 200 mg	Standard Adult Dose: • SQV 1000 mg plus RTV 100 mg twice a day with food or within 2 hours after a meal PK in Pregnancy: • Based on limited data, SQV exposure may be reduced in pregnancy, but this effect is not sufficient to warrant a dose change. Dosing in Pregnancy: • No change in dose indicated.	SQV **should not be used** during pregnancy. **Contraindicated** in patients with pre-existing cardiac conduction system disease. Baseline ECG recommended before starting, because PR and/or QT interval prolongations have been observed. Low placental transfer to fetus.[b] Insufficient data to assess for teratogenicity in humans. No evidence of teratogenicity in rats or rabbits. Must be boosted with low-dose RTV.	December 7, 2018
Tipranavir (TPV) *Aptivus* **Note:** Must be combined with RTV for PK boosting	TPV (Aptivus) *Capsules:* • 250 mg *Oral Solution:* • 100 mg/mL	Standard Adult Dose: • TPV/r 500 mg/200 mg twice daily *With RTV Tablets:* • Take with food. *With RTV Capsules or Solution:* • Take without regard to food; however, administering with food may help make the dose more tolerable. Dosing in Pregnancy: • Insufficient data to make dosing recommendation PK in Pregnancy: • Limited PK data in human pregnancy	TPV **should not be used** during pregnancy. Moderate placental transfer to fetus reported in 1 patient.[b] Insufficient data to assess teratogenicity in humans. No evidence of teratogenicity in rats or rabbits. Must be given as low-dose, RTV-boosted regimen.	December 7, 2018

Table 10. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy[a] (page 16 of 21)

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations	Use in Pregnancy	Last Reviewed
Entry and Attachment Inhibitors				
Enfuvirtide (T-20) *Fuzeon*	T-20 (Fuzeon) *Injectible:* • Supplied as lyophilized powder. Each vial contains 108 mg of T-20; reconstitute with 1 mL of sterile water for injection for SQ delivery of approximately 90 mg/1 mL.	T-20 is indicated for advanced HIV disease and must be used in combination with other ARV drugs to which the patient's virus is susceptible, as determined by resistance testing. Standard Adult Dose: • T-20 90 mg (1 mL) twice daily without regard to meals PK in Pregnancy: • No PK data in human pregnancy. Dosing in Pregnancy: • Insufficient data to make dosing recommendation.	Minimal to low placental transfer to fetus.[b] No data on human teratogenicity.	December 7, 2018
Ibalizumab (IBA) *Trogarzo*	IBA (Trogarzo) *Solution:* • Solution for IV infusion is available in single-dose vials	Standard Adult Dose *IBA (Trogarzo):* • IBA 2000-mg loading dose, followed by IBA 800-mg maintenance doses administered every 2 weeks Dosing in Pregnancy: • Insufficient data are available to make dosing recommendation. PK in Pregnancy: • No PK studies have been reported in human pregnancy.	No data are available, but placental transfer of IBA, a monoclonal antibody, is possible. Insufficient data are available to assess for teratogenicity in humans.	December 7, 2018
Maraviroc (MVC) *Selzentry*	MVC (Selzentry) *Tablets:* • 150 mg • 300 mg	Standard Adult Dose: • MVC 300 mg twice daily with or without food • MVC should only be used for patients with CCR5-tropic virus (and no X4-tropic virus). Dose Adjustments: • Increase to MVC 600 mg BID when used with potent CYP3A inducers: EFV, ETR, and rifampin. • Decrease to MVC 150 mg BID when used with CYP3A inhibitors: all PIs except TPV/r, itraconazole.	No evidence of teratogenicity in rats or rabbits; insufficient data to assess for teratogenicity in humans. MVC placental passage category should be moderate.[b]	December 7, 2018

Table 10. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy[a] (page 17 of 21)

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations	Use in Pregnancy	Last Reviewed
Maraviroc, continued		PK in Pregnancy: • A PK study in human pregnancy demonstrated a 20% to 30% overall decrease in AUC, but C_{trough} exceeded the recommended minimal concentration of 50 ng/mL. Dosing in Pregnancy: • Standard adult dosing adjusted for concomitant ARV use appears appropriate.		
Integrase Inhibitors				
Bictegravir/ Emtricitabine/ Tenofovir Alafenamide (BIC/FTC/TAF) *Biktarvy* **Note:** BIC is not available as a single-entity formulation.	BIC/FTC/TAF (Biktarvy): • BIC 50 mg plus FTC 200 mg plus TAF 25 mg tablet	Standard Adult Dose *BIC/FTC/TAF (Biktarvy):* • 1 tablet once daily with or without food Dosing in Pregnancy: • There is insufficient data to make a dosing recommendation. PK in Pregnancy: • No PK studies have been reported in human pregnancy. • For guidance about use of combination products in pregnancy, please see the specific sections on other components (i.e., FTC, TAF).	No data are available on placental transfer of BIC. Insufficient data to assess for teratogenicity in humans. No evidence of teratogenicity in rats or rabbits. To maximize BIC absorption, doses should not be administered within 2 hours of ingestion of any preparation containing minerals such as iron or calcium, including prenatal vitamins.	December 7, 2018

Table 10. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy[a] (page 18 of 21)

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations	Use in Pregnancy	Last Reviewed
Dolutegravir (DTG) *Tivicay* (DTG/RPV) *Juluca* (DTG/ABC/3TC) *Triumeq*	DTG (Tivicay) *Tablet:* • DTG 50 mg tablet DTG/RPV (Juluca): • DTG 50 mg plus RPV 25 mg tablet DTG/ABC/3TC (Triumeq): • DTG 50 mg plus ABC 600 mg plus 3TC 300 mg tablet	Standard Adult Doses *In ARV-Naive or ARV-Experienced (but Integrase Inhibitor-Naive) Patients* *DTG (Tivicay):* • 1 tablet once daily, without regard to food *DTG/RPV (Juluca):* • 1 tablet once daily with food *DTG/ABC/3TC (Triumeq):* • 1 tablet once daily, without regard to food *ARV-Naive or ARV-Experienced (but Integrase Inhibitor-Naive) if Given with EFV, FPV/r, TPV/r, or Rifampin; or Integrase Inhibitor-Experienced* *DTG (Tivicay):* • 1 tablet twice daily, without regard to food PK in Pregnancy: • AUC may be decreased during the third trimester compared with postpartum, but good viral suppression observed in third-trimester recipients. Dosing in Pregnancy: • No change in dose indicated. • For guidance about use of combination products in pregnancy, please see the specific sections on other components (i.e., ABC, 3TC, RPV)	High placental transfer to fetus.[b] No evidence of teratogenicity in mice, rats, or rabbits. Preliminary data suggest a possible increased risk of NTDs in infants born to women who initiated DTG prior to pregnancy and were receiving it at the time of conception. Dolutegravir **should not be initiated** during the first trimester of pregnancy (less than 14 weeks [up to 13 6/7 weeks] gestational age by LMP.) For more information see Interim Guidance about the Use of Dolutegravir in Pregnancy in Recommendations for Use of Antiretroviral Drugs During Pregnancy. To maximize DTG absorption, doses should not be administered within 2 hours of ingestion of any preparation containing minerals such as iron or calcium, including prenatal vitamins.	December 7, 2018
Elvitegravir (EVG) **Note:** As of October 2017, Vitekta (i.e., EVG as a single-entity formulation) is no longer available (EVG/COBI/FTC/TAF) *Genvoya* (EVG/COBI/FTC/TDF) *Stribild*	EVG/COBI/FTC/TAF (Genvoya): • EVG 150 mg plus COBI 150 mg plus FTC 200 mg plus TAF 10 mg tablet EVG/COBI/FTC/TDF (Stribild): • EVG 150 mg plus COBI 150 mg plus FTC 200 mg plus TDF 300 mg tablet	Standard Adult Dose (Genvoya and Stribild): • 1 tablet once daily with food Dosing in Pregnancy: • Insufficient data to make dosing recommendation PK in Pregnancy: • PK studies in women who received EVG/c demonstrated significant reduction in EVG plasma exposure during pregnancy.	Evidence of high placental transfer of EVG and low transfer of COBI.[b] Insufficient data to assess for teratogenicity in humans. No evidence of teratogenicity in rats or rabbits. EVG/COBI **is not recommended** for use in pregnancy. For women who become pregnant while taking EVG/c, consider switching to a more effective, recommended regimen. If an EVG/COBI regimen is continued, doses should not be administered within 2	December 7, 2018

Table 10. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy[a] (page 19 of 21)

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations	Use in Pregnancy	Last Reviewed
Elvitegravir, continued			hours of ingestion of any preparation containing minerals such as iron or calcium, including prenatal vitamins.	
Raltegravir (RAL) *Isentress* *Isentress HD*	RAL (Isentress) *Film-Coated Tablets:* • 400 mg *Chewable Tablets:* • 25 mg • 100 mg RAL (Isentress HD) *Film-Coated Tablets:* • 600 mg	Standard Adult Doses: • RAL 400-mg, film-coated tablets twice daily without regard to food • Two RAL 600-mg, film-coated tablets (1200 mg) once daily for ARV-naive patients or patients who are already virologically suppressed on an initial regimen of RAL 400 mg twice daily without regard to food • Chewable and oral suspension doses are not interchangeable with either film-coated tablets or each other *With Rifampin:* • Two RAL 400-mg, film-coated tablets (800 mg) twice daily without regard to food PK in Pregnancy: • Decreased drug concentrations in third trimester not of sufficient magnitude to warrant a change in dosing. Dosing in Pregnancy: • No change in dose is indicated. • Once-daily dosing (i.e., two RAL 600-mg, film-coated tablets) **should not be used** in pregnant women until more information is available.	High placental transfer to fetus.[b] No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects). Case report of markedly elevated liver transaminases with RAL use in late pregnancy. Severe, potentially life-threatening, and fatal skin and HSRs have been reported in nonpregnant adults. Chewable tablets contain phenylalanine. To maximize RAL absorption, doses should not be administered within 2 hours of ingestion of any preparation containing minerals such as iron or calcium, including prenatal vitamins.	December 7, 2018

Table 10. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy[a] (page 20 of 21)

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations	Use in Pregnancy	Last Reviewed
Pharmaco-Enhancers				
Cobicistat (COBI) *Tybost* (ATV/COBI) *Evotaz* (EVG/COBI/FTC/TAF) *Genvoya* (DRV/COBI) *Prezcobix* (EVG/COBI/FTC/TDF) *Stribild* (DRV/COBI/FTC/TAF) *Symtuza*	COBI (Tybost) *Tablet:* • COBI 150 mg ATV/COBI (Evotaz): • ATV/COBI 300 mg/50 mg tablet EVG/COBI/FTC/TAF (Genvoya): • EVG 150 mg plus COBI 150 mg plus FTC 200 mg plus TAF 10 mg tablet DRV/COBI (Prezcobix): • DRV/COBI 800 mg/150 mg tablet EVG/COBI/FTC/TDF (Stribild): • EVG 150 mg plus COBI 150 mg plus FTC 200 mg plus TDF 300 mg tablet DRV/COBI/FTC/TAF (Symtuza): • DRV 800 mg plus COBI 150 mg plus FTC 200 mg plus TAF 10 mg tablet	Standard Adult Doses *COBI (Tybost):* • As an alternative PK booster with ATV or DRV: 1 tablet (150 mg) once daily with food *ATV/COBI (Evotaz):* • 1 tablet once daily with food *EVG/COBI/FTC/TAF (Genvoya):* • 1 tablet once daily with food *DRV/COBI (Prezcobix):* • 1 tablet once daily with food *EVG/COBI/FTC/TDF (Stribild):* • 1 tablet once daily with food *DRV/COBI/FTC/TAF (Symtuza):* • 1 tablet once daily with food PK in Pregnancy: • Based on limited data, COBI exposure and pharmaco-enhancing effect on DRV and EVG are markedly reduced in pregnancy. • No data are available on the pharmaco-enhancing effect of COBI on ATV. • When coadministered with COBI, TAF exposure is not significantly different between pregnancy and the postpartum period. Dosing in Pregnancy: • While COBI exposure is markedly reduced during pregnancy, higher than standard doses have not been studied. The Panel recommends RTV as the preferred pharmaco-enhancer for PIs and INSTIs during pregnancy until more data are available on COBI activity during pregnancy. • For guidance about the use of combination products in pregnancy, please see the specific sections on other components (i.e., FTC, TAF, TDF, ATV, DRV, EVG).	Low placental transfer to fetus.[b] Insufficient data to assess for teratogenicity in humans. No evidence of teratogenicity in rats or rabbits. Use of COBI-boosted ATV, DRV, or EVG **is not recommended** in pregnancy.	December 7, 2018

Table 10. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy[a] (page 21 of 21)

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations	Use in Pregnancy	Last Reviewed
Ritonavir (RTV) *Norvir*	RTV (Norvir) *Capsules:* • 100 mg *Tablets:* • 100 mg *Oral Solution:* • 80 mg/mL *Powder:* • 100 mg/sachet	Standard Adult Dose as PK Booster for Other PIs: • RTV 100–400 mg per day in 1–2 divided doses (refer to other PIs for specific dosing recommendations.) *Tablet:* • Take with food. *Capsule or Oral Solution:* • To improve tolerability, take with food if possible. PK in Pregnancy: • Lower levels seen during pregnancy than during postpartum. Dosing in Pregnancy: • No dosage adjustment necessary when used as booster.	Low placental transfer to fetus.[b] No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects). Should only be used as low-dose booster for other PIs. Oral solution contains 43% alcohol and is therefore not recommended during pregnancy, because there is no known safe level of alcohol exposure during pregnancy.	December 7, 2018

[a] Individual ARV drug dosages may need to be adjusted in patients with renal or hepatic insufficiency (for details, see the Adult and Adolescent Guidelines, Appendix B, Table 8).

[b] Placental transfer categories are determined by mean or median cord blood/maternal delivery plasma drug ratio:

High: >0.6 **Moderate:** 0.3–0.6 **Low:** <0.3

[c] Only indicated for use in chronic HBV virus infection in adults.

[d] Generic formulation available

[e] WHO recommends maximum dose of 30 mg twice daily regardless of weight.

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; ATV/r = atazanavir/ritonavir; AUC = area under the curve; BIC = bictegravir; CD4 = CD4 T lymphocyte; COBI = cobicistat; d4T = stavudine; ddI = didanosine; DOR = doravirine; DRV = darunavir; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG = elvitegravir; FDA = Food and Drug Administration; FDC = fixed-dose combination; FPV = fosamprenavir; FPV/r = fosamprenavir/ritonavir; FTC = emtricitabine; HBV = hepatitis b virus; HSR = hypersensitivity reaction; IBA =ibalizumab; IDV = indinavir; IDV/r = indinavir/ritonavir; INSTI = integrase strand transfer inhibitor; LPV/r = lopinavir/ritonavir; MVC = maraviroc; NFV = nelfinavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NTD = neural tube defect; NVP = nevirapine; PI = protease inhibitor; PK = pharmacokinetic; PPI = proton pump inhibitor; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SQ = subcutaneous; SQV = saquinavir; SQV/r = saquinavir/ritonavir; T-20 = enfuvirtide; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TID = 3 times a day; TPV = tipranavir; TPV/r = tipranavir/ritonavir; WHO = World Health Organization; ZDV = zidovudine

Supplement: Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy

Glossary of Terms for Supplement
Carcinogenic: Producing or tending to produce cancer • Some agents, such as certain chemicals or forms of radiation, are both mutagenic and clastogenic. • Genetic mutations and/or chromosomal damage can contribute to cancer formation.
Clastogenic: Causing disruption of or breakages in chromosomes
Genotoxic: Damaging to genetic material such as DNA and chromosomes
Mutagenic: Inducing or capable of inducing genetic mutation
Teratogenic: Interfering with fetal development and resulting in birth defects

Nucleoside and Nucleotide Analogue Reverse Transcriptase Inhibitors

Data are available from clinical trials in human pregnancy for the nucleoside reverse transcriptase inhibitors (NRTIs) zidovudine, abacavir, lamivudine, didanosine, emtricitabine, and stavudine and the nucleotide NRTI tenofovir disoproxil fumarate (TDF). The nucleoside analogue drugs require three intracellular phosphorylation steps to form the triphosphate nucleoside, which is the active drug moiety. TDF, an acyclic nucleotide analogue drug, contains a monophosphate component attached to the adenine base and, hence, requires only two phosphorylation steps to form the active moiety.

For information regarding the nucleoside analogue drug class and potential mitochondrial toxicity in pregnancy and to the infant, see Recommendations for Use of Antiretroviral Drugs During Pregnancy and Long-Term Follow-Up of Infants Exposed to Antiretroviral Drugs.

Abacavir (Ziagen, ABC)

(Last updated December 7, 2018; last reviewed December 7, 2018)

The available human and animal data suggest that abacavir does not increase the risk of major birth defects overall compared with the background rate.[1]

Animal Studies

Carcinogenicity

Abacavir is mutagenic and clastogenic in some *in vitro* and *in vivo* assays. In long-term carcinogenicity studies in mice and rats, malignant tumors of the preputial gland of males and the clitoral gland of females were observed in both species, and malignant hepatic tumors and nonmalignant hepatic and thyroid tumors were observed in female rats. The tumors were seen in rodents at doses that were 6 to 32 times that of human therapeutic exposure.[1]

Reproduction/Fertility

No effect of abacavir on reproduction or fertility in male and female rodents has been seen at doses of up to 500 mg/kg/day (about 8 times that of human therapeutic exposure based on body surface area).

Teratogenicity/Adverse Pregnancy Outcomes

Abacavir is associated with developmental toxicity (decreased fetal body weight and reduced crown-rump length) and increased incidence of fetal anasarca and skeletal malformations in rats treated with abacavir during organogenesis at doses of 1000 mg/kg (about 35 times that of human therapeutic exposure based on area under the curve [AUC]). Toxicity to the developing embryo and fetus (i.e., increased resorptions and decreased fetal body weight) occurred with administration of abacavir 500 mg/kg/day to pregnant rodents. The offspring of female rats were treated with abacavir 500 mg/kg, beginning at embryo implantation and

ending at weaning. In these animals, an increased incidence of stillbirth and lower body weight was seen throughout life. However, in rabbits, no evidence of drug-related developmental toxicity was observed and no increase in fetal malformations was observed at doses up to abacavir 700 mg/kg (about 8.5 times that of human therapeutic exposure).[1]

Placental and Breast Milk Passage

Abacavir crosses the placenta and is excreted into the breast milk of lactating rats.[1]

Human Studies in Pregnancy

Pharmacokinetics

In pregnant women, pharmacokinetic (PK) studies of abacavir 300 mg twice daily[2] and 600 mg daily concluded[3] that the PKs during pregnancy are equivalent to the PKs observed during the postpartum period. A population PK study (that analyzed 266 plasma samples from 150 pregnant women) found no effect of any co-variate (including age, body weight, pregnancy or gestational age) on abacavir PKs.[4] Thus, no dose adjustment for abacavir is needed during pregnancy.

Placental and Breast Milk Passage

Placental transfer of abacavir is high, with ratios of cord blood to maternal plasma concentration at delivery of approximately 1.0.[2,5] In the Mma Bana study,[6] the median breast milk-to-plasma ratio for abacavir was 0.85 in the 15 women tested at 1 month postpartum, and the drug was detected in the plasma of one out of nine breastfeeding infants whose mothers were receiving abacavir.

Teratogenicity/Adverse Pregnancy Outcomes

In the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposures to abacavir in humans have been monitored to be able to detect at least a 1.5-fold increase in risk of overall birth defects. No such increase in birth defects has been observed with abacavir. Among cases of first-trimester abacavir exposure reported to the Antiretroviral Pregnancy Registry, the prevalence of birth defects was 2.83% (32 out of 1,131 births; 95% CI, 1.94% to 3.97%).[7] This prevalence is similar to the prevalence of birth defects in the U.S. population, which is 2.72%, according to Centers for Disease Control and Prevention surveillance. First-trimester exposure to abacavir was not associated with birth defects in the SMARTT study (adjusted odds ratio [aOR] 0.94 [0.53–1.65]),[8] in the French Perinatal Study (aOR 1.01 [0.73–1.41]),[9] or in a series of 897 births to women with HIV in Spain between 2000 and 2009 (aOR 0.99 [0.34–2.87]).[10]

Safety

Serious hypersensitivity reactions have been associated with abacavir therapy in nonpregnant adults, but these reactions have rarely been fatal; symptoms include fever, skin rash, fatigue, and gastrointestinal symptoms such as nausea, vomiting, diarrhea, or abdominal pain. Abacavir should not be restarted following a hypersensitivity reaction, because more severe symptoms will occur within hours and may include life-threatening hypotension and death. Patients who test positive for HLA-B*5701 are at the highest risk of hypersensitivity reactions and should not receive abacavir; HLA screening should be done before initiation of abacavir. Two meta-analyses have confirmed the association between this genotype and the hypersensitivity reaction.[11,12]

In the PHACS/SMARTT cohort (median follow-up: 2.4 years), after adjusting for birth cohort and other factors, use of abacavir by the mother during pregnancy led to no increase in the likelihood of adverse events for the infant in the following domains: metabolic, growth and development, cardiac, neurological, neurodevelopmental.[13]

Excerpt from Table 10[a]

Note: When using FDCs, refer to other sections in Appendix B and Table 10 for information about the dosing and safety of individual drug components of the FDC during pregnancy.

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations	Use in Pregnancy
Abacavir (ABC) *Ziagen* (ABC/3TC) *Epzicom* (ABC/3TC/ZDV) *Trizivir* (ABC/DTG/3TC) *Triumeq* **Note:** Generics are available for some formulations.	ABC (Ziagen)[d] *Tablet:* • 300 mg *Solution:* • 20 mg/mL ABC/3TC (Epzicom):[d] • ABC 600 mg plus 3TC 300 mg tablet ABC/3TC/ZDV (Trizivir):[d] • ABC 300 mg plus 3TC 150 mg plus ZDV 300 mg tablet ABC/DTG/3TC (Triumeq): • ABC 600 mg plus 3TC 300 mg plus DTG 50 mg tablet	Standard Adult Doses *ABC (Ziagen):* • ABC 300 mg twice daily or ABC 600 mg once daily, without regard to food *ABC/3TC (Epzicom):* • 1 tablet once daily without regard to food *ABC/3TC/ZDV (Trizivir):* • 1 tablet twice daily without regard to food *ABC/DTG/3TC (Triumeq):* • 1 tablet daily without regard to food Dosing in Pregnancy: • No change in dose indicated. PK in Pregnancy: • PK not significantly altered in pregnancy. • For guidance about use of combination products in pregnancy, please see the specific sections on other components (i.e., 3TC, ZDV, DTG).	High placental transfer to fetus.[b] No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects). HSRs occur in approximately 5% to 8% of nonpregnant individuals. A small percentage of reactions are fatal, and these fatal reactions are usually associated with re-challenge. Rate of reactions during pregnancy is unknown. Testing for HLA-B*5701 identifies patients at risk of reactions and should be done and documented as negative before starting ABC. Patients should be educated regarding symptoms of HSR.

[a] Individual ARV drug dosages may need to be adjusted in patients with renal or hepatic insufficiency (for details, see the Adult and Adolescent Guidelines. Appendix B, Table 8).

[b] Placental transfer categories are determined by mean or median cord blood/maternal delivery plasma drug ratio:

High: >0.6 **Moderate:** 0.3–0.6 **Low:** <0.3

[d] Generic formulation available.

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; DTG = dolutegravir; HSR = hypersensitivity reactions; PK = pharmacokinetic; ZDV = zidovudine

References

1. Abacavir [package insert]. Food and Drug Administration. 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/020977s033s034,020978s036s037lbl.pdf.
2. Best BM, Mirochnick M, Capparelli EV, et al. Impact of pregnancy on abacavir pharmacokinetics. *AIDS*. 2006;20(4):553-560. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16470119.
3. Schalkwijk S, Colbers A, Konopnicki D, et al. The pharmacokinetics of abacavir 600 mg once daily in HIV-1-positive pregnant women. *AIDS*. 2016;30(8):1239-1244. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26836789.
4. Fauchet F, Treluyer JM, Preta LH, et al. Population pharmacokinetics of abacavir in pregnant women. *Antimicrob Agents Chemother*. 2014;58(10):6287-6289. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25070097.
5. Chappuy H, Treluyer JM, Jullien V, et al. Maternal-fetal transfer and amniotic fluid accumulation of nucleoside analogue reverse transcriptase inhibitors in human immunodeficiency virus-infected pregnant women. *Antimicrob Agents Chemother*. 2004;48(11):4332-4336. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15504861.
6. Shapiro RL, Rossi S, Ogwu A, et al. Therapeutic levels of lopinavir in late pregnancy and abacavir passage into breast milk in the Mma Bana Study, Botswana. *Antivir Ther*. 2013;18(4):585-590. Available at: http://www.ncbi.nlm.nih.gov/

pubmed/23183881.

7. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral pregnancy registry international interim report for 1 January 1989–31 January 2018. Wilmington, NC: Registry Coordinating Center. 2018. Available at: http://www.apregistry.com/.
8. Williams PL, Crain MJ, Yildirim C, et al. Congenital anomalies and *in utero* antiretroviral exposure in human immunodeficiency virus-exposed uninfected infants. *JAMA Pediatr*. 2015;169(1):48-55. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25383770.
9. Sibiude J, Le Chenadec J, Bonnet D, et al. *In utero* exposure to zidovudine and heart anomalies in the ANRS French perinatal cohort and the nested PRIMEVA randomized trial. *Clin Infect Dis*. 2015. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25838291.
10. Prieto LM, Gonzalez-Tome MI, Munoz E, et al. Birth defects in a cohort of infants born to HIV-infected women in Spain, 2000-2009. *BMC Infect Dis*. 2014;14:700. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25808698.
11. Sousa-Pinto B, Pinto-Ramos J, Correia C, et al. Pharmacogenetics of abacavir hypersensitivity: A systematic review and meta-analysis of the association with HLA-B*57:01. *J Allergy Clin Immunol*. 2015;136(4):1092-1094 e1093. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25934581.
12. Tangamornsuksan W, Lohitnavy O, Kongkaew C, et al. Association of HLA-B*5701 genotypes and abacavir-induced hypersensitivity reaction: a systematic review and meta-analysis. *J Pharm Pharm Sci*. 2015;18(1):68-76. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25877443.
13. Williams PL, Hazra R, Van Dyke RB, et al. Antiretroviral exposure during pregnancy and adverse outcomes in HIV-exposed uninfected infants and children using a trigger-based design. *AIDS*. 2016;30(1):133-144. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26731758.

Didanosine (Videx, ddI)

(Last updated December 7, 2018; last reviewed December 7, 2018)

Didanosine is classified as Food and Drug Administration (FDA) Pregnancy Category B.[1]

Didanosine **is not recommended** for use in pregnant women with HIV due to its toxicity.

Animal Studies

Carcinogenicity

Didanosine is both mutagenic and clastogenic in several *in vitro* and *in vivo* assays. Long-term animal carcinogenicity screening studies of 0.7 times to 1.7 times human exposure in mice and 3 times human exposure in rats have been negative.[1]

Reproduction/Fertility

At approximately 12 times the estimated human exposure, didanosine was slightly toxic to female rats and their pups during mid and late lactation. These rats showed reduced food intake and body weight gains; however, the physical and functional development of the offspring was not impaired and there were no major changes in the F2 generation.

Teratogenicity/Adverse Pregnancy Outcomes

No evidence of teratogenicity or toxicity was observed in pregnant rats and rabbits with exposures of didanosine that were 12 times and 14 times, respectively, the exposures seen in humans.

Placental and Breast Milk Passage

A study in rats showed that didanosine and/or its metabolites are transferred to the fetus through the placenta.

Human Studies in Pregnancy

Pharmacokinetics

A Phase 1 study (PACTG 249) of didanosine was conducted in 14 pregnant women with HIV who were enrolled at gestational age 26 to 36 weeks and treated through 6 weeks postpartum.[2] The drug was well tolerated during pregnancy by the women and the fetuses. Pharmacokinetic (PK) parameters after oral administration were not significantly affected by pregnancy, and dose modification from the usual adult dosage is not needed.

Placental and Breast Milk Passage

Placental transfer of didanosine was low-moderate in a Phase 1/2 safety and PK study.[2] This was confirmed in a study of 100 pregnant women with HIV who were receiving nucleoside reverse transcriptase inhibitors (NRTIs), generally as part of a two- or three-drug combination antiretroviral (ARV) regimen. At the time of delivery, cord-to-maternal-blood ratio for didanosine (n = 10) was 0.38 (range 0.0–2.0). In 15 of 24 samples (62%), cord blood concentrations for didanosine were below the limits of detection.[3]

It is not known whether didanosine is excreted in human breast milk.

Teratogenicity/Adverse Pregnancy Outcomes

The French Perinatal Cohort reported that head and neck birth defects were associated with first-trimester exposure to didanosine (0.5%, adjusted odds ratio [aOR] 3.4, 95% CI, 1.1–10.4, $P = 0.04$).[4] Though the PHACS/SMARTT cohort found no association between any individual NRTIs and birth defects, after adjusting for birth cohort and other factors, didanosine administered in combination with stavudine was associated with an overall increase in congenital abnormalities;[5] it should be noted that the combination of didanosine and stavudine **should not be used** in pregnant women with HIV (or anyone with HIV) because of a higher risk of toxicity. Among 897 births to women with HIV in a Spanish cohort, there was no significant difference between the rate of birth defects after first-trimester exposure and the rate of birth defects after second- and third-trimester exposure (odds ratio [OR] 0.61, 95% CI, 0.16–2.27).[6] In the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposures to didanosine in humans have been monitored to be able to detect at least a 2-fold increase in

the risk of overall birth defects.[7] Among cases of first-trimester didanosine exposure reported to the Antiretroviral Pregnancy Registry, prevalence of birth defects was 4.68% (20 of 427 births; 95% CI, 2.88% to 7.14%) compared with 2.72% in the U.S. population, based on Centers for Disease Control and Prevention surveillance.[7] All defects were reviewed in detail by the Registry, and no pattern of defects was discovered. The rate and types of defects will continue to be closely monitored.

Safety

Lactic acidosis, fatal in some cases, has been described in pregnant women receiving the combination of didanosine and stavudine along with other ARV agents;[8-10] the FDA and Bristol-Myers Squibb have issued a warning to health care professionals that pregnant women may be at increased risk of fatal lactic acidosis when prescribed didanosine and stavudine in combination.

The PHACS/SMARTT cohort found that after adjusting for birth cohort and other factors, didanosine administered in combination with stavudine was associated with the occurrence of neurodevelopmental disability. However, there was no increase in the likelihood of adverse events in the following domains with didanosine alone: metabolic, growth and development, cardiac, neurological, neurodevelopmental, behavior, language, and hearing.[11,12] As noted above, the combination of didanosine and stavudine should not be used in pregnant women with HIV (or anyone with HIV) because of a high risk of toxicity.

In a multivariate analysis of the association between *in utero* ARV exposure and risk of cancer in HIV-exposed, uninfected infants, the French Perinatal Study reported a 5.5-fold (95% CI, 2.1–14.4) increase in cancer incidence with first-trimester didanosine exposure.[13]

Excerpt from Table 10[a]

Generic Name (Abbreviation) *Trade Name*	**Formulation**	**Dosing Recommendations**	**Use in Pregnancy**
Didanosine (ddI) *Videx* *Videx EC*	ddI (Videx) *Buffered Tablets (Non-EC):* • No longer available *Solution:* • 10 mg/mL oral solution Videx EC (EC Beadlets) Capsules: • 125 mg • 200 mg • 250 mg • 400 mg Generic Delayed-Release Capsules: • 200 mg • 250 mg • 400 mg	Standard Adult Doses *Body Weight ≥60 kg:* • ddI 400 mg once daily *With TDF:* • ddI 250 mg once daily; take 1/2 hour before or 2 hours after a meal. *Body Weight <60 kg:* • ddI 250 mg once daily *With TDF:* • ddI 200 mg once daily; take 1/2 hour before or 2 hours after a meal. **Note:** Preferred dosing with oral solution is twice daily (total daily dose divided into 2 doses). Take 1/2 hour before or 2 hours after a meal. Dosing in Pregnancy: • No change in dose indicated. PK in Pregnancy: • PK is not significantly altered in pregnancy.	ddI **is not recommended** for pregnant women. Low-moderate placental transfer to fetus.[b] ddI **should not be used** with d4T. Lactic acidosis, sometimes fatal, has been reported in pregnant women receiving ddI and d4T together.

[a] Individual ARV drug dosages may need to be adjusted in patients with renal or hepatic insufficiency (for details, see the Adult and Adolescent Guidelines. Appendix B, Table 8).

[b] Placental transfer categories are determined by mean or median cord blood/maternal delivery plasma drug ratio:

High: >0.6 **Moderate:** 0.3–0.6 **Low:** <0.3

Key to Acronyms: ARV = antiretroviral; d4T = stavudine; ddI = didanosine; EC = enteric coated; FDC = fixed-dose combination; PK = pharmacokinetic; TDF = tenofovir disoproxil fumarate

References

1. Didanosine [package insert]. Food and Drug Administration. 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021183s028lbl.pdf.
2. Wang Y, Livingston E, Patil S, et al. Pharmacokinetics of didanosine in antepartum and postpartum human immunodeficiency virus-infected pregnant women and their neonates: an AIDS clinical trials group study. *J Infect Dis*. 1999;180(5):1536-1541. Available at: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=10515813.
3. Chappuy H, Treluyer JM, Jullien V, et al. Maternal-fetal transfer and amniotic fluid accumulation of nucleoside analogue reverse transcriptase inhibitors in human immunodeficiency virus-infected pregnant women. *Antimicrob Agents Chemother*. 2004;48(11):4332-4336. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15504861.
4. Sibiude J, Mandelbrot L, Blanche S, et al. Association between prenatal exposure to antiretroviral therapy and birth defects: an analysis of the French perinatal cohort study (ANRS CO1/CO11). *PLoS Med*. 2014;11(4):e1001635. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24781315.
5. Williams PL, Crain M, Yildirim C, et al. Congenital anomalies and *in utero* antiretroviral exposure in HIV-exposed uninfected infants. *JAMA*. 2015. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4286442/.
6. Prieto LM, Gonzalez-Tome MI, Munoz E, et al. Birth defects in a cohort of infants born to HIV-infected women in Spain, 2000–2009. *BMC Infect Dis*. 2014;14:700. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25808698.
7. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral Pregnancy Registry international interim report 1 January 1989–31 January 2018. Wilmington, NC: Registry Coordinating Center. 2018. Available at: http://www.apregistry.com/.
8. Mandelbrot L, Kermarrec N, Marcollet A, et al. Case report: nucleoside analogue-induced lactic acidosis in the third trimester of pregnancy. *AIDS*. 2003;17(2):272-273. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12545093.
9. Sarner L, Fakoya A. Acute onset lactic acidosis and pancreatitis in the third trimester of pregnancy in HIV-1 positive women taking antiretroviral medication. *Sex Transm Infect*. 2002;78(1):58-59. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11872862.
10. Bristol-Myers Squibb Company. Healthcare provider important drug warning letter. 2001. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2002/21183s1ltr.pdf
11. Williams PL, Hazra R, Van Dyke RB, et al. Antiretroviral exposure during pregnancy and adverse outcomes in HIV-exposed uninfected infants and children using a trigger-based design. *AIDS*. 2016;30(1):133-144. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26731758.
12. Van Dyke RB, Chadwick EG, Hazra R, Williams PL, Seage GR 3rd. The PHACS SMARTT study: assessment of the safety of in utero exposure to antiretroviral drugs. *Front Immunol*. 2016;7:199. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27242802.
13. Hleyhel M, Goujon S, Delteil C, et al. Risk of cancer in children exposed to didanosine *in utero*. *AIDS*. 2016;30(8):1245-1256. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26854809.

Emtricitabine (Emtriva, FTC)

(Last updated December 7, 2018; last reviewed December 7, 2018)

Emtricitabine is classified as Food and Drug Administration Pregnancy Category B.

Animal Studies

Carcinogenicity

Emtricitabine was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests. In long-term carcinogenicity studies of oral emtricitabine, no drug-related increases in tumor incidence were found in mice (at doses up to 26 times the human systemic exposure) or in rats (at doses up to 31 times the human systemic exposure) at the therapeutic dose.[1]

Reproduction/Fertility

No effect of emtricitabine on reproduction or fertility was observed with doses that produced systemic drug exposures (as measured by area under the curve [AUC]) that were approximately 60-fold higher in female and male mice and 140-fold higher in male rats than human exposure at the recommended therapeutic dose.[1]

Teratogenicity/Adverse Pregnancy Outcomes

No fetal variations or malformations were observed with emtricitabine dosing in mice that resulted in systemic drug exposure 60-fold higher than that observed in humans at recommended doses or in rabbits with dosing resulting in drug exposure 120-fold higher than human exposure.[1]

Placental and Breast Milk Passage

Emtricitabine has been shown to cross the placenta in mice and rabbits; the average fetal/maternal drug concentration was 0.4 in mice and 0.5 in rabbits.[2]

Human Studies in Pregnancy

Pharmacokinetics

In the IMPAACT P1026s study, emtricitabine exposure was modestly lower during the third trimester (geometric mean 8.0 mcg*h/mL; 90% CI, 7.1–8.9) than during the postpartum period (9.7 mcg*h/mL; 90% CI, 8.6–10.9). Fifty-eight percent of pregnant women (15 of 26 women) versus 95% of postpartum women (21 of 22 women) met the AUC target (≤30% reduction from typical exposure for nonpregnant historical controls). Trough emtricitabine levels were also lower during pregnancy (C_{24} geometric mean concentration [GMT] 58 ng/mL; 90% CI, 37–63) than during the postpartum period (C_{24} GMT 85 ng/mL; 90% CI, 70–100).[3] Similar differences in pharmacokinetic parameters of emtricitabine were found among women during pregnancy or after delivery in the PACTG 394 study[4] and in a European study.[5,6] The increase in emtricitabine clearance during pregnancy correlated with the normal pregnancy-related increase in glomerular filtration rate.[6] These changes are not believed to be large enough to warrant dose adjustment during pregnancy.

Placental and Breast Milk Passage

Emtricitabine has been shown to have high placental transfer in pregnant women. In a study of 15 women who received emtricitabine during pregnancy, the mean cord-to-maternal-blood ratio was 1.2 (90% CI, 1.0–1.5).[3] In eight women who were given a single dose of emtricitabine 600 mg with tenofovir disoproxil fumarate (TDF) 900 mg, the median cord blood emtricitabine concentration was 717 ng/mL (range 21–1,072), and the median cord blood/maternal plasma ratio was 0.85 (range 0.46–1.07).[4]

Emtricitabine is excreted into human milk. Among women in Uganda and Nigeria who were taking first-line antiretroviral therapy that contained emtricitabine 200 mg, emtricitabine concentrations in breast milk peaked later than they did in maternal plasma (at 4–8 hours compared with 2–4 hours) and were three-fold higher than maternal plasma concentrations. Emtricitabine was detectable in three infants (19%).[7] In a study in the Ivory

Coast, five women with HIV who exclusively breastfed their newborn infants were given emtricitabine 400 mg, TDF 600 mg, and nevirapine 200 mg at onset of labor, followed by emtricitabine 200 mg and TDF 300 mg once daily for 7 days postpartum. The median minimal and maximal concentrations of emtricitabine in breast milk were 177 ng/mL and 679 ng/mL, respectively (interquartile ranges [IQR] 105–254 ng/mL and 658–743 ng/mL, respectively), well above the estimated emtricitabine IC_{50} for HIV-1.[8] In a study of 50 women without HIV who received 200 mg emtricitabine and 300 mg TDF orally daily as pre-exposure prophylaxis (PrEP), median peak and trough breast milk concentrations of emtricitabine were 212.5 ng/mL (IQR 140.0–405.0) and 183.0 ng/mL (IQR 113.0–250.0), respectively. Emtricitabine was detectable in 47 of 49 infants at a median (IQR) concentration of 13.2 ng/mL (9.3–16.7), corresponding to estimated daily infant ingestion of a 31.9-mcg/kg dose (IQR 21.0–60.8) of emtricitabine, or 0.5% of the daily dose for treating infants.[9]

Teratogenicity/Adverse Pregnancy Outcomes

A study of pregnancies conducted during an HIV PrEP trial randomized participants without HIV to receive placebo, TDF, or TDF plus emtricitabine. No increase in the incidence of congenital anomalies was observed in the TDF-plus-emtricitabine arm.[10] There was no overall difference between the rate of pregnancy loss in the TDF-plus-emtricitabine arm and the rate of pregnancy loss in the TDF-alone arm of this PrEP study. In the U.S. PHACS/SMARTT cohort study, emtricitabine exposure was not associated with an increase in specific or overall birth defect risk.[11] In a large French cohort, emtricitabine exposure in the first trimester was associated with lower risk of birth defects.[12] In the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposures to emtricitabine in humans have been monitored to be able to detect at least a 1.5-fold increased risk of overall birth defects and a two-fold increase in cardiovascular and genitourinary defects (the most common classes). No such increase in birth defects has been observed with emtricitabine. Among cases of first-trimester emtricitabine exposure reported to the Antiretroviral Pregnancy Registry , the prevalence of birth defects was 2.44% (68 of 2,785 births; 95% CI, 1.90% to 3.09%), compared with a 2.72% total prevalence in the U.S. population, based on Centers for Disease Control and Prevention surveillance.[13]

Other Safety Information

In the U.S. PHACS/SMARTT cohort study, after adjusting for birth cohort and other factors, maternal use of emtricitabine led to no increase in the likelihood of adverse metabolic, growth and development, cardiac, neurological, or neurodevelopmental outcomes.[14]

Excerpt from Table 10[a]

Note: When using FDCs, refer to other sections in Appendix B and Table 10 for information about the dosing and safety of individual drug components of the FDC during pregnancy.

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations	Use in Pregnancy
Emtricitabine (FTC) *Emtriva* (FTC/TDF) *Truvada* (FTC/EFV/TDF) *Atripla* (FTC/RPV/TDF) *Complera* (FTC/EVG/COBI/TDF) *Stribild* (FTC/TAF) *Descovy* (FTC/RPV/TAF) *Odefsey* (FTC/EVG/COBI/TAF) *Genvoya* (FTC/BIC/TAF) *Biktarvy* (FTC/DRV/COBI/TAF) *Symtuza*	FTC (Emtriva) *Capsule:* • 200 mg *Oral Solution:* • 10 mg/mL FTC/TDF (Truvada): • FTC 200 mg plus TDF 300 mg tablet FTC/EFV/TDF (Atripla): • FTC 200 mg plus TDF 300 mg plus EFVc 600 mg tablet FTC/RPV/TDF (Complera): • FTC 200 mg plus TDF 300 mg plus RPV 25 mg tablet FTC/EVG/COBI/TDF (Stribild): • FTC 200 mg plus TDF 300 mg plus EVG 150 mg plus COBI 150 mg tablet FTC/TAF (Descovy): • FTC 200 mg plus TAF 25 mg tablet FTC/RPV/TAF (Odefsey): • FTC 200 mg plus TAF 25 mg plus RPV 25 mg tablet FTC/EVG/COBI/TAF (Genvoya): • FTC 200 mg plus TAF 10 mg plus EVG 150 mg plus COBI 150 mg tablet FTC/BIC/TAF (Biktarvy): • FTC 200 mg plus TAF 25 mg plus BIC 50 mg tablet FTC/DRV/COBI/TAF (Symtuza): • DRV 800 mg plus COBI 150 mg plus FTC 200 mg plus TAF 10 mg tablet	Standard Adult Doses *FTC (Emtriva)* *Capsule:* • 200 mg once daily without regard to food *Oral Solution:* • 240 mg (24 mL) once daily without regard to food *FTC/TDF (Truvada):* • 1 tablet once daily without regard to food *FTC/TDF/EFV (Atripla):* • 1 tablet once daily at or before bedtime • Take on an empty stomach to reduce side effects. *FTC/TDF/RPV (Complera):* • 1 tablet once daily with food *FTC/TDF/EVG/COBI (Stribild):* • 1 tablet once daily with food *FTC/TAF (Descovy):* • 1 tablet once daily with or without food *FTC/TAF/RPV (Odefsey):* • 1 tablet once daily with food *FTC/TAF/EVG/COBI (Genvoya):* • 1 tablet once daily with food *FTC/TAF/BIC (Biktarvy):* • 1 tablet once daily with or without food *DRV/COBI/FTC/TAF (Symtuza):* • 1 tablet once daily with food Dosing in Pregnancy: • No change in FTC dose indicated. PK in Pregnancy: • PK of FTC is not significantly altered in pregnancy. • For guidance about use of combination products in pregnancy, please see the specific sections on other components (i.e., TDF, TAF, EFV, RPV, DRV, EVG, BIC, COBI)	High placental transfer to fetus.[b] No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects). If patient is HBV-coinfected, it is possible that a HBV flare may occur if the drug is stopped; see HIV/Hepatitis B Virus Coinfection.

[a] Individual ARV drug dosages may need to be adjusted in patients with renal or hepatic insufficiency (for details, see the Adult and Adolescent Guidelines, Appendix B, Table 8).

[b] Placental transfer categories are determined by mean or median cord blood/maternal delivery plasma drug ratio:

High: >0.6 **Moderate:** 0.3–0.6 **Low:** <0.3

Key to Acronyms: BIC = bictegravir; COBI = cobicistat; DRV = darunavir; EFV = efavirenz; EVG = elvitegravir; FDC = fixed-dose combination; FTC = emtricitabine; HBV = hepatitis B virus; PK = pharmacokinetic; RPV = rilpivirine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

References

1. Emtriva [package insert]. Food and Drug Administration. 2017. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021500s028,021896s025lbl.pdf.
2. Szczech GM, Wang LH, Walsh JP, Rousseau FS. Reproductive toxicology profile of emtricitabine in mice and rabbits. *Reprod Toxicol*. 2003;17(1):95-108. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12507664.
3. Stek AM, Best BM, Luo W, et al. Effect of pregnancy on emtricitabine pharmacokinetics. *HIV Med*. 2012;13(4):226-235. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22129166.
4. Flynn PM, Mirochnick M, Shapiro DE, et al. Pharmacokinetics and safety of single-dose tenofovir disoproxil fumarate and emtricitabine in HIV-1-infected pregnant women and their infants. *Antimicrob Agents Chemother*. 2011;55(12):5914-5922. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21896911.
5. Colbers AP, Hawkins DA, Gingelmaier A, et al. The pharmacokinetics, safety and efficacy of tenofovir and emtricitabine in HIV-1-infected pregnant women. *AIDS*. 2013;27(5):739-748. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23169329.
6. Valade E, Treluyer JM, Dabis F, et al. Modified renal function in pregnancy: impact on emtricitabine pharmacokinetics. *Br J Clin Pharmacol*. 2014;78(6):1378-1386. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24995851.
7. Waitt C, Olagunju A, Nakalema S, et al. Plasma and breast milk pharmacokinetics of emtricitabine, tenofovir and lamivudine using dried blood and breast milk spots in nursing African mother-infant pairs. *J Antimicrob Chemother*. 2018;73(4):1013-1019. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29309634.
8. Benaboud S, Pruvost A, Coffie PA, et al. Concentrations of tenofovir and emtricitabine in breast milk of HIV-1-infected women in Abidjan, Cote d'Ivoire, in the ANRS 12109 TEmAA study, step 2. *Antimicrob Agents Chemother*. 2011;55(3):1315-1317. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21173182.
9. Mugwanya KK, Hendrix CW, Mugo NR, et al. Pre-exposure prophylaxis use by breastfeeding HIV-uninfected women: a prospective short-term study of antiretroviral excretion in breast milk and infant absorption. *PLoS Med*. 2016;13(9):e1002132. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27676257.
10. Mugo NR, Hong T, Celum C, et al. Pregnancy incidence and outcomes among women receiving preexposure prophylaxis for HIV prevention: a randomized clinical trial. *JAMA*. 2014;312(4):362-371. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25038355.
11. Williams PL, Crain M, Yildirim C, et al. Congenital anomalies and in utero antiretroviral exposure in human immunodeficiency virus-exposed uninfected infants. *JAMA Pediatr*. 2015;169(1):45-55. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25383770.
12. Sibiude J, Mandelbrot L, Blanche S, et al. Association between prenatal exposure to antiretroviral therapy and birth defects: an analysis of the French perinatal cohort study (ANRS CO1/CO11). *PLoS Med*. 2014;11(4):e1001635. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24781315.
13. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral pregnancy registry international interim report for 1 January 1989–31 January 2018. Wilmington, NC: Registry Coordinating Center. 2018. Available at: http://www.apregistry.com/.
14. Williams PL, Hazra R, Van Dyke RB, et al. Antiretroviral exposure during pregnancy and adverse outcomes in HIV-exposed uninfected infants and children using a trigger-based design. *AIDS*. 2016;30(1):133-144. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26731758.

Lamivudine (Epivir, 3TC)

(Last updated December 7, 2018; last reviewed December 7, 2018)

Available evidence suggests that lamivudine use by pregnant women is not associated with an increased risk of adverse fetal or pregnancy outcomes.

Animal Studies

Carcinogenicity

Lamivudine has weak mutagenic activity in one *in vitro* assay, but there was no evidence of *in vivo* genotoxicity in rats at 35 times to 45 times the exposure in humans receiving standard dosing. Long-term animal studies have shown no evidence of carcinogenicity at 10 times and 58 times human exposure in mice and rats, respectively.[1]

Reproduction/Fertility

Lamivudine administered to rats at doses up to 4000 mg/kg/day, which produced plasma levels 47 times to 70 times those seen in humans wo received standard dosing, revealed no evidence of impaired fertility and no effects on the offspring's survival, growth, and development up to the time of weaning.[1]

Teratogenicity/Adverse Pregnancy Outcomes

There is no evidence of lamivudine-induced teratogenicity at 35 times human plasma levels in rats and rabbits. Early embryo lethality was seen in rabbits at exposures that were similar to human therapeutic exposure, but no early embryo lethality was seen in rats with lamivudine exposures that were 35 times the human exposure level.[1]

Placental and Breast Milk Passage

In studies of pregnant rats, lamivudine was transferred to the fetus through the placenta.[1]

Human Studies in Pregnancy

Pharmacokinetics

Two separate studies have reported that pregnancy does not significantly affect lamivudine pharmacokinetic parameters.[2,3] This was confirmed in an analysis of 114 pregnant women, 123 women in labor, and 47 nonpregnant women, in which all participants received standard once-daily or twice-daily lamivudine doses.[4] Pregnant women had a 22% higher apparent clearance than nonpregnant and postpartum women, but this increase did not lead to subtherapeutic exposure. The level of lamivudine exposure in pregnant women, although lower than exposure in nonpregnant and parturient women, was relatively close to results reported previously for nonpregnant adults.[4] Thus, no dose adjustment for lamivudine is necessary during pregnancy.

Placental and Breast Milk Passage

Lamivudine readily crosses the placenta in humans, achieving cord blood levels comparable to maternal plasma concentrations.[3] In a study of 123 mother/infant pairs, the placental transfer, expressed as fetal-to-maternal area under the curve (AUC) ratio, was 0.86, and the lamivudine amniotic fluid accumulation, expressed as the amniotic fluid-to-fetal AUC ratio, was 2.9.[4] Other studies have also noted accumulation of lamivudine in amniotic fluid due to urinary excretion of lamivudine by the fetus into amniotic fluid.[2]

Lamivudine is excreted into human breast milk. In a study in Kenya of 67 nursing mothers who received a combination regimen of zidovudine, lamivudine, and nevirapine, the median breast milk lamivudine concentration was 1,214 ng/mL and the median ratio of lamivudine concentration in breast milk to that in plasma was 2.56.[5] In infants who were exposed to lamivudine only via breast milk, the median plasma lamivudine concentration was 23 ng/mL (IC_{50} of lamivudine against wild-type HIV = 0.6–21 ng/mL). In a separate study of breastfeeding women in Malawi who were receiving lamivudine in combination with tenofovir disoproxil fumarate and efavirenz, concentrations of lamivudine in breast milk were higher than those in maternal plasma at 1 month (3.29-fold higher) and 12 months (2.35-fold higher) after delivery. Infant

plasma levels at ages 6 and 12 months, on the other hand, revealed median lamivudine concentrations of only 2.5 ng/mL (with an interquartile range [IQR] of 2.5–7.6) and 0 ng/mL (with an IQR of 0–2.5), respectively.[6]

Teratogenicity/Adverse Pregnancy Outcomes

In a large French cohort, lamivudine exposure in the first trimester was associated with an increased risk of overall birth defects (adjusted odds ratio = 1.37; 95% CI, 1.06–1.73), but there was no affected organ system or specific birth defect that predominated.[7] However, in the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposures to lamivudine have been monitored to detect at least a 1.5-fold increase in risk of overall birth defects and a two-fold increase in the risk of cardiovascular and genitourinary defects (the most common classes of birth defects in the general population). No such increase in the risk of birth defects has been observed with lamivudine. Among cases of first-trimester lamivudine exposure reported to the Antiretroviral Pregnancy Registry, the prevalence of birth defects was 3.0% (151 of 5,008 births; 95% CI, 2.6% to 3.5%) compared with a 2.7% total prevalence in the U.S. population, based on Centers for Disease Control and Prevention surveillance.[8]

An analysis of Antiretroviral Pregnancy Registry data demonstrated a lower risk of spontaneous abortions, induced abortions, and preterm births with use of lamivudine-containing regimens compared with use of non-lamivudine antiretroviral regimens.[9]

Other Safety Information

In a large U.S. cohort study of infants without HIV born to women living with HIV, lamivudine exposure during pregnancy was not associated with increased risk of adverse infant outcomes in any of the growth, hearing, language, neurology, neurodevelopment, metabolic, hematologic/clinical chemistry, and blood lactate domains assessed.[10]

Excerpt from Table 10[a]

Note: When using FDCs, refer to other sections in Appendix B and Table 10 for information about the dosing and safety of the individual drug components of the FDC during pregnancy.

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations	Use in Pregnancy
Lamivudine (3TC) *Epivir* (3TC/TDF) *Cimduo* (3TC/ZDV) *Combivir* (3TC/DOR/TDF) *Delstrigo* (3TC/ABC) *Epzicom* (3TC/EFV/TDF) *Symfi* (3TC/EFV/TDF) *Symfi Lo* (3TC/TDF) *Temixys* (3TC/ABC/DTG) *Triumeq* (3TC/ABC/ZDV) *Trizivir* **Note:** Generic available for some formulations	3TC (Epivir)[d] *Tablets:* • 150 mg • 300 mg *Oral Solution:* • 10 mg/mL 3TC/TDF (Cimduo): • 3TC 300 mg plus TDF 300 mg tablet 3TC/ZDV (Combivir):[d] • 3TC 150 mg plus ZDV 300 mg tablet 3TC/DOR/TDF (Delstrigo): • 3TC 300 mg plus DOR 100 mg plus TDF 300 mg tablet 3TC/ABC (Epzicom):[d] • 3TC 300 mg plus ABC 600 mg tablet 3TC/EFV/TDF (Symfi): • 3TC 300 mg plus EFV 600 mg plus TDF 300 mg tablet 3TC/EFV/TDF (Symfi Lo): • 3TC 300 mg plus EFV 400 mg plus TDF 300 mg tablet 3TC/TDF (Temixys): • 3TC 300 mg plus TDF 300 mg tablet 3TC/ABC/DTG (Triumeq): • 3TC 300 mg plus ABC 600 mg plus DTG 50 mg tablet 3TC/ABC/ZDV (Trizivir):[d] • 3TC 150 mg plus ABC 300 mg plus ZDV 300 mg tablet	Standard Adult Doses *3TC (Epivir):* • 3TC 150 mg twice daily or 300 mg once daily, without regard to food *3TC/TDF (Cimduo):* • 1 tablet once daily without regard to food *3TC/ZDV (Combivir):* • 1 tablet twice daily without regard to food *3TC/DOR/TDF (Delstrigo):* • 1 tablet once daily without regard to food *3TC/ABC (Epzicom):* • 1 tablet once daily without regard to food *3TC/EFV/TDF (Symfi or Symfi Lo):* • 1 tablet once daily on an empty stomach and preferably at bedtime *3TC/ABC/DTG (Triumeq):* • 1 tablet once daily without regard to food *3TC/TDF (Temixys):* • 1 tablet once daily without regard to food *3TC/ABC/ZDV (Trizivir):* • 1 tablet twice daily without regard to food PK in Pregnancy: • PK not significantly altered in pregnancy. Dosing in Pregnancy: • No change in dose indicated. For guidance about use of combination products in pregnancy, please see the specific sections on other components (i.e., ABC, DOR, DTG, EFV, TDF, ZDV).	High placental transfer to fetus.[b] No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects). If patient has HIV/HBV coinfection, it is possible that an HBV flare may occur if the drug is stopped; see HIV/Hepatitis B Virus Coinfection. **Note:** 3TC products developed specifically for treatment of HBV (e.g., Epivir-HBV) contain a lower dose of 3TC that **is not appropriate** for treatment of HIV.

[a] Individual ARV drug dosages may need to be adjusted in patients with renal or hepatic insufficiency (for details, see the Adult and Adolescent Guidelines, Appendix B, Table 8).

[b] Placental transfer categories are determined by mean or median cord blood/maternal delivery plasma drug ratio:

High: >0.6 **Moderate:** 0.3–0.6 **Low:** <0.3

[d] Generic formulation available

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; DOR = doravirine; DTG = dolutegravir; EFV = efavirenz; HBV = hepatitis B virus; PK = pharmacokinetic; TDF = tenofovir disoproxil fumarate; ZDV = zidovudine

References

1. Lamivudine [package insert]. 2018. Food and Drug Administration. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/020564s038,020596s037lbl.pdf.
2. Mandelbrot L, Peytavin G, Firtion G, Farinotti R. Maternal-fetal transfer and amniotic fluid accumulation of lamivudine in human immunodeficiency virus-infected pregnant women. *Am J Obstet Gynecol*. 2001;184(2):153-158. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11174495.
3. Moodley J, Moodley D, Pillay K, et al. Pharmacokinetics and antiretroviral activity of lamivudine alone or when coadministered with zidovudine in human immunodeficiency virus type 1-infected pregnant women and their offspring. *J Infect Dis*. 1998;178(5):1327-1333. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9780252.
4. Benaboud S, Treluyer JM, Urien S, et al. Pregnancy-related effects on lamivudine pharmacokinetics in a population study with 228 women. *Antimicrob Agents Chemother*. 2012;56(2):776-782. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22106227.
5. Mirochnick M, Thomas T, Capparelli E, et al. Antiretroviral concentrations in breast-feeding infants of mothers receiving highly active antiretroviral therapy. *Antimicrob Agents Chemother*. 2009;53(3):1170-1176. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19114673.
6. Palombi L, Pirillo MF, Marchei E, et al. Concentrations of tenofovir, lamivudine and efavirenz in mothers and children enrolled under the option B-plus approach in Malawi. *J Antimicrob Chemother*. 2016;71(4):1027-1030. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26679247.
7. Sibiude J, Mandelbrot L, Blanche S, et al. Association between prenatal exposure to antiretroviral therapy and birth defects: an analysis of the French perinatal cohort study (ANRS CO1/CO11). *PLoS Med*. 2014;11(4):e1001635. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24781315.
8. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral pregnancy registry international interim report for 1 January 1989–31 January 2018. Wilmington, NC: Registry Coordinating Center. 2018. Available at: http://www.apregistry.com/.
9. Vannappagari V, Koram N, Albano J, Tilson H, Gee C. Abacavir and lamivudine exposures during pregnancy and non-defect adverse pregnancy outcomes: data from the antiretroviral pregnancy registry. *J Acquir Immune Defic Syndr*. 2015;68(3):359-364. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25469525.
10. Williams PL, Hazra R, Van Dyke RB, et al. Antiretroviral exposure during pregnancy and adverse outcomes in HIV-exposed uninfected infants and children using a trigger-based design. *AIDS*. 2016;30(1):133-144. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26731758.

Stavudine (Zerit, d4T)

(Last updated December 7, 2018; last reviewed December 7, 2018)

Stavudine is classified as Food and Drug Administration (FDA) Pregnancy Category C.

Stavudine **is not recommended** for use in pregnant women with HIV due to its toxicity.

Animal Studies

Carcinogenicity

Stavudine is clastogenic in *in vitro* and *in vivo* assays but not mutagenic in *in vitro* assays. In 2-year carcinogenicity studies in mice and rats, stavudine was noncarcinogenic at doses that produced exposures 39 times (in mice) and 168 times (in rats) the human exposure observed at the recommended therapeutic dose. At higher levels of exposure (250 times [in mice] and 732 times [in rats] the human exposure seen at therapeutic doses), benign and malignant liver tumors occurred in mice and rats, and urinary bladder tumors occurred in male rats.[1]

Reproduction/Fertility

Stavudine has no demonstrated effect on reproduction or fertility in rodents. No evidence of impaired fertility was seen in rats with exposures (based on C_{max}) up to 216 times the exposures observed following a clinical dosage of stavudine 1 mg/kg/day.[1] A dose-related cytotoxic effect has been observed on preimplantation mouse embryos, with inhibition of blastocyst formation occurring at a concentration of 100 μM and inhibition of post-blastocyst development occurring at 10 μM.[2]

Teratogenicity/Adverse Pregnancy Outcomes

No evidence of teratogenicity was noted in rats or rabbits with stavudine exposures (based on C_{max}) up to 399 times and 183 times, respectively, the exposures seen at a clinical dosage of stavudine 1 mg/kg/day. In rat fetuses, the incidence of a common skeletal variation—unossified or incomplete ossification of sternebra—increased at 399 times human exposure (i.e., the exposure in adult humans who received a standard dose), although no effect was observed at 216 times human exposure. A slight post-implantation loss was noted at 216 times human exposure, with no effect noted at approximately 135 times human exposure. An increase in early rat neonatal mortality (birth to day 4) occurred at 399 times human exposure, although survival of neonates was unaffected at approximately 135 times human exposure.[1]

Placental and Breast Milk Passage

A study in rats showed that stavudine is transferred to the fetus through the placenta. The concentration in fetal tissue was approximately one-half the concentration in maternal plasma.[1] In primates (pig-tailed macaques), the ratio of fetal plasma concentrations/maternal plasma concentrations was approximately 0.80.[3]

Stavudine is excreted into the breast milk of lactating rats.[1]

Human Studies in Pregnancy

Pharmacokinetics

In a Phase 1/2 short-term safety and pharmacokinetic (PK) study of combination stavudine and lamivudine in pregnant women living with HIV and their infants (PACTG 332), both drugs were well tolerated, with maternal stavudine PK parameters similar to those seen in nonpregnant adults.[4]

Placental and Breast Milk Passage

Stavudine crosses the human placenta, resulting in cord blood concentration/maternal blood concentration ratios of 1.0 to 1.3.[5] Stavudine also crosses into human breast milk, resulting in breast milk concentration/maternal plasma concentration ratios of 1.0 to 1.76. Concentrations in nursing infants were negligible.[6,7]

Teratogenicity/Adverse Pregnancy Outcomes

No association was found between first-trimester exposure to stavudine and birth defects in a large French cohort study that had 70% power to detect an increased adjusted odds ratio of 1.5.[8] In the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposures to stavudine in humans have been monitored to be able to detect at least a two-fold increased risk of overall birth defects. No such increase in birth defects has been observed with stavudine. Among cases of first-trimester stavudine exposure reported to the Antiretroviral Pregnancy Registry, the prevalence of birth defects was 2.6% (21 of 811 births; 95% CI, 1.6% to 3.9%) compared with a total prevalence in the U.S. population of 2.7%, based on Centers for Disease Control and Prevention surveillance.[9]

Other Safety Data

Cases of lactic acidosis, including some fatal cases, have been described in pregnant women receiving the combination of didanosine and stavudine along with other antiretroviral (ARV) agents.[10-12] The FDA and Bristol-Myers Squibb issued a warning to health care professionals that pregnant women may be at increased risk of fatal lactic acidosis when prescribed didanosine and stavudine in combination (see Recommendations for Use of Antiretroviral Drugs During Pregnancy and Long-Term Follow-Up of Infants Exposed to Antiretroviral Drugs). Didanosine and stavudine **should not be prescribed together** for pregnant women.

In a U.S. cohort study evaluation of the safety of ARV drugs used during pregnancy, children without HIV born to women with HIV who received didanosine plus stavudine during the pregnancy had an increased risk of both adverse neurodevelopmental (relative risk [RR] of 12.40; 95% CI, 5.29–29.08) and language (RR of 4.84, 95% CI, 1.14–20.51) outcomes compared to children whose mothers did not receive these drugs during pregnancy.[13]

Stavudine **is not recommended** for use in pregnant women with HIV due to its toxicity.

Excerpt from Table 10[a]

Generic Name (Abbreviation) *Trade Name*	**Formulation**	**Dosing Recommendations**	**Use in Pregnancy**
Stavudine (d4T) *Zerit* **Note:** Generic products are available for all formulations.	d4T (Zerit) *Capsules:* • 15 mg • 20 mg • 30 mg • 40 mg *Oral Solution:* • 1 mg/mL following reconstitution **Note:** Extended-release capsule formulation (Zerit XR) has been discontinued by the manufacturer.	Standard Adult Doses[e] *Body Weight ≥60 kg:* • 40 mg twice daily without regard to meals *Body Weight <60 kg:* • 30 mg twice daily without regard to meals Dosing in Pregnancy: • No change in dose indicated. PK in Pregnancy: • PK not significantly altered in pregnancy.	d4T **is not recommended** for pregnant women. High placental transfer.[b] No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects). Lactic acidosis, sometimes fatal, has been reported in pregn aant women receiving ddI and d4T together.

[a] Individual ARV drug dosages may need to be adjusted in patients with renal or hepatic insufficiency (for details, see Adult and Adolescent Guidelines, Appendix B, Table 8).

[b] Placental transfer categories—Mean or median cord blood/maternal delivery plasma drug ratio:

High: >0.6 **Moderate:** 0.3–0.6 **Low:** <0.3

[e] WHO recommends maximum dose of 30 mg twice daily regardless of weight.

Key to Acronyms: ARV = antiretroviral; d4T = stavudine; ddI = didanosine; PK = pharmacokinetic; WHO = World Health Organization

References

1. Stauvidine [package insert]. Food and Drug Administration. 2017. Available at: http://packageinserts.bms.com/pi/pi_zerit.pdf.
2. Toltzis P, Mourton T, Magnuson T. Comparative embryonic cytotoxicity of antiretroviral nucleosides. *J Infect Dis*. 1994;169(5):1100-1102. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8169400.
3. Odinecs A, Nosbisch C, Keller RD, Baughman WL, Unadkat JD. In vivo maternal-fetal pharmacokinetics of stavudine (2',3'-didehydro-3'-deoxythymidine) in pigtailed macaques (Macaca nemestrina). *Antimicrob Agents Chemother*. 1996;40(1):196-202. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8787905.
4. Wade NA, Unadkat JD, Huang S, et al. Pharmacokinetics and safety of stavudine in HIV-infected pregnant women and their infants: pediatric AIDS clinical trials group protocol 332. *J Infect Dis*. 2004;190(12):2167-2174. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15551216.
5. McCormack SA, Best BM. Protecting the fetus against HIV infection: a systematic review of placental transfer of antiretrovirals. *Clin Pharmacokinet*. 2014;53(11):989-1004. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25223699.
6. Fogel JM, Taha TE, Sun J, et al. Stavudine concentrations in women receiving postpartum antiretroviral treatment and their breastfeeding infants. *J Acquir Immune Defic Syndr*. 2012;60(5):462-465. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22614899.
7. Palombi L, Pirillo MF, Andreotti M, et al. Antiretroviral prophylaxis for breastfeeding transmission in Malawi: drug concentrations, virological efficacy and safety. *Antivir Ther*. 2012;17(8):1511-1519. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22910456.
8. Sibiude J, Mandelbrot L, Blanche S, et al. Association between prenatal exposure to antiretroviral therapy and birth defects: an analysis of the French perinatal cohort study (ANRS CO1/CO11). *PLoS Med*. 2014;11(4):e1001635. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24781315.
9. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral pregnancy registry international interim report for 1 January 1989–31 January 2018.Wilmington, NC: Registry Coordinating Center. 2018. Available at: http://www.apregistry.com/.
10. Bristol-Myers Squibb Company. Healthcare provider important drug warning letter. 2001. Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm173947.htm.
11. Sarner L, Fakoya A. Acute onset lactic acidosis and pancreatitis in the third trimester of pregnancy in HIV-1 positive women taking antiretroviral medication. *Sex Transm Infect*. 2002;78(1):58-59. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11872862.
12. Mandelbrot L, Kermarrec N, Marcollet A, et al. Case report: nucleoside analogue-induced lactic acidosis in the third trimester of pregnancy. *AIDS*. 2003;17(2):272-273. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12545093.
13. Williams PL, Hazra R, Van Dyke RB, et al. Antiretroviral exposure during pregnancy and adverse outcomes in HIV-exposed uninfected infants and children using a trigger-based design. *AIDS*. 2016;30(1):133-144. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26731758.

Tenofovir Alafenamide (Vemlidy, TAF)

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Tenofovir alafenamide (TAF) is an orally bioavailable form of tenofovir. Data on its use in human pregnancy is insufficient to inform a drug-associated risk determination for birth defects or miscarriage.

Animal Studies

Carcinogenicity

Because TAF is rapidly converted to tenofovir, and tenofovir exposure in rats and mice is lower after TAF administration than after tenofovir disoproxil fumarate (TDF) administration, carcinogenicity studies were performed with TDF. Long-term oral carcinogenicity studies of tenofovir in mice and rats were carried out at 167 times (mice) and 55 times (rats) tenofovir exposure than that seen after TAF administration at recommended doses in humans. In female mice, liver adenomas were increased. In rats, no carcinogenic findings were observed.[1,2]

Reproduction/Fertility

Reproduction studies have been performed in rats and rabbits at TAF exposures similar to and 53 times higher than human exposure, respectively, and revealed no evidence of impaired fertility or mating performance associated with TAF administration.[1-3]

Teratogenicity/Adverse Pregnancy Outcomes

No effects on early embryonic development were seen when TAF was administered to male or female rats at 62 times the human therapeutic exposure.[1-3]

Placental and Breast Milk Passage

Rat studies demonstrated secretion of tenofovir in breast milk after administration of TDF; whether TAF is present in animal milk is unknown.[1,3]

Human Studies in Pregnancy

Pharmacokinetics

Pharmacokinetics (PKs) of TAF have been reported in 31 women taking TAF 25 mg without any pharmaco-enhancer, and in 27 women taking TAF 10 mg boosted with cobicistat 150 mg.[4] This study evaluated plasma TAF exposures with and without boosting in pregnant and postpartum women relative to those in non-pregnant adults. No significant differences in PKs were seen between pregnant and postpartum women taking boosted TAF. Among women taking unboosted TAF, the significantly different plasma exposures during pregnancy and postpartum were driven by higher exposures postpartum.

Placental and Breast Milk Passage

TAF was below the assay limit of quantification (<3.9 ng/mL) in 15 of 15 cord blood samples tested.[4] Maternal plasma TAF at delivery was measurable in 2 of the 15 paired samples.

Teratogenicity/Adverse Pregnancy Outcomes

In the Antiretroviral Pregnancy Registry, the number of reported cases of TAF exposures is insufficient to draw any conclusions about risk of birth defects.[5]

Excerpt from Table 10[a]

Note: When using FDCs, refer to other sections in Appendix B and Table 10 for information about the dosing and safety of individual drug components of the FDC during pregnancy.

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations	Use in Pregnancy
Tenofovir Alafenamide (TAF) *Vemlidy* (TAF/BIC/FTC) *Biktarvy* (TAF/FTC) *Descovy* (TAF/EVG/COBI/FTC) *Genvoya* (TAF/FTC/RPV) *Odefsey* (TAF/DRV/COBI/FTC) *Symtuza* **Note:** Generic available for some formulations.	TAF (Vemlidy)[d] *Tablet:* • 25 mg TAF/BIC/FTC (Biktarvy): • TAF 25 mg plus BIC 50 mg plus FTC 200 mg tablet TAF/FTC (Descovy): • TAF 25 mg plus FTC 200 mg tablet TAF/EVG/COBI/FTC (Genvoya): • TAF 10 mg plus EVG 150 mg plus COBI 150 mg plus FTC 200 mg tablet TAF/FTC/RPV (Odefsey): • TAF 25 mg plus FTC 200 mg plus RPV 25 mg tablet TAF/DRV/COBI/FTC (Symtuza): • TAF 10 mg plus DRV 800 mg plus COBI 150 mg plus FTC 200 mg tablet	Standard Adult Dose *TAF (Vemlidy):* • 1 tablet once daily with food *TAF/BIC/FTC (Biktarvy):* • 1 tablet once daily with or without food *TAF/FTC (Descovy):* • 1 tablet once daily with or without food • Same dose (TAF 25 mg) can be used with or without pharmaco-enhancers. *TAF/EVG/COBI/FTC (Genvoya):* • 1 tablet once daily with food *TAF/FTC/RPV (Odefsey):* • 1 tablet once daily with food *TAF/DRV/COBI/FTC (Symtuza):* • 1 tablet once daily with food PK in Pregnancy: • Plasma PK not significantly altered in pregnancy. Dosing in Pregnancy: • No change in dose indicated. • For guidance about use of combination products in pregnancy, please see the specific sections on other components (i.e., BIC, COBI. DRV, EVG, FTC, RPV).	Low placental transfer to fetus.[b] Insufficient data to assess for teratogenicity in humans. No evidence of teratogenicity in rats. Renal function should be monitored because of potential for renal toxicity.

[a] Individual ARV drug dosages may need to be adjusted in patients with renal or hepatic insufficiency (for details, see the Adult and Adolescent Guidelines, Appendix B, Table 8).

[b] Placental transfer categories are determined by mean or median cord blood/maternal delivery plasma drug ratio:

High: >0.6 **Moderate:** 0.3–0.6 **Low:** <0.3

[d] Generic formulation available

Key to Acronyms: COBI = cobicistat; BIC = bictegravir; DRV = darunavir; EVG = elvitegravir; FDC = fixed-dose combination; FTC = emtricitabine; PK = pharmacokinetic; RPV = rilpivirine; TAF = tenofovir alafenamide

References

1. Emtricitabine/rilpivirine/tenofovir alafenamide (Odefsey) [package insert]. Food and Drug Administration. 2016. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/208351s000lbl.pdf.

2. Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (Genvoya) [package insert]. Food and Drug Administration. 2016. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/207561s003lbl.pdf.

3. Emtricitabine/tenofovir alafenamide (Descovy) [package insert]. Food and Drug Administration. 2016. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/208215s000lbl.pdf.

4. 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.

5. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral pregnancy registry international interim report for 1 January 1989–31 January 2018. Wilmington, NC: Registry Coordinating Center. 2018. Available at: http://www.apregistry.com/.

Tenofovir Disoproxil Fumarate (Viread, TDF)

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Tenofovir disoproxil fumarate (TDF), an orally bioavailable form of tenofovir, is classified as Food and Drug Administration Pregnancy Category B.[1] For information about tenofovir alafenamide (TAF), see the TAF section.

Animal Studies

Carcinogenicity

Tenofovir is mutagenic in one of two *in vitro* assays and has no evidence of clastogenic activity. Long-term oral carcinogenicity studies of tenofovir were carried out at 16 times (in mice) and 5 times (in rats) the exposure in humans taking standard dosing. In female mice, liver adenomas were increased at exposures 16 times those observed in humans who received therapeutic doses. In rats, there was no evidence of carcinogenicity at exposures up to 5 times those observed in humans who received the therapeutic dose.[1]

Reproduction/Fertility

Reproduction studies have been performed in rats and rabbits at doses of tenofovir up to 14 times and 19 times the human dose, respectively, based on body surface area comparisons. These studies revealed no evidence of impaired fertility or harm to the fetus associated with tenofovir. There were also no effects on fertility, mating performance, or early embryonic development when tenofovir was administered to male rats (600 mg/kg/day; equivalent to 10 times the human dose based on body surface area) for 28 days before mating and to female rats from 15 days before mating through Day 7 of gestation. There was, however, an alteration of the estrous cycle in female rats who were administered tenofovir 600 mg/kg/day.[1]

Teratogenicity/Adverse Pregnancy Outcomes

Fetal monkeys with chronic high-level exposure to tenofovir (exposure equivalent to 25 times the area under the curve [AUC] achieved with therapeutic dosing in humans) had lower fetal circulating insulin-like growth factor (IGF)-1, higher IGF binding protein-3 levels, and lower body weights compared to tenofovir-unexposed fetal monkeys. A slight reduction in fetal bone porosity was also observed. These effects were observed within 2 months of maternal treatment.[1]

Placental and Breast Milk Passage

Intravenous administration of tenofovir to pregnant cynomolgus monkeys resulted in a fetal/maternal plasma concentration of 17%, demonstrating that tenofovir crosses the placenta.[2]

Human Studies in Pregnancy

Pharmacokinetics

In a retrospective population pharmacokinetic study of 46 pregnant women and 156 nonpregnant women who were receiving combination regimens that included TDF, pregnant women had a 39% higher apparent clearance of tenofovir compared with nonpregnant women. Apparent clearance decreased slightly but significantly with increasing age.[3] In the P1026s study of 37 pregnant women who received TDF-based combination therapy at 30 to 36 weeks' gestation and 6 to 12 weeks postpartum, the percentage of women with tenofovir AUC exceeding the target of 1.99 μg•hour/mL (the 10th percentile in nonpregnant adults) was lower in the third trimester (73%, 27 of 37 women) than postpartum (84%, 27 of 32 women). Trough levels and AUCs were 17% to 20% lower during the third trimester compared to postpartum. The median weight of the women below the target exposure (97.9 kg) was significantly higher than the median weight of the women who met the target exposure (74.2 kg).[4] In another study of 34 women who received TDF plus emtricitabine in the third trimester and postpartum, tenofovir AUC, peak, and trough were all about 25% lower in pregnant women than in postpartum women, but these decreased exposures were not associated with virologic failure.[5] In a study of women who did not have HIV and who were using TDF as part of pre-exposure prophylaxis (PrEP), intracellular concentrations of tenofovir diphosphate (TFV-DP) in pregnant

women were about 70% of those in nonpregnant women, even after adjusting for adherence.[6]

Standard dosing of TDF during pregnancy continues to be recommended.

Placental and Breast Milk Passage

In studies of pregnant women on chronic TDF, the cord-to-maternal-blood ratio of tenofovir ranged from 0.60 to 1.03, indicating high placental transfer.[4,5,7,8] In studies of pregnant women who received single-dose TDF (with and without emtricitabine) during labor, the median tenofovir cord-to-maternal-blood ratio at delivery ranged from 0.55 to 0.73.[9,10] Intracellular tenofovir concentrations were detected in the peripheral blood mononuclear cells from cord blood in all infants after a single maternal dose of TDF 600 mg with emtricitabine 400 mg, but intracellular TFV-DP was detectable in only two of 36 infants (5.5%).[11]

In a study of 50 breastfeeding women without HIV infection who received TDF/emtricitabine (under directly observed therapy for 10 days) as PrEP, median peak and trough time-averaged tenofovir breast milk concentrations were similar at 3.2 ng/mL (interquartile range [IQR] 2.3–4.7) and 3.3 ng/mL (IQR 2.3–4.4), respectively. The infant plasma tenofovir concentration was unquantifiable (<0.31 ng/mL) in 94% of infants (46 of 49 infants); in the three infants with detectable tenofovir, the level was 0.9 ng/mL in two and 17.4 ng/mL in one. Based on this study's results, the median tenofovir dose ingested through breast milk was estimated to be 0.47 mcg/kg, or <0.01% of the proposed daily 6 mg/kg pediatric TDF dose.[12] In a study of 59 breastfeeding women who received TDF/lamivudine/efavirenz in Uganda and Nigeria, no infant had detectable tenofovir in plasma.[13]

Reproduction/Fertility

In a retrospective analysis of 7,275 women (1,199 of whom were receiving TDF-based antiretroviral therapy) women who used TDF had a slightly lower pregnancy rate than women who did not use TDF, but the findings were limited by the observational nature of the data, and additional studies are needed for confirmation.[14]

Teratogenicity/Adverse Pregnancy Outcomes

In a study of 431 pregnancies that occurred during an HIV PrEP trial in which women who did not have HIV infection were randomized to receive placebo, TDF, or TDF plus emtricitabine, there was no difference in risk of congenital anomalies between the TDF-containing arms and placebo arms.[15] No association was seen between maternal TDF use and the occurrence of birth defects among offspring in three large U.S. cohorts of children born to women with HIV: PACTG 219/219C (n = 2,202, with 214 first-trimester TDF exposures), P1025 (n = 1,112, with 138 first-trimester TDF exposures),[16,17] and PHACS (n = 2,580, with 431 first-trimester TDF exposures).[18] In the French Perinatal Cohort, no association was found between birth defects and use of TDF with a power of 70% for an odds ratio of 1.5 (n = 13,124, with 823 first-trimester TDF exposures).[19] Among 382 pregnancies that occurred in 302 women in Uganda and Zimbabwe who participated in the DART trial—approximately two-thirds of whom received TDF during >90% of their pregnancies—TDF use was not associated with birth defect risk.[20] Finally, in the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposures to TDF have been monitored to be able to detect at least a 1.5-fold increased risk of overall birth defects and a two-fold increase in risk of birth defects in the cardiovascular and genitourinary systems. No increase in birth defects has been observed with TDF. Among the cases of first-trimester TDF exposure reported to the Antiretroviral Pregnancy Registry, the prevalence of birth defects was 2.3% (82 of 3,535 births; 95% CI, 1.9% to 2.9%), compared with a total prevalence of 2.7% in the U.S. population, based on Centers for Disease Control and Prevention surveillance.[21]

In the PHACS study from the United States, 449 of the 2,029 infants (21%) who were exposed to HIV but who were uninfected had *in utero* exposure to TDF. TDF-exposed infants and infants without exposure to TDF had similar rates of low birthweight (LBW), small-for-gestational-age (SGA), and newborn length-for-age and head circumference-for-age z-scores (LAZ and HCAZ, respectively).[22] In a different U.S. cohort study, P1025, maternal TDF use was similarly not associated with differences in body size parameters at birth.[23] A fetal ultrasound study in South Africa demonstrated no association between duration of maternal

TDF use and long-bone (femur and humerus) growth.[24] This same research group also demonstrated that the duration of *in utero* tenofovir exposure was not related to infant length at birth.[25] However, in a Dutch study of 74 HIV-exposed infants (including nine with *in utero* TDF exposure), maternal TDF use was linked to an increased risk of LBW (<2,500 g).[26]

In the largely Africa-based PROMISE trial, pregnant women with HIV but without advanced disease or immunosuppression (defined as CD4 counts ≥350 cells/mm^3) were randomized at ≥14 weeks' (median 26 weeks') gestation to receive zidovudine alone, zidovudine/lamivudine plus lopinavir/ritonavir (LPV/r) (zidovudine-based ART), or TDF/emtricitabine plus LPV/r (tenofovir-based ART). The tenofovir-based ART arm and zidovudine-based ART arms showed no significant differences in the incidence of LBW infants (<2,500 g; 16.9% vs. 20.4%, $P = 0.3$) or the incidence of preterm delivery (delivery at <37 weeks; 18.5% vs 19.7%, $P = 0.77$). However, tenofovir-based ART was associated with higher rates of very preterm delivery (delivery before 34 weeks; 6.0% vs. 2.6%, $P = 0.04$) and early infant death (4.4% vs. 0.6%, $P = 0.001$) than zidovudine-based ART.[27] The greater number of early infant deaths was likely attributable to poor outcomes of very preterm infants in the settings where the trial took place, but the higher rate of very preterm delivery in the tenofovir-based ART arm remains unexplained. Potential explanations include a lower than expected severe preterm delivery rate in the zidovudine-based ART arm or increased tenofovir exposure due to coadministration with LPV/r (LPV/r doses were increased in late pregnancy).

In contrast to the PROMISE trial results, in a large observational study in Botswana of >11,000 births among women with HIV who received ART during pregnancy and gave birth between August 2014 and August 2016, the risk of any adverse birth outcome was lower in those who received TDF/emtricitabine/efavirenz than in those who received any other regimen (TDF/emtricitabine plus nevirapine, adjusted relative risk [ARR], 1.15; TDF/emtricitabine plus lopinavir/ritonavir, ARR 1.31; zidovudine/lamivudine plus nevirapine, ARR 1.30; zidovudine/lamivudine plus LPV/r, ARR 1.21) Furthermore, TDF/emtricitabine/efavirenz was associated with a lower risk of SGA than all other regimens, and zidovudine/lamivudine plus lopinavir/ritonavir was associated with higher risk of preterm birth, very preterm birth, and neonatal death than TDF/emtricitabine/efavirenz. Finally, among infants exposed to ART from conception, TDF/emtricitabine/efavirenz was associated with lower risk for adverse birth outcomes than other ART regimens.[28]

In a combined analysis of data from 4,646 births that occurred during the PHACS and P1025 studies, women who received TDF/lamivudine plus lopinavir/ritonavir and those who received zidovudine/lamivudine plus lopinavir/ritonavir during pregnancy had no significant differences in the risks of preterm delivery overall (defined as a gestational age of <37 weeks), very preterm delivery (<34 weeks), LBW infants (<2,500 g), and very LBW infants (<1,500 g).[29]

Additionally, a placebo-controlled trial of TDF 300 mg that was initiated at 28 weeks' gestation in Thai women with hepatitis B (but not HIV infection) permits an assessment of the potential impact of TDF on birth outcomes when TDF is used in pregnancy without other antiviral drugs and outside the context of maternal HIV infection. In this study, 322 deliveries resulted in 323 live births (including two twin pairs and one stillbirth in the TDF arm). No difference was observed in birthweights (median birth weight was 3,028 g in the TDF arm and 3,061 g in the placebo arm) or frequency of preterm delivery (8 of 162 infants [5%] in TDF arm, with none at <35 weeks; 13 of 160 infants [8%] in the placebo arm, including 3 of 160 infants [2%] delivered at 32–34 weeks) between the TDF and placebo arms.[30]

Finally, in an observational, multicenter Canadian study of 2,787 mother-infant pairs in which the mothers received ART during pregnancy, the rate of preterm delivery (defined as delivery at <37 weeks) was significantly higher in mothers who received TDF-containing ART than in mothers who received ART that did not contain TDF (19.4% vs. 15.2%, $P = 0.024$). This difference was not associated with whether the regimen also included a protease inhibitor, non-nucleoside reverse transcriptase inhibitor, or integrase strand transfer inhibitor.[31]

In all, there remains some concern for a link between maternal TDF use and preterm birth or LBW, but the evidence is mixed; the role of potential cofactors and/or confounders requires further investigation.

Other Safety Data

Maternal Safety Outcomes

In a United Kingdom cohort of 71 pregnant women receiving TDF, retrospective analysis of serum creatinine and estimated glomerular filtration rate (eGFR) measured throughout pregnancy and 6 weeks after delivery revealed no decline in renal function during pregnancy and normal renal function (>90 mL/min) at 6 weeks postpartum (one woman's postpartum eGFR was 60 mL/min).[32]

Infant Safety Outcomes

In the U.S. PHACS/SMARTT cohort study, after adjusting for birth cohort and other factors, maternal use of TDF led to no increase in the likelihood of adverse metabolic, growth/development, cardiac, neurological, or neurodevelopmental outcomes.[33]

In the DART trial described above, there were no differences in infant growth rates or infant mortality between infants born to mothers who received TDF during pregnancy and those born to mothers who received other ARV drugs.[20] In the U.S. PHACS Study, there was no difference at birth in rates of LBW, SGA, or newborn LAZ and HCAZ between infants who were exposed to combination drug regimens that contained TDF and those who were exposed to regimens that did not contain TDF. However, at age 1 year, infants exposed to combination regimens with TDF had a slight but significantly lower adjusted mean LAZ and HCAZ than those without TDF exposure (LAZ: -0.17 vs. -0.03, $P = 0.04$; HCAZ: 0.17 vs. 0.42, $P = 0.02$) but no difference in weight-for-age z-score (WAZ). There were no significant differences between infants with and without TDF exposure at age 1 year when defining low LAZ or HCAZ as ≤1.5 z-score. Thus, these slightly lower mean LAZ and HCAZ scores are of uncertain significance.[22] In the U.S. P1025 study, maternal TDF use was similarly not associated with differences in body size parameters at birth; however, among the 1,496 infants that were followed for 6 months, TDF exposure after the first trimester was associated with being underweight (WAZ <5%) at age 6 months (OR [95% CI]: 2.06 [1.01, 3.95], $P = 0.04$) when compared to no exposure.[23]

A Kenyan cohort study also found an association between maternal TDF use (compared to ART without TDF) and lower 6-week WAZ despite no difference in weight at birth; however, TDF exposure was not associated with WAZ differences at age 9 months, and no associations were found with any other anthropometric measures at the 6-week or 9-month time points.[34] In the Dutch study of 74 HIV-exposed infants, maternal TDF use was linked to lower 6-month HAZ and WAZ after adjusting for differences in birthweight and prematurity.[26]

On the other hand, results from a South African study demonstrated that the duration of *in utero* tenofovir exposure was not related to infant length at birth or to linear growth through the first 48 weeks of life.[25]

Finally, in the placebo-controlled trial that involved Thai women with hepatitis B infection (but not HIV infection) who initiated TDF at 28 weeks' gestation, there was no difference in growth outcomes at age 6 months between infants in the maternal TDF and placebo arms.[30]

In all, there is inconsistent evidence that maternal TDF use during pregnancy may be associated with transient, small growth delays during the first year of life. These delays are of uncertain clinical significance.[35]

In a cross-sectional study of 68 children aged 1 to 6 years who were exposed to HIV (but uninfected) and who had *in utero* exposure to combination regimens with (n = 33) or without (n = 35) TDF, quantitative bone ultrasound measures and bone metabolism marker levels were similar for both groups.[36] Another study evaluated whole body dual-energy X-ray absorptiometry (DXA) scans performed within 4 weeks of birth among 74 infants who were exposed to >8 weeks of TDF *in utero* and 69 infants with no TDF exposure. The adjusted mean whole-body bone mineral content (BMC) was significantly lower in the TDF group by 6.3 g ($P = 0.004$), as was the whole-body-less-head BMC (-2.6 g, $P = 0.056$). The duration and clinical significance of these findings require further longitudinal evaluation.[37]

A study of 136 infants in Malawi whose mothers received TDF/emtricitabine/efavirenz during pregnancy (with no control group for comparison) documented low-grade, transient abnormalities of serum phosphate and serum creatinine at ages 6 and 12 months.[38]

Excerpt from Table 10[a]

Note: When using FDCs, refer to other sections in Appendix B and Table 10 for information about the dosing and safety of individual drug components of the FDC during pregnancy.

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations	Use in Pregnancy
Tenofovir Disoproxil Fumarate (TDF) *Viread* (TDF/EFV/FTC) *Atripla* (TDF/3TC) *Cimduo* (TDF/FTC/RPV) *Complera* (TDF/DOR/3TC) *Delstrigo* (TDF/EVG/COBI /FTC) *Stribild* (TDF/EFV/3TC) *Symfi* (TDF/EFV/3TC) *Symfi Lo* (TDF/3TC) *Temixys* (TDF/FTC) *Truvada* **Note:** Generic available for some formulations	TDF (Viread) *Tablet:*[d] • 300 mg *Powder:* • 40 mg/1 g oral powder TDF/EFV/FTC (Atripla): • TDF 300 mg plus EFV 600 mg plus FTC 200 mg tablet TDF/3TC (Cimduo): • TDF 300 mg plus 3TC 300 mg tablet TDF/FTC/RPV (Complera): • TDF 300 mg plus FTC 200 mg plus RPV 25 mg tablet TDF/DOR/3TC (Delstrigo): • TDF 300 mg plus DOR 100 mg plus 3TC 300 mg tablet TDF/EVG/COBI /FTC (Stribild): • TDF 300 mg plus EVG 150 mg plus COBI 150 mg plus FTC 200 mg tablet TDF/EFV/3TC (Symfi): • TDF 300 mg plus EFV 600 mg plus 3TC 300 mg tablet TDF/EFV/3TC (Symfi Lo): • TDF 300 mg plus EFV 400 mg plus 3TC 300 mg tablet TDF/3TC (Temixys): • TDF 300 mg plus 3TC 300 mg tablet TDF/FTC (Truvada): • TDF 300 mg plus FTC 200 mg tablet	Standard Adult Doses *TDF (Viread)* *Tablet:* • TDF 300 mg once daily without regard to food *Powder:* • TDF 8 mg/kg (up to a maximum of TDF 300 mg). Take with food. *TDF/EFV/FTC (Atripla):* • 1 tablet once daily at or before bedtime. Take on an empty stomach to reduce side effects. *TDF/3TC (Cimduo):* • 1 tablet once daily without regard to food *TDF/FTC/RPV (Complera):* • 1 tablet once daily with food *TDF/DOR/3TC (Delstrigo):* • 1 tablet once daily without regard to food. *TDF/EVG/COBI/FTC (Stribild):* • 1 tablet once daily with food *TDF/EFV/3TC (Symfi or Symfi Lo):* • 1 tablet once daily on an empty stomach and preferably at bedtime *TDF/3TC (Temixys):* • 1 tablet once daily without regard to food *TDF/FTC (Truvada):* • 1 tablet once daily without regard to food PK in Pregnancy: • AUC is lower in third trimester than postpartum, but trough levels are adequate. Dosing in Pregnancy: • No change in dose is indicated. For guidance about use of combination products in pregnancy, please see the specific sections on other components (i.e., 3TC, COBI, DOR, EFV, EVG, FTC, RPV)	High placental transfer to fetus.[b] No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects). Studies in monkeys (at doses approximately 2-fold higher than those for human therapeutic use) show decreased fetal growth and reduction in fetal bone porosity within 2 months of starting maternal therapy. Human studies demonstrate no consistent link to low birth weight, but data are conflicting about potential effects on growth outcomes later in infancy. If patient is HBV coinfected, it is possible that an HBV flare may occur if TDF is stopped; see HIV/Hepatitis B Virus Coinfection. Renal function should be monitored because of potential for renal toxicity.

[a] Individual ARV drug dosages may need to be adjusted in patients with renal or hepatic insufficiency (for details, see the Adult and Adolescent Guidelines, Appendix B, Table 8).

[b] Placental transfer categories are determined by mean or median cord blood/maternal delivery plasma drug ratio:

High: >0.6 **Moderate:** 0.3–0.6 **Low:** <0.3

[d] Generic formulation available.

Key to Acronyms: AUC = area under the curve; 3TC = lamivudine; COBI = cobicistat; DOR = doravirine; EFV = efavirenz; EVG = elvitegravir; FDC = fixed-dose combination; FTC = emtricitabine; HBV = hepatitis B virus; PK = pharmacokinetic; RPV = rilpivirine; TDF = tenofovir disoproxil fumarate

References

1. Tenofovir disproxil fumarate (Viread) [package insert]. Food and Drug Administration. 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021356s056,022577s012lbl.pdf.
2. Tarantal AF, Marthas ML, Shaw JP, Cundy K, Bischofberger N. Administration of 9-[2-(R)-(phosphonomethoxy)propyl] adenine (PMPA) to gravid and infant rhesus macaques (Macaca mulatta): safety and efficacy studies. *J Acquir Immune Defic Syndr Hum Retrovirol*. 1999;20(4):323-333. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10096575.
3. Benaboud S, Hirt D, Launay O, et al. Pregnancy-related effects on tenofovir pharmacokinetics: a population study with 186 women. *Antimicrob Agents Chemother*. 2012;56(2):857-862. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22123690.
4. Best BM, Burchett S, Li H, et al. Pharmacokinetics of tenofovir during pregnancy and postpartum. *HIV Med*. 2015;16(8):502-511. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25959631.
5. Colbers AP, Hawkins DA, Gingelmaier A, et al. The pharmacokinetics, safety and efficacy of tenofovir and emtricitabine in HIV-1-infected pregnant women. *AIDS*. 2013;27(5):739-748. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23169329.
6. Prya M, Anderson PL, Mugwanya KK, et al. Concentrations of TFV-DP during pregnancy among women using PrEP. Abstract 809. Presented at: Conference on Retroviruses and Opportunistic Infections. 2018. Boston, Massachusetts. Available at: http://www.croiconference.org/sessions/concentrations-tfv-dp-during-pregnancy-among-women-using-prep.
7. Bonora S, de Requena DG, Chiesa E, et al. Transplacental passage of tenofovir and other ARVs at delivery. Presented at: 14th Conference on Retoviruses and Opportunistic Infections. 2007. Los Angeles, CA.
8. Hirt D, Urien S, Ekouevi DK, et al. Population pharmacokinetics of tenofovir in HIV-1-infected pregnant women and their neonates (ANRS 12109). *Clin Pharmacol Ther*. 2009;85(2):182-189. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18987623.
9. Flynn PM, Mirochnick M, Shapiro DE, et al. Pharmacokinetics and safety of single-dose tenofovir disoproxil fumarate and emtricitabine in HIV-1-infected pregnant women and their infants. *Antimicrob Agents Chemother*. 2011;55(12):5914-5922. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21896911.
10. Mirochnick M, Taha T, Kreitchmann R, et al. Pharmacokinetics and safety of tenofovir in HIV-infected women during labor and their infants during the first week of life. *J Acquir Immune Defic Syndr*. 2014;65(1):33-41. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23979002.
11. Hirt D, Ekouevi DK, Pruvost A, et al. Plasma and intracellular tenofovir pharmacokinetics in the neonate (ANRS 12109 trial, step 2). *Antimicrob Agents Chemother*. 2011;55(6):2961-2967. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21464249.
12. Mugwanya KK, Hendrix CW, Mugo NR, et al. Pre-exposure prophylaxis use by breastfeeding HIV-uninfected women: a prospective short-term study of antiretroviral excretion in breast milk and infant absorption. *PLoS Med*. 2016;13(9):e1002132. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27676257.
13. Waitt C, Olagunju A, Nakalema S, et al. Plasma and breast milk pharmacokinetics of emtricitabine, tenofovir and lamivudine using dried blood and breast milk spots in nursing African mother-infant pairs. *J Antimicrob Chemother*. 2018. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29309634.
14. Maskew M, Westreich D, Firnhaber C, Sanne I. Tenofovir use and pregnancy among women initiating HAART. *AIDS*. 2012;26(18):2393-2397. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22951630.
15. Mugo NR, Hong T, Celum C, et al. Pregnancy incidence and outcomes among women receiving preexposure prophylaxis for HIV prevention: a randomized clinical trial. *JAMA*. 2014;312(4):362-371. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25038355.
16. Brogly SB, Abzug MJ, Watts DH, et al. Birth defects among children born to human immunodeficiency virus-infected women: pediatric AIDS clinical trials protocols 219 and 219C. *Pediatr Infect Dis J*. 2010;29(8):721-727. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20539252.
17. Knapp KM, Brogly SB, Muenz DG, et al. Prevalence of congenital anomalies in infants with *in utero* exposure to antiretrovirals. *Pediatr Infect Dis J*. 2012;31(2):164-170. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21983213.
18. Williams PL, Crain M, Yildirim C, et al. Congenital anomalies and *in utero* antiretroviral exposure in human immunodeficiency virus-exposed uninfected infants. *JAMA Pediatr*. 2015;169(1):45-55. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25383770.
19. Sibiude J, Mandelbrot L, Blanche S, et al. Association between prenatal exposure to antiretroviral therapy and birth defects: an analysis of the French perinatal cohort study (ANRS CO1/CO11). *PLoS Med*. 2014;11(4):e1001635. Available

at: http://www.ncbi.nlm.nih.gov/pubmed/24781315.

20. Gibb DM, Kizito H, Russell EC, et al. Pregnancy and infant outcomes among HIV-infected women taking long-term ART with and without tenofovir in the DART trial. *PLoS Med*. 2012;9(5):e1001217. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22615543.
21. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral pregnancy registry international interim report for 1 January 1989–31 January 2018. Wilmington, NC: Registry Coordinating Center. 2018. Available at: http://www.apregistry.com/.
22. Siberry GK, Williams PL, Mendez H, et al. Safety of tenofovir use during pregnancy: early growth outcomes in HIV-exposed uninfected infants. *AIDS*. 2012;26(9):1151-1159. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22382151.
23. Ransom CE, Huo Y, Patel K, et al. Infant growth outcomes after maternal tenofovir disoproxil fumarate use during pregnancy. *J Acquir Immune Defic Syndr*. 2013;64(4):374-381. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24169122.
24. Jao J, Abrams EJ, Phillips T, Petro G, Zerbe A, Myer L. *In utero* tenofovir exposure Is not associated with fetal long bone growth. *Clin Infect Dis*. 2016. Available at: http://www.ncbi.nlm.nih.gov/pubmed/27009251.
25. le Roux SM, Jao J, Brittain K, et al. Tenofovir exposure *in utero* and linear growth in HIV-exposed, uninfected infants. *AIDS*. 2017;31(1):97-104. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27898591.
26. Denneman L, Cohen S, Godfried MH, et al. In-utero exposure to tenofovir is associated with impaired fetal and infant growth: need for follow-up studies in combination antiretroviral therapy/HIV-exposed infants. *AIDS*. 2016;30(13):2135-2137. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27465280.
27. 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.
28. Zash R, Jacobsen DM, Mayondi G, et al. Dolutegravir/tenofovir/emtricitabine (DTG/TDF/FTC) started in pregnancy is as safe as efavirenz/tenofovir/emtricitabine (EFV/TDF/FTC) in nationwide birth outcomes surveillance in Botswana. Presented at: 9th International AIDS Society Conference. 2017. Paris, France.
29. Rough K, Seage GR, 3rd, Williams PL, et al. Birth outcomes for pregnant women with HIV using tenofovir-emtricitabine. *N Engl J Med*. 2018;378(17):1593-1603. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29694825.
30. Jourdain G, Ngo-Giang-Huong N, Harrison L, et al. Tenofovir versus placebo to prevent perinatal transmission of hepatitis B. *N Engl J Med*. 2018;378(10):911-923. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29514030.
31. Brophy J, Lee T, Bitnun A, Kakkar F, et al. Is tenofovir use in pregnancy associated with preterm delivery? A Canadian perinatal HIV surveillence program analysis. Presented at: 9th IAS Conference on HIV Science. 2017. Paris, France. Available at: http://programme.ias2017.org/PAGMaterial/eposters/3898.pdf.
32. Flanagan S, Barnes L, Anderson J, Barber T. The effect of tenofovir on renal function in HIV-positive pregnant women. *J Int AIDS Soc*. 2014;17(4 Suppl 3):19694. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25397444.
33. Williams PL, Hazra R, Van Dyke RB, et al. Antiretroviral exposure during pregnancy and adverse outcomes in HIV-exposed uninfected infants and children using a trigger-based design. *AIDS*. 2016;30(1):133-144. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26731758.
34. Pintye J, Langat A, Singa B, et al. Maternal tenofovir disoproxil fumarate use in pregnancy and growth outcomes among HIV-exposed uninfected infants in Kenya. *Infect Dis Obstet Gynecol*. 2015;2015:276851. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26823647.
35. Liotta G, Floridia M, Andreotti M, et al. Growth indices in breastfed infants pre and postnatally exposed to tenofovir compared with tenofovir-unexposed infants. *AIDS*. 2016;30(3):525-527. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26765942.
36. Vigano A, Mora S, Giacomet V, et al. *In utero* exposure to tenofovir disoproxil fumarate does not impair growth and bone health in HIV-uninfected children born to HIV-infected mothers. *Antivir Ther*. 2011;16(8):1259-1266. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22155907.
37. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26060285.
38. Floridia M, Liotta G, Andreotti M, et al. Serum phosphate and creatinine levels in the first year of life in infants born to HIV-positive mothers receiving tenofovir-based combination regimens during pregnancy and prolonged breastfeeding in an option B+ program in Malawi. *J Acquir Immune Defic Syndr*. 2016;73(5):e90-e91. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27559686.

Zidovudine (Retrovir, AZT, ZDV)

(Last updated December 7, 2018; last reviewed December 7, 2018)

Available evidence does not suggest that zidovudine use by pregnant women is associated with an increased risk of adverse fetal or pregnancy outcomes.[1]

Animal Studies

Carcinogenicity

Zidovudine was shown to be mutagenic in two *in vitro* assays and clastogenic in one *in vitro* assay and two *in vivo* assays, but not cytogenic in a single-dose *in vivo* rat study. Long-term carcinogenicity studies have been performed with zidovudine in mice and rats.[2] In mice, seven late-appearing (>19 months) vaginal neoplasms (five nonmetastasizing squamous cell carcinomas, one squamous cell papilloma, and one squamous polyp) occurred in animals given the highest dose. One late-appearing squamous cell papilloma occurred in the vagina of an animal given an intermediate dose. No vaginal tumors were found at the lowest dose. In rats, two late-appearing (>20 months), nonmetastasizing vaginal squamous cell carcinomas occurred in animals given the highest dose. No vaginal tumors occurred at the low or middle dose in rats. No other drug-related tumors were observed in either sex in either species. At doses that produced tumors in mice and rats, the estimated drug exposure (as measured by area under the curve [AUC]) was approximately three times (mice) and 24 times (rats) the estimated human exposure at the recommended therapeutic dose of 100 mg every 4 hours. How predictive the results of rodent carcinogenicity studies may be for humans is unknown.[1]

Two trans-placental carcinogenicity studies were conducted in mice.[3,4] In one study, zidovudine was administered at doses of 20 mg/kg/day or 40 mg/kg/day from gestational day 10 through parturition and lactation, with postnatal dosing continuing in offspring for 24 months.[4] The drug doses administered in this study produced zidovudine exposures approximately three times the estimated human exposure at recommended doses. After 24 months, an increase in incidence of vaginal tumors was noted with no increase in tumors in the liver or lung or any other organ in either gender. These findings are consistent with results of the standard oral carcinogenicity study in mice, as described earlier. In a second study, zidovudine was administered at maximum tolerated doses of 12.5 mg/day or 25 mg/day (~1000 mg/kg nonpregnant body weight or ~450 mg/kg of term body weight) to pregnant mice from days 12 to 18 of gestation.[3] There was an increase in the number of tumors in the lung, liver, and female reproductive tracts in the offspring of mice receiving the higher dose of zidovudine.

Reproduction/Fertility

When administered to male and female rats at doses up to seven times the usual adult dose based on body surface area, zidovudine had no effect on fertility, as judged by rates of conception. Zidovudine has been shown to have no effect on reproduction or fertility in rodents. A dose-related cytotoxic effect on preimplantation mouse embryos can occur, with inhibition of blastocyst and post-blastocyst development at zidovudine concentrations similar to levels achieved with human therapeutic doses.[5]

Teratogenicity/Adverse Pregnancy Outcomes

In animal reproduction studies, administration of oral zidovudine to female rats prior to mating and throughout gestation resulted in embryotoxicity at doses that produced systemic exposure (expressed as AUC) approximately 33 times higher than human exposures at the recommended clinical dose. However, no embryotoxicity was observed after administration to pregnant rats during organogenesis at doses that produced AUC approximately 117 times higher than clinical exposures. Administration of oral zidovudine to pregnant rabbits during organogenesis resulted in embryotoxicity at doses that produced exposures approximately 108 times higher than the clinical exposure. No embryotoxicity was observed at doses that produced exposures approximately 23 times higher than clinical exposures.[1]

In an additional teratology study in rats, a dose of 3000 mg/kg/day (very near the oral median lethal dose in rats of 3683 mg/kg) caused marked maternal toxicity and an increase in incidence of fetal malformations. This dose resulted in peak zidovudine plasma concentrations 350 times peak human plasma concentrations

(estimated AUC in rats at this dose level was 300 times the daily AUC in humans given 600 mg/day). No evidence of teratogenicity was seen in this experiment at doses of 600 mg/kg/day or less.

Human Studies in Pregnancy

Pharmacokinetics

Zidovudine pharmacokinetics (PK) are not significantly altered by pregnancy, and standard adult doses are recommended.[6,7] A population PK analysis following oral and intravenous (IV) zidovudine doses during pregnancy and labor found high fetal exposure to zidovudine with current IV intrapartum dosing regimens. Simulations from this modeling suggested that reduced intrapartum zidovudine dosing regimens might provide lower but still adequate fetal zidovudine exposures.[8] However, standard dosing of IV zidovudine during labor continues to be recommended. In pregnant women, as with nonpregnant adults, intracellular zidovudine triphosphate concentrations do not vary with plasma concentrations, over a wide range of plasma zidovudine concentrations.[9]

Placental and Breast Milk Passage

Zidovudine rapidly crosses the human placenta, achieving cord-to-maternal-blood ratios of about 0.80. The ratio of zidovudine in amniotic fluid to that in maternal plasma is 1.5.[10] Zidovudine is excreted into human breast milk with breast milk-to-maternal-plasma zidovudine concentration ratios ranging from 0.44 to 1.35. No zidovudine was detectable in the plasma of nursing infants who received zidovudine only via breast milk.[11-13]

Teratogenicity/Adverse Pregnancy Outcomes

In PACTG 076, the incidence of minor and major congenital abnormalities was similar between groups that received either zidovudine or placebo, and no specific patterns of defects were seen.[6,14] Similarly, no increase in birth defects was detected among infants enrolled in the large observational cohorts PACTG 219/219C and P1025.[15,16] A previous report from the Women and Infants Transmission Study described a 10-fold increased risk of hypospadias among infants who received zidovudine, but this finding was not confirmed in a more detailed analysis.[17,18] In the PHACS/SMARTT cohort, there was no association between first-trimester exposure to zidovudine and congenital anomalies.[19] In the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposures to zidovudine have been monitored to be able to detect at least a 1.5-fold increased risk of overall birth defects and a 2-fold increased incidence of defects in the more common classes, including the cardiovascular and genitourinary systems. No such increase in birth defects has been observed with zidovudine. With first-trimester zidovudine exposure, the prevalence of birth defects was 3.2% (134 of 4,178 births; 95% CI, 2.7% to 3.8%), compared with a total prevalence in the U.S. population of 2.72%, based on Centers for Disease Control and Prevention surveillance.[20] Similarly, a series of 897 infants exposed to HIV born in Spain during 2000 through 2009 reported no increase in birth defects among infants with first-trimester zidovudine exposure (adjusted odds ratio [aOR] 1.21, 0.56–2.63).[21] A Bayesian analysis that combined a meta-analysis with data from Medicaid Analytic eXtract found no association between zidovudine exposure during the first trimester and most congenital malformations.[22]

The French Perinatal Cohort reported that first-trimester zidovudine exposure was associated with congenital heart defects (1.5% of 3,262 exposures vs. 0.7% of nonexposures; aOR 2.2, 95% CI, 1.5–3.2). However, an analysis of cardiac defects among all prenatal zidovudine-exposed infants in the Antiretroviral Pregnancy Registry (n = 13,703) reported no difference in the prevalence of ventricular septal defect and congenital heart defects among infants exposed to zidovudine-containing regimens (9 of 4,000 infants exposed during the first trimester, rate 0.23; 22 of 9,047 infants with later exposure, rate 0.24, $P = 1.00$) and zidovudine-non-containing regimens (2 of 1,839 infants exposed during the first trimester, rate 0.11; 3 of 538 infants with later exposure, rate 0.56, $P = 0.08$).[23]

In the PRIMEVA trial, mothers were randomized to receive antepartum treatment with zidovudine/lamivudine/lopinavir/ritonavir or lopinavir/ritonavir (LPV/r). Female infants of women in the first group had a higher left ventricular shortening fraction at 1 month and increased posterior wall thickness at 1 year,

suggestive of myocardial remodeling, when compared to infants whose mothers received LPV/r alone.[24] In a study that performed fetal echocardiography on 42 fetuses who had been exposed to HIV but who were not infected and 84 fetuses without HIV exposure, multivariate analysis revealed that maternal zidovudine treatment was associated with thicker myocardial walls and smaller left ventricular cavities among infants exposed to zidovudine compared to other infants with or without HIV exposure. Maternal zidovudine treatment was the only factor significantly associated with fetal cardiac changes.[25]

Cancer has been observed no more frequently among zidovudine-exposed infants than among other HIV-exposed or HIV-unexposed infants in a long-term follow-up study for the original PACTG 076 study,[26] in prospective cohort studies,[27] and in matches between HIV surveillance and cancer registries.[28,29]

Other Safety Information

In the placebo-controlled perinatal trial PACTG 076, no difference in disease progression was seen between women who received zidovudine and those who received a placebo, based on follow-up through 4 years postpartum.[30]

No differences in immunologic, neurologic, or growth parameters were seen between PACTG 076 infants with *in utero* zidovudine exposure and those who received a placebo, based on nearly 6 years of follow-up.[14,26]

Mitochondrial dysfunction in mothers and infants exposed to nucleoside reverse transcriptase inhibitors (NRTIs) during pregnancy has been described in some case reports, case series, prospective cohorts, and surveillance systems, but not in others. The result of the dysfunction, although fatal in a few cases, is more often asymptomatic and self-limited (e.g., leukopenia, anemia). At present, the risk of NRTI-associated mitochondrial dysfunction in these mother-infant pairs, while a recognized possibility, does not outweigh the clear benefit of these drugs in preventing perinatal HIV transmission.

The PHACS/SMARTT cohort used a "trigger-based design" in which several domains (e.g., metabolic) had predetermined "triggers;" children meeting the definition of a trigger were further investigated to determine if they had met the definition of a "case" in that domain. The study found that after adjusting for birth cohort and other factors, zidovudine was associated with increased risk of meeting the study's definition of a metabolic case (adjusted relative risk 1.69; 95% CI, 1.08–2.64).[31,32]

Excerpt from Table 10[a]

Note: When using FDCs, refer to other sections in Appendix B and Table 10 for information about the dosing and safety of individual drug components of the FDC during pregnancy.

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations	Use in Pregnancy
Zidovudine (ZDV) *Retrovir* (ZDV/3TC) *Combivir* (ZDV/ABC/3TC) *Trizivir* **Note:** Generics are approved for all formulations.	ZDV (Retrovir) *Capsule:* • 100 mg *Tablet:* • 300 mg *Oral Solution:* • 10 mg/mL *Intravenous Solution:* • 10 mg/mL ZDV/3TC (Combivir): • ZDV 300 mg plus 3TC 150 mg tablet ZDV/ABC/3TC (Trizivir): • ZDV 300 mg plus 3TC 150 mg plus ABC 300 mg tablet	Standard Adult Dose *ZDV (Retrovir):* • ZDV 300 mg BID or ZDV 200 mg TID without regard to food *Active Labor:* • ZDV 2 mg/kg IV loading dose, followed by ZDV 1 mg/kg/hour continuous infusion from beginning of active labor until delivery *Combivir:* • 1 tablet twice daily without regard to food *Trizivir:* • 1 tablet twice daily without regard to food Dosing in Pregnancy: • No change in dose is indicated. PK in Pregnancy: • PK is not significantly altered in pregnancy. • For guidance about use of combination products in pregnancy, please see the specific sections on other components (i.e., ABC, 3TC)	High placental transfer to fetus.[b] No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects).

[a] Individual ARV drug dosages may need to be adjusted in patients with renal or hepatic insufficiency (for details, see the Adult and Adolescent Antiretroviral Guidelines, Appendix B, Table 8).

[b] Placental transfer categories are determined by mean or median cord blood/maternal delivery plasma drug ratio:

High: >0.6 **Moderate:** 0.3–0.6 **Low:** <0.3

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral BID = twice daily; FDC = fixed-dose combination; IV = intravenous; PK = pharmacokinetic; TID = three times a day; ZDV = zidovudine

References

1. Zidovudine [package insert]. Food and Drug Administration. 2017. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2017/019655s055,019910s042,019951s033lbl.pdf.
2. Ayers KM, Clive D, Tucker WE, Jr., Hajian G, de Miranda P. Nonclinical toxicology studies with zidovudine: genetic toxicity tests and carcinogenicity bioassays in mice and rats. *Fundam Appl Toxicol*. 1996;32(2):148-158. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8921318.
3. Olivero OA, Anderson LM, Diwan BAea. Transplacental effects of 3'-azido-2',3'-dideoxythymidine (AZT): tumorigenicity in mice and genotoxicity in mice and monkeys. *J National Cancer Inst*. 1997;89(21):1602-1608. Available at: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9362158&dopt=Abstract.
4. Ayers KM, Torrey CE, Reynolds DJ. A transplacental carcinogenicity bioassay in CD-1 mice with zidovudine. *Fundam Appl Toxicol*. 1997;38(2):195-198. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9299194.
5. Toltzis P, Marx CM, Kleinman N, Levine EM, Schmidt EV. Zidovudine-associated embryonic toxicity in mice. *J Infect Dis*. 1991;163(6):1212-1218. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2037787.
6. Connor EM, Sperling RS, Gelber R, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. Pediatric AIDS clinical trials group protocol 076 study group. *N Engl J Med*. 1994;331(18):1173-1180. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7935654.
7. O'Sullivan MJ, Boyer PJ, Scott GBea. The pharmacokinetics and safety of zidovudine in the third trimester

of pregnancy for women infected with human immunodeficiency virus and their infants: phase I acquired immunodeficiency syndrome clinical trials group study (protocol 082). Zidovudine collaborative working group. *Am J Obstet Gynecol*. 1993;168(5):1510-1516. Available at: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=8098905.

8. Fauchet F, Treluyer JM, Valade E, et al. Maternal and fetal zidovudine pharmacokinetics during pregnancy and labour: too high dose infused at labour? *Br J Clin Pharmacol*. 2014;78(6):1387-1396. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25040510.
9. Kinai E, Kato S, Hosokawa S, et al. High Plasma concentrations of zidovudine (AZT) do not parallel intracellular concentrations of AZT-triphosphates in infants during prevention of mother-to-child HIV-1 transmission. *J Acquir Immune Defic Syndr*. 2016;72(3):246-253. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26859826.
10. Bennetto-Hood C, Bryson YJ, Stek A, King JR, Mirochnick M, Acosta EP. Zidovudine, lamivudine, and nelfinavir concentrations in amniotic fluid and maternal serum. *HIV Clin Trials*. 2009;10(1):41-47. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19362995.
11. Mirochnick M, Thomas T, Capparelli E, et al. Antiretroviral concentrations in breast-feeding infants of mothers receiving highly active antiretroviral therapy. *Antimicrob Agents Chemother*. 2009;53(3):1170-1176. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19114673.
12. Palombi L, Pirillo MF, Andreotti M, et al. Antiretroviral prophylaxis for breastfeeding transmission in Malawi: drug concentrations, virological efficacy and safety. *Antivir Ther*. 2012;17(8):1511-1519. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22910456.
13. Corbett AH, Kayira D, White NR, et al. Antiretroviral pharmacokinetics in mothers and breastfeeding infants from 6 to 24 weeks post partum: results of the BAN study. *Antivir Ther*. 2014. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24464632.
14. Sperling RS, Shapiro DE, McSherry GD, et al. Safety of the maternal-infant zidovudine regimen utilized in the pediatric AIDS clinical trial group 076 study. *AIDS*. 1998;12(14):1805-1813. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9792381.
15. Brogly SB, Abzug MJ, Watts DH, et al. Birth defects among children born to human immunodeficiency virus-infected women: pediatric AIDS clinical trials protocols 219 and 219C. *Pediatr Infect Dis J*. 2010;29(8):721-727. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20539252.
16. Knapp KM, Brogly SB, Muenz DG, et al. Prevalence of congenital anomalies in infants with in utero exposure to antiretrovirals. *Pediatr Infect Dis J*. 2012;31(2):164-170. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21983213.
17. Watts DH, Li D, Handelsman E, et al. Assessment of birth defects according to maternal therapy among infants in the women and infants transmission study. *J Acquir Immune Defic Syndr*. 2007;44(3):299-305. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17159659.
18. Vannappagari V, et al. Zidovudine exposure during pregnancy and hypospadias in infants: data from the antiretroviral pregnancy registry, 1989-2011. Abstract no. MOPE070. Presented at: 19th International AIDS Conference. 2012. Washington, DC.
19. Williams PL, Crain M, Yildirim C, et al. Congenital anomalies and in utero antiretroviral exposure in human immunodeficiency virus-exposed uninfected infants. *JAMA Pediatr*. 2015;169(1):45-55. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25383770.
20. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral pregnancy registry international interim report for 1 January 1989–31 January 2018. Wilmington, NC: Registry Coordinating Center. 2018. Available at: http://www.apregistry.com/.
21. Prieto LM, Gonzalez-Tome MI, Munoz E, et al. Birth defects in a cohort of infants born to HIV-infected women in Spain, 2000–2009. *BMC Infect Dis*. 2014;14:700. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25808698.
22. Rough K, Sun JW, Seage GR, 3rd, et al. Zidovudine use in pregnancy and congenital malformations. *AIDS*. 2017;31(12):1733-1743. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28537936.
23. Vannappagari V, Albano JD, Koram N, Tilson H, Scheuerle AE, Napier MD. Prenatal exposure to zidovudine and risk for ventricular septal defects and congenital heart defects: data from the antiretroviral pregnancy registry. *Eur J Obstet Gynecol Reprod Biol*. 2016;197:6-10. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26687320.
24. Sibiude J, Le Chenadec J, Bonnet D, et al. In utero exposure to zidovudine and heart anomalies in the ANRS French perinatal cohort and the nested PRIMEVA randomized trial. *Clin Infect Dis*. 2015. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25838291.
25. Garcia-Otero L, Lopez M, Gomez O, et al. Zidovudine treatment in HIV-infected pregnant women is associated with fetal cardiac remodelling. *AIDS*. 2016;30(9):1393-1401. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26919731.
26. Culnane M, Fowler M, Lee SS, et al. Lack of long-term effects of in utero exposure to zidovudine among uninfected children born to HIV-infected women. Pediatric AIDS clinical trials group protocol 219/076 teams. *JAMA*.

1999;281(2):151-157. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9917118.

27. Hanson IC, Antonelli TA, Sperling RS, et al. Lack of tumors in infants with perinatal HIV-1 exposure and fetal/neonatal exposure to zidovudine. *J Acquir Immune Defic Syndr Hum Retrovirol*. 1999;20(5):463-467. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10225228.
28. Ivy W, 3rd, Nesheim SR, Paul SM, et al. Cancer among children with perinatal exposure to HIV and antiretroviral medications—New Jersey, 1995–2010. *J Acquir Immune Defic Syndr*. 2015;70(1):62-66. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26017660.
29. Hankin C, Lyall H, Peckham C, Tookey P. Monitoring death and cancer in children born to HIV-infected women in England and Wales: use of HIV surveillance and national routine data. *AIDS*. 2007;21(7):867-869. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17415042.
30. Bardeguez AD, Shapiro DE, Mofenson LM, et al. Effect of cessation of zidovudine prophylaxis to reduce vertical transmission on maternal HIV disease progression and survival. *J Acquir Immune Defic Syndr*. 2003;32(2):170-181. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12571527.
31. Williams PL, Hazra R, Van Dyke RB, et al. Antiretroviral exposure during pregnancy and adverse outcomes in HIV-exposed uninfected infants and children using a trigger-based design. *AIDS*. 2016;30(1):133-144. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26731758.
32. Van Dyke RB, Chadwick EG, Hazra R, Williams PL, Seage GR, 3rd. The PHACS SMARTT study: assessment of the safety of *in utero* exposure to antiretroviral drugs. *Front Immunol*. 2016;7:199. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27242802.

Glossary of Terms for Supplement
Carcinogenic: Producing or tending to produce cancer • Some agents, such as certain chemicals or forms of radiation, are both mutagenic and clastogenic. • Genetic mutations and/or chromosomal damage can contribute to cancer formation.
Clastogenic: Causing disruption of or breakages in chromosomes
Genotoxic: Damaging to genetic material such as DNA and chromosomes
Mutagenic: Inducing or capable of inducing genetic mutation
Teratogenic: Interfering with fetal development and resulting in birth defects

Five non-nucleoside reverse transcriptase inhibitors (NNRTIs) have been approved by the U.S. Food and Drug Administration (FDA): delavirdine, efavirenz, etravirine, nevirapine, and rilpivirine. Delavirdine is no longer available in the United States and therefore will not be reviewed in this section.

Doravirine (Pifeltro, DOR)

(Last updated December 7, 2018; last reviewed December 7, 2018)

There are insufficient human data on the use of doravirine in pregnancy to inform a drug-associated risk determination for birth defects and miscarriage.

Animal Studies

Carcinogenicity

Doravirine was not carcinogenic in long-term oral carcinogenicity studies in mice and rats at exposures up to 6 times and 7 times, respectively, the exposure seen in humans who received the recommended dose. A statistically significant incidence of thyroid parafollicular cell adenoma and carcinoma was observed among female rats who received a high dose of doravirine; however, this incidence was similar to the incidence observed among historical controls of the same species. Doravirine was not genotoxic in a battery of *in vitro* or *in vivo* mutagenicity assays.[1]

Reproduction/Fertility

In rats, doravirine did not affect fertility, reproductive performance, or early embryonic development at exposures (area under the curve [AUC]) that were approximately 7 times the exposure seen in humans who received the recommended dose.[1]

Teratogenicity/Adverse Pregnancy Outcomes

No adverse embryo-fetal effects were observed in rats and rabbits at doravirine exposures (AUC) that were approximately 9 times (in rats) and 8 times (in rabbits) the exposures seen in humans who received the recommended dose. Similarly, no adverse developmental findings were reported in a prenatal/postnatal study in rats at doravirine exposures that were approximately 9 times the exposure seen in humans who received the recommended dose.[1]

Placental and Breast Milk Passage

Embryo-fetal studies in rats and rabbits demonstrate placental passage of doravirine. Fetal plasma concentrations observed on gestation day 20 were up to 40% (in rabbits) and 52% (in rats) of maternal concentrations. Doravirine was excreted into the milk of lactating rats at concentrations approximately 1.5 times the maternal concentrations measured 2 hours post-dose on lactation day 14.[1]

Human Studies in Pregnancy

Pharmacokinetics

No pharmacokinetic studies of doravirine in pregnant women have been reported.

Placental and Breast Milk Passage

No data are available on placental or breast milk passage of doravirine in humans.

Teratogenicity/Adverse Pregnancy Outcomes

No data are available to inform the risk for birth defects following exposure to doravirine.

Excerpt from Table 10[a]

Note: When using FDCs, refer to other sections in Appendix B and Table 10 for information about the dosing and safety of the individual drug components of the FDC during pregnancy.

Generic Name (Abbreviation) *Trade Name*)	**Formulation**	**Dosing Recommendations**	**Use in Pregnancy**
Doravirine (DOR) *Pifeltro* (DOR/3TC/TDF) *Delstrigo*	DOR (Pifeltro): • 100 mg tablet DOR/3TC/TDF (Delstrigo): • DOR 100 mg plus 3TC 300 mg plus TDF 300 mg tablet	Standard Adult Dose *DOR (Pifeltro):* • 100 mg once daily with or without food *DOR/3TC/TDF (Delstrigo):* • 1 tablet once daily with or without food PK in Pregnancy: • No PK studies in human pregnancy. Dosing in Pregnancy: • Insufficient data to make dosing recommendation. For guidance about use of combination products in pregnancy, please see the specific sections on other components (i.e., 3TC, TDF)	No human data are available on placental transfer of DOR, but animal studies suggest that DOR crosses the placenta. Insufficient data to assess for teratogenicity in humans. No evidence of teratogenicity in rats or rabbits.

[a] Individual ARV drug doses may need to be adjusted in patients with renal or hepatic insufficiency (for details, see the Adult and Adolescent Guidelines, Appendix B, Table 8).

Key to Acronyms: 3TC = lamivudine; ARV = antiretroviral; DOR = doravirine; FDC = fixed-dose combination; PK = pharmacokinetic; TDF = tenofovir disoproxil fumarate

References

1. Doravirine [package insert]. Food and Drug Administration. 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210806s000lbl.pdf.

Efavirenz (Sustiva, EFV)

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The Food and Drug Administration (FDA) cautions that efavirenz should not be used in the first trimester of pregnancy because of the potential risk of neural tube defects, which have been observed among children exposed to efavirenz *in utero* and in animal studies.[1]

However, the current Perinatal Guidelines, based on a review of updated evidence, do not include a restriction on the use of efavirenz in pregnant women or in women who are planning to become pregnant. This is consistent with both the British HIV Association guidelines and World Health Organization (WHO) guidelines for use of antiretroviral (ARV) drugs in pregnancy.

Animal Studies

Carcinogenicity

Efavirenz was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests. A study that evaluated the genotoxicity of efavirenz in mice noted DNA damage in brain cells after daily dosing for 36 days; no damage was seen in liver, heart, or peripheral blood cells.[2] Long-term animal carcinogenicity studies with efavirenz have been completed in mice and rats. At systemic drug exposures that were approximately 1.7-fold higher than the exposures seen in humans who received standard therapeutic doses, no increase in tumor incidence above background was observed in male mice. In female mice, an increase in tumor incidence above background was seen in hepatocellular adenomas and carcinomas and pulmonary alveolar/bronchiolar adenomas. No increase in tumor incidence above background was observed in male and female rats with systemic efavirenz exposures that were lower than those seen in humans who received therapeutic doses.[1]

Reproduction/Fertility

No effect of efavirenz on reproduction or fertility in rodents has been seen.[1]

Teratogenicity/Adverse Pregnancy Outcomes

An increase in fetal resorption was observed in female rats at efavirenz doses that produced peak plasma concentrations and area under the curve (AUC) values that were less than or equal to those achieved in humans who received the recommended dose of efavirenz 600 mg once daily. Efavirenz produced no reproductive toxicities when given to pregnant rabbits at doses that produced peak plasma concentrations similar to and AUC values approximately half of those achieved in humans administered efavirenz (600 mg once daily).[1]

Central nervous system (CNS) malformations and cleft palate were observed in three of 20 infants born to pregnant cynomolgus monkeys that received efavirenz between gestational day 20 and gestational day 150 at a dose of efavirenz 60 mg/kg/day. This dose resulted in plasma concentrations that were 1.3 times that of systemic human therapeutic exposure, with fetal umbilical venous drug concentrations that were approximately 0.7 times the maternal values.[3] The malformations included anencephaly and unilateral anophthalmia in one fetus, microphthalmia in another fetus, and cleft palate in a third fetus.[1]

Placental and Breast Milk Passage

Efavirenz readily crosses the placenta in rats, rabbits, and primates, producing cord blood concentrations similar to concentrations in maternal plasma. Maternal and fetal blood concentrations in pregnant rabbits and cynomolgus monkeys are equivalent, while fetal concentrations in rats exceeded maternal concentrations.[1]

Human Studies in Pregnancy

Pharmacokinetics/Pharmacogenomics

In an intensive sampling pharmacokinetic (PK) study of 25 pregnant women who received efavirenz during the third trimester, efavirenz clearance was slightly increased and trough levels were decreased compared with levels measured postpartum.[4] These differences are not of sufficient magnitude to warrant dose adjustment during pregnancy. A review of this study plus four others that measured efavirenz concentrations in pregnant

women found that efavirenz concentrations were not significantly affected by pregnancy and that high rates of HIV RNA suppression at delivery were achieved with efavirenz-based regimens.[5]

In a pharmacogenomics study, nonpregnant individuals with the cytochrome P (CYP) 2B6 516 TT genotype had >3-fold increases in both short-term and long-term efavirenz exposure, as measured by plasma and hair drug levels. This suggests that there could be significant variation in drug levels with CYP2B6 polymorphisms.[6] The frequency of this allele varies between different ethnic populations, with a prevalence of 3.4% in white people, 6.7% in Hispanic people, and 20% in African Americans.[4]

Placental and Breast Milk Passage

In a study of 25 mother-infant pairs, the median efavirenz cord blood/maternal blood concentration ratio was 0.49 (range 0.37–0.74).[4] In a study of 13 women in Rwanda, efavirenz was given during the last trimester of pregnancy and for 6 months after delivery.[7] Efavirenz concentrations were measured in maternal plasma, breast milk, and infant plasma. Efavirenz concentration was significantly higher in maternal plasma than in skim breast milk (with a mean breast milk to mean maternal plasma concentration ratio of 0.54) and higher in skim breast milk than in infant plasma (with a mean skim breast milk to mean newborn plasma concentration ratio of 4.08). Mean infant plasma efavirenz concentrations were 860 ng/mL, and the mean infant plasma efavirenz concentration was 13.1% of maternal plasma concentrations. All infants had detectable plasma concentrations of efavirenz, and eight of 13 newborns had plasma efavirenz concentrations below the minimum therapeutic concentration of 1,000 ng/mL recommended for treatment of adults with HIV. In a study of 51 women in Nigeria who received efavirenz 600 mg daily, the median milk/maternal plasma concentration ratio was 0.82 (range 0.51–1.1) and the median (range) infant efavirenz concentration was 178 ng/mL (range 88–340 ng/mL).[8] In a study of 56 mother-infant pairs in which the mothers received efavirenz-based therapy during pregnancy and breastfeeding, infant plasma drug concentration levels at delivery and hair drug concentration levels at age 12 weeks suggested moderate *in utero* transfer of efavirenz during pregnancy and breastfeeding, with approximately one-third of transfer occurring postpartum (40% cumulative transfer, with 15% of transfer occurring during breastfeeding).[9] All mothers and infants had detectable efavirenz plasma levels at 0, 8, and 12 weeks, and mean infant-to-maternal hair concentration at 12 weeks postpartum was 0.40 for efavirenz. No data currently are available about the safety and PK of efavirenz in neonates.

Teratogenicity/Adverse Pregnancy Outcomes

In pregnancies with prospectively reported exposure to efavirenz-based regimens in the Antiretroviral Pregnancy Registry through January 2018 birth defects were observed in 24 of 1,023 live births with first-trimester exposure (2.35%, 95% CI, 1.51% to 3.47%).[10] Although these data provide sufficient numbers of first-trimester exposures to rule out a 1.5-fold or greater increase in the risk of overall birth defects, the low incidence of neural tube defects in the general population means that a larger number of exposures are still needed to be able to definitively rule out an increased risk of this specific defect. Prospective reports to the Antiretroviral Pregnancy Registry of defects after first-trimester efavirenz exposure have documented one neural tube defect case (sacral aplasia, myelomeningocele, and hydrocephalus with fetal alcohol syndrome) and one case of bilateral facial clefts, anophthalmia, and amniotic band syndrome. An undefined abnormality of the cerebral vermis was seen on ultrasound and reported in 2014; however, at birth and with follow-up, the infant is developing normally as per the parents, who have also declined further testing.[10] Among retrospective reports, there are six reports of CNS defects, including three cases of meningomyelocele in infants born to mothers who received efavirenz during the first trimester.[1] Retrospective reports can be biased toward reporting of more unusual and severe cases and are less likely to be representative of the general population's experience.

In an updated meta-analysis of 23 studies (including Antiretroviral Pregnancy Registry data), there were 44 infants with birth defects among 2,026 live births to women who received efavirenz during the first trimester. The rate of overall birth defects was 1.63% (95% CI, 0.78% to 2.48%).[11] The rate of overall birth defects was similar among women who received efavirenz-containing regimens and women who received regimens that did not contain efavirenz during the first trimester (pooled relative risk [RR] 0.78; 95% CI, 0.56–1.08). Across all births, one neural tube defect (myelomeningocele) was observed, giving a point prevalence of 0.05% (95% CI, <0.01 to 0.28), which is within the range reported in the general population. However, the number of reported

first-trimester efavirenz exposures remains insufficient to rule out a significant increase in low-incidence birth defects (incidence of neural tube defects in the general U.S. population is 0.02% to 0.2%).

A French study of 13,124 live births between 1994 and 2010 included an analysis of 372 infants born after first-trimester efavirenz exposure.[12] In the primary analysis that used the European Surveillance of Congenital Anomalies (EUROCAT) classification system, no increase in the incidence of birth defects was detected among infants with first-trimester efavirenz exposure compared to those without efavirenz exposure in pregnancy (adjusted odds ratio 1.16; 95% CI, 0.73–1.85). In a secondary analysis that used the modified Metropolitan Atlanta Congenital Defect Program classification used by the Antiretroviral Pregnancy Registry, an association was found between first-trimester efavirenz exposure and neurologic defects. However, none of the four defects (ventricular dilatation with anomalies of the white substance, partial agenesis of the corpus callosum, subependymal cyst, and pachygyria) were neural tube defects, and none of the defects had common embryology.[13] First-trimester efavirenz exposure was not associated with an increased risk of defects in a Pediatric HIV/AIDS Cohort Study analysis that included 2,580 live births, 94 of which involved first-trimester efavirenz exposure,[14] or an analysis of a national cohort in Italy that included 1,257 pregnancies, 80 of which involved first-trimester efavirenz exposure.[15]

Although two studies (Pediatric AIDS Clinical Trials Group [PACTG] protocol 219/219C and PACTG protocol P1025) reported a higher rate of birth defects among infants with first-trimester exposure to efavirenz than among those without exposure, the number of exposures was small in both studies (35 exposures in PACTG 219/219C and 42 in P1025), and there is overlap in defect cases between the two studies.[16-18] Thus, additional data are needed on first-trimester efavirenz exposures to more conclusively determine if the risk of neural tube defects is elevated.

The FDA advises women to avoid becoming pregnant while taking efavirenz and advises health care providers to avoid administration during the first trimester of pregnancy, as fetal harm may occur. Although the limited data on first-trimester efavirenz exposure cannot rule out a two- or three-fold increased incidence of a rare outcome, such as neural tube defects, the available data from the meta-analysis on >2,000 births suggest that there is no large increase in the risk of neural tube defects with first-trimester exposure (e.g., a 10-fold increase to a rate of 1%). As a result, the current Perinatal Guidelines do not restrict the use of efavirenz in pregnancy or in women who are planning to become pregnant; this is consistent with the British HIV Association guidelines and WHO guidelines for use of ARV drugs in pregnancy, both of which note that efavirenz can be used throughout pregnancy.[19,20] Efavirenz should be continued in pregnant women who are receiving a virologically suppressive, efavirenz-based regimen, because ARV drug changes during pregnancy may be associated with loss of viral control and an increased risk of perinatal transmission.[21]

Additional Information

PK interactions between efavirenz and some hormonal contraceptives have been reported, with the potential for failure of the progesterone component. This may potentially affect the efficacy of emergency contraception, combined oral contraceptive pills, progestin-only pills, and progestin implants.[22-25] A retrospective chart review study suggests that efavirenz may decrease the efficacy of levonorgestrel implants (e.g., Jadelle).[26] Pregnancy occurred in 15 of 115 women (12.4%) who were on efavirenz and using Jadelle; no pregnancies occurred among 208 women who were on nevirapine-based regimens, and no pregnancies occurred among 13 women who were on lopinavir/ritonavir (LPV/r)-based regimens ($P < 0.001$) (see Preconception Counseling and Care). In a prospective clinical trial by Scarsi et al., three out of 20 Ugandan women (15%) became pregnant between 36 and 48 weeks with the combination of levonorgestrel and an efavirenz-based antiretroviral therapy (ART) regimen. When compared to ART-naive women, the women on efavirenz-based regimens had lower levonorgestrel PKs.[27]

P1026s evaluated the interaction between the etonogestrel-releasing implant and three ARV drug regimens (atazanavir/ritonavir, LPV/r, efavirenz) in postpartum women who chose an etonogestrel implant for contraception. There was no significant change in the concentration levels of the ARV drugs after insertion of

the etonogestrel implant. However, of the three ARV drug regimens, efavirenz use was associated with greatly decreased etonogestrel concentrations, to levels that could impair contraceptive efficacy.[28] A nonrandomized parallel group study in Ugandan women with HIV characterized the PKs of etonogestrel released from a contraceptive implant. Women who were receiving either efavirenz-based regimens or nevirapine-based regimens were compared to women who were ART-naive and not receiving ART. At 24 weeks, etonogestrel concentrations were 82% lower in women who were taking efavirenz than in ART-naive women. No significant changes in etonogestrel concentration were observed when etonogestrel was combined with nevirapine.[29] An ACTG study (A5316) evaluated pharmacokinetic interactions between etonogestrel and ethinyl estradiol from a vaginal ring and efavirenz or atazanavir/ritonavir (ATV/r). When compared to women who had yet to start an ART regimen, women in the efavirenz group had etonogestrel levels that were 76% to 79% lower and ethynyl estradiol plasma concentrations that were 53% to 57% lower over 21 days.[30] Thus, women receiving efavirenz and using combined oral contraceptive pills, progestin-only pills, the contraceptive vaginal ring, or progestin implants should be informed of the possible decreased effectiveness of these contraceptive methods and strongly advised to also use barrier contraception.

Alternative contraceptive regimens for which efficacy is not reduced while using concomitant efavirenz may also be considered. A study that evaluated the interaction between efavirenz and depot medroxyprogesterone acetate (DMPA) in 17 women found no change in the PK profile of either efavirenz or DMPA with concomitant use.[31] DMPA levels remained above the level needed for inhibition of ovulation throughout the dosing interval. In addition, intrauterine devices (both copper-containing and levonorgestrel-containing devices) would be expected to maintain efficacy when used with efavirenz-based regimens.

Excerpt from Table 10[a]

Note: When using FDCs, refer to other sections in Appendix B and Table 10 for information about the dosing and safety of individual drug components of the FDC during pregnancy.

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations	Use in Pregnancy
Efavirenz (EFV) *Sustiva* (EFV/FTC/TDF) *Atripla* (EFV/3TC/TDF) *Symfi* (EFV/3TC/TDF) *Symfi Lo* **Note:** Generic available for some formulations.	EFV (Sustiva)[d] *Capsules:* • 50 mg • 200 mg *Tablet:* • 600 mg EFV/FTC/TDF (Atripla): • EFV 600 mg plus FTC 200 mg tablet TDF 300 mg plus EFV/3TC/TDF (Symfi): • EFV 600 mg plus 3TC 300 mg plus TDF 300 mg tablet EFV/3TC/TDF (Symfi Lo): • EFV 400 mg plus 3TC 300 mg plus TDF 300 mg tablet	Standard Adult Doses *EFV (Sustiva):* • EFV 600 mg once daily at or before bedtime, on an empty stomach to reduce side effects *EFV/FTC/TDF (Atripla):* • 1 tablet once daily at or before bedtime, on an empty stomach to reduce side effects *EFV/3TC/TDF (Symfi or Symfi Lo):* • 1 tablet once daily on an empty stomach and preferably at bedtime PK in Pregnancy: • AUC is decreased during the third trimester compared with postpartum, but nearly all third-trimester participants exceeded target exposure. Dosing in Pregnancy: • No change in dose is indicated. • For guidance about use of combination products in pregnancy, please see the specific sections on other components (i.e., 3TC, FTC, TDF)	Moderate placental transfer to fetus.[b] The FDA advises women to avoid becoming pregnant while taking EFV and advises health care providers to avoid administration during the first trimester of pregnancy, as fetal harm may occur. Although the limited data on first-trimester EFV exposure cannot rule out a 2-fold or 3-fold increased incidence of a rare outcome such as neural tube defects, the available data from a meta-analysis of >2,000 births suggest that there is no large increase in the risk of neural tube defects with first-trimester exposure (e.g., a 10-fold increase to a rate of 1%). As a result, the current Perinatal Guidelines do not restrict the use of EFV in pregnant women or in women who are planning to become pregnant. This is consistent with both the British HIV Association and WHO guidelines for use of ARV drugs in pregnancy. EFV should be continued in pregnant women who are on a virologically suppressive, EFV-based regimen, because ARV drug changes during pregnancy may be associated with loss of viral control and an increased risk of perinatal transmission (see Pregnant Women Living with HIV Who are Currently Receiving Antiretroviral Therapy).

Excerpt from Table 10[a]

[a] Individual ARV drug doses may need to be adjusted in patients with renal or hepatic insufficiency (for details, see the Adult and Adolescent Guidelines, Appendix B, Table 8).

[b] Placental transfer categories are determined by mean or median cord blood/maternal delivery plasma drug ratio:

High: > 0.6 **Moderate:** 0.3–0.6 **Low:** < 0.3

[d] Generic formulation is available.

Key to Acronyms: 3TC = lamivudine; ARV = antiretroviral; AUC = area under the curve; EFV = efavirenz; FDA = Food and Drug Administration; FDC = fixed-dose combination; FTC = emtricitabine; PK = pharmacokinetic; TDF = tenofovir disoproxil fumarate; WHO = World Health Organization

References

1. Efavirenz [package insert]. Food and Drug Administration. 2017. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021360s044,020972s056lbl.pdf.
2. de Oliveira HM, Damiani AP, Dias Rde O, Romao PR, Andrade VM. Effect of antiretroviral drugs on the DNA damage in mice. *Environ Toxicol and Pharmacol*. 2014;37(1):390-395. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24441026.
3. Nightingale SL. From the food and drug administration. *JAMA*. 1998;280(17):1472. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9809716.
4. Cressey TR, Stek A, Capparelli E, et al. Efavirenz pharmacokinetics during the third trimester of pregnancy and postpartum. *J Acquir Immune Defic Syndr*. 2012;59(3):245-252. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22083071.
5. Hill A, Ford N, Boffito M, Pozniak A, Cressey TR. Does pregnancy affect the pharmacokinetics of efavirenz? *AIDS*. 2014;28(10):1542-1543. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24896806.
6. Gandhi M, Greenblatt RM, Bacchetti P, et al. A single-nucleotide polymorphism in CYP2B6 leads to >3-fold increases in efavirenz concentrations in plasma and hair among HIV-infected women. *J Infect Dis*. 2012;206(9):1453-1461. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22927450.
7. Schneider E, Whitmore S, Glynn KM, et al. Revised surveillance case definitions for HIV infection among adults, adolescents, and children aged <18 months and for HIV infection and AIDS among children aged 18 months to <13 years—United States, 2008. *MMWR Recomm Rep*. 2008;57(RR-10):1-12. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19052530.
8. Olagunju A, Siccardi M, et al. Pharmacogenetics of efavirenz excretion into human breast milk and transfer To breastfed infants. Presented at: Conference on Retroviruses and Opportunistic Infections. 2014. Boston, MA.
9. Gandhi M, Mwesigwa J, Aweeka F, et al. Hair and plasma data show that lopinavir, ritonavir, and efavirenz all transfer from mother to infant in utero, but only efavirenz transfers via breastfeeding. *J Acquir Immune Defic Syndr*. 2013;63(5):578-584. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24135775.
10. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral pregnancy registry international interim report for 1 January 1989–31 January 2018. Wilmington, NC: Registry Coordinating Center. 2018. Available at: http://www.apregistry.com/.
11. Ford N, Mofenson L, Shubber Z, et al. Safety of efavirenz in the first trimester of pregnancy: an updated systematic review and meta-analysis. *AIDS*. 2014;28 Suppl 2:S123-131. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24849471.
12. Sibiude J, Mandelbrot L, Blanche S, et al. Association between prenatal exposure to antiretroviral therapy and birth defects: an analysis of the French perinatal cohort study (ANRS CO1/CO11). *PLoS Med*. 2014;11(4):e1001635. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24781315.
13. Mofenson LM, Watts DH. Safety of pediatric HIV elimination: the growing population of HIV- and antiretroviral-exposed but uninfected infants. *PLoS Med*. 2014;11(4):e1001636. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24781352.
14. Williams PL, Crain MJ, Yildirim C, et al. Congenital anomalies and in utero antiretroviral exposure in human immunodeficiency virus-exposed uninfected infants. *JAMA Pediatr*. 2015;169(1):48-55. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25383770.

15. Floridia M, Mastroiacovo P, Tamburrini E, et al. Birth defects in a national cohort of pregnant women with HIV infection in Italy, 2001-2011. *BJOG*. 2013;120(12):1466-1475. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23721372.

16. Knapp KM, Brogly SB, Muenz DG, et al. Prevalence of congenital anomalies in infants with in utero exposure to antiretrovirals. *Pediatr Infect Dis J*. 2012;31(2):164-170. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21983213.

17. Brogly SB, Abzug MJ, Watts DH, et al. Birth defects among children born to human immunodeficiency virus-infected women: pediatric AIDS clinical trials protocols 219 and 219C. *Pediatr Infect Dis J*. 2010;29(8):721-727. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20539252.

18. Ford N, Calmy A. Efavirenz is not a known teratogen. *Pediatr Infect Dis J*. 2012;31(9):999; author reply 1000. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22609611.

19. de Ruiter A, Taylor GP, Clayden P, et al. British HIV Association guidelines for the management of HIV infection in pregnant women 2012 (2014 interim review). *HIV Med*. 2014;15 Suppl 4:1-77. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25604045.

20. World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventin HIV infecition—recommendations for a public health approach; second edition 2016. 2016; http://www.who.int/hiv/pub/arv/arv-2016/en/.

21. Floridia M, Ravizza M, Pinnetti C, et al. Treatment change in pregnancy is a significant risk factor for detectable HIV-1 RNA in plasma at end of pregnancy. *HIV Clin Trials*. 2010;11(6):303-311. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21239358.

22. Tseng A, Hills-Nieminen C. Drug interactions between antiretrovirals and hormonal contraceptives. *Expert Opin Drug Metab Toxicol*. 2013. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23425052.

23. Landolt NK, Phanuphak N, Ubolyam S, et al. Efavirenz, in contrast to nevirapine, is associated with unfavorable progesterone and antiretroviral levels when co-administered with combined oral contraceptives. *J Acquir Immune Defic Syndr*. 2012. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23187949.

24. Leticee N, Viard JP, Yamgnane A, Karmochkine M, Benachi A. Contraceptive failure of etonogestrel implant in patients treated with antiretrovirals including efavirenz. *Contraception*. 2012;85(4):425-427. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22036046.

25. Carten ML, Kiser JJ, Kwara A, Mawhinney S, Cu-Uvin S. Pharmacokinetic interactions between the hormonal emergency contraception, levonorgestrel (Plan B), and Efavirenz. *Infect Dis Obstet Gynecol*. 2012;2012:137192. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22536010.

26. Perry SH, Swamy P, Preidis GA, Mwanyumba A, Motsa N, Sarero HN. Implementing the jadelle implant for women living with HIV in a resource-limited setting in sub-Saharan Africa: concerns for drug interactions leading to unintended pregnancies. *AIDS*. 2014. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24401645.

27. Scarsi KK, Darin KM, Nakalema S, et al. Unintended pregnancies observed with combined use of the levonorgestrel contraceptive implant and efavirenz-based antiretroviral therapy: a three-arm pharmacokinetic evaluation over 48 weeks. *Clin Infect Dis*. 2015. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26646680.

28. Kreitchmann R, Stek A, Best B, et al. Interaction between etonogestrel-releasing implant and 3 antiretroviral regimens. Presented at: Conference on Retroviruses and Opportunistic Infections. 2017. Seattle, WA.

29. Chappell CA, Lamorde M, Nakalema S, et al. Efavirenz decreases etonogestrel exposure: a pharmacokinetic evaluation of implantable contraception with antiretroviral therapy. *AIDS*. 2017;31(14):1965-1972. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28692531.

30. Scarsi KK, Cramer Y, Gingrich D, et al. Vaginal contraceptive hormone exposure profoundly altered by EFV- and ATV/R-based ART. Abstract 141. Presented at: Conference on Retroviruses and Opportunistic Infections. 2018. Boston, Massachusetts. Available at: http://www.croiconference.org/sessions/vaginal-contraceptive-hormone-exposure-profoundly-altered-efv-and-atvr-based-art.

31. Cohn SE, Park JG, Watts DH, et al. Depo-medroxyprogesterone in women on antiretroviral therapy: effective contraception and lack of clinically significant interactions. *Clin Pharmacol Ther*. 2007;81(2):222-227. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17192768.

Etravirine (Intelence, ETR)

(Last updated December 7, 2018; last reviewed December 7, 2018)

Etravirine is classified as Food and Drug Administration Pregnancy Category B.

Animal Studies

Carcinogenicity

Etravirine was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests.[1] Etravirine was evaluated for carcinogenic potential in mice and rats for up to approximately 104 weeks. Due to intolerance of the formulation, areas under the concentration-time curve (AUC) for etravirine were 0.6-fold (in mice) and 0.2-fold to 0.7-fold (in rats) compared to the typical AUC in humans receiving standard dosing. In rats and male mice, no significant findings were noted. In female mice, increased incidences of hepatocellular carcinoma and hepatocellular adenomas or carcinomas combined were seen. It is unclear whether these liver tumor findings in mice are relevant to humans.[1]

Reproduction/Fertility

Etravirine had no effect on fertility and early embryonic development when tested in pregnant rats at doses that resulted in systemic drug exposures equivalent to those observed in humans who received the recommended dose (400 mg/day).[1]

Teratogenicity/Adverse Pregnancy Outcomes

Animal reproduction studies in rats and rabbits revealed no evidence of fetal toxicity or altered development at systemic exposures equivalent to those seen in humans who received the recommended dose of etravirine 400 mg/day.[1]

Human Studies in Pregnancy

Pharmacokinetics

Etravirine pharmacokinetics (PKs) in pregnant women have been reported in two studies. Ramgopal et al. found that total etravirine AUC, C_{min}, and C_{max} were increased approximately 1.1-fold to 1.4-fold in the second trimester (n = 13) and third trimester (n = 10) compared with levels in the same women postpartum (n = 10). Differences in unbound etravirine concentrations were less pronounced, with least-squares mean ratios of approximately 0.9 to 1.2.[2] Similarly, Mulligan et al. found 1.3-fold to 1.9-fold increases in total etravirine AUC, C_{min}, and C_{max} during the third trimester (n = 13) compared with levels in the same women postpartum (n = 8).[3] Etravirine was well tolerated in both of these studies.

Placental and Breast Milk Passage

In seven mother-infant pairs, the median ratio of cord blood to maternal plasma etravirine concentration at delivery was 0.52 (with a range of 0.19–4.25).[3] In another study, the median ratio of cord blood to maternal plasma concentration in 10 mother-infant pairs was 0.32 (with a range of 0.19–0.63).[2] Placental passage of etravirine was described in a report on the use of etravirine, darunavir/ritonavir, and enfuvirtide in a woman who gave birth to twins. Cord blood etravirine levels were 414 ng/mL in Twin 1 and 345 ng/mL in Twin 2 (no maternal plasma etravirine concentration at delivery was reported).[4]

Plasma and breast milk concentrations were measured on postpartum days 5 and 14 in eight women who began taking etravirine on postpartum day 1.[5] Plasma PKs were similar between days 5 and 14 and were similar to published PK parameters of etravirine in nonpregnant adults. Etravirine $AUC_{0\text{-}12h}$ in breast milk was higher in mature milk (Day 14) than in colostrum/transitional milk (Day 5): 12,954 ± 10,200 ng*h/mL versus 4,372 ± 3,016 ng*h/mL ($P = 0.046$). Median etravirine concentrations in plasma and breast milk on Day 5 were 300 ng/mL and 241 ng/mL, respectively (within-subject breast milk/plasma ratio of 109%). Median plasma and breast milk concentrations on day 14 were 197 ng/mL and 798 ng/mL (within-subject breast milk/plasma ratio of 327%). The maximum etravirine concentration in breast milk was significantly

higher than in plasma (1,245 ± 1,159 ng/mL vs. 531 ± 336 ng/mL, $P = 0.04$). Two women had detectable HIV RNA in breast milk on Day 14 despite suppressed plasma viral loads. Etravirine concentrations in the plasma and breast milk of these women were similar to those observed in women with undetectable HIV RNA in breast milk. Etravirine penetrates well and may accumulate in breast milk.

Teratogenicity/Adverse Pregnancy Outcomes

In eight reported cases of etravirine use in pregnancy, no maternal, fetal, or neonatal toxicity was noted.[4,6] One infant was born with a small accessory auricle on the right ear but no other malformations, and no birth defects were noted in the other children.[4] Among cases of first-trimester etravirine exposure reported to the Antiretroviral Pregnancy Registry, one defect has been noted out of 66 live births; due to this low number of cases to date, no conclusions can be made about risk of birth defects.[7]

Excerpt from Table 10[a]

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations	Use in Pregnancy
Etravirine (ETR) *Intelence*	Tablets: • 25 mg • 100 mg • 200 mg For patients unable to swallow tablets whole, the tablets may be dispersed in a glass of water.	Standard Adult Dose: • 200 mg twice daily with food PK in Pregnancy: • PK data in pregnancy (n = 26) suggest that etravirine exposure during pregnancy increases 1.2-fold to 1.6-fold. Dosing in Pregnancy: • No change in dose indicated.	Variable placental transfer, usually in the moderate to high categories, ranging from 0.19–4.25 (data from 19 mother-infant pairs).[b] Insufficient data to assess for teratogenicity in humans. No evidence of teratogenicity in rats or rabbits.

[a] Individual ARV drug dosages may need to be adjusted in patients with renal or hepatic insufficiency (for details, see the Adult and Adolescent Guidelines Appendix B, Table 8).

[b] Placental transfer categories are determined by mean or median cord blood/maternal delivery plasma drug ratio:

High: >0.6 **Moderate:** 0.3–0.6 **Low:** <0.3

Key to Acronyms: ARV = antiretroviral; ETR= etravirine; PK = pharmacokinetic

References

1. Etravirine [package insert]. Food and Drug Administration. 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/022187s024lbl.pdf.
2. 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.
3. Mulligan N, Schalkwijk S, Best BM, et al. Etravirine pharmacokinetics in HIV-infected pregnant women. *Front Pharmacol*. 2016;7:239. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27540363.
4. Furco A, Gosrani B, Nicholas S, et al. Successful use of darunavir, etravirine, enfuvirtide and tenofovir/emtricitabine in pregnant woman with multiclass HIV resistance. *AIDS*. 2009;23(3):434-435. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19188762.
5. Spencer L, Liu S, Wang C, Neely M, Louie S, Kovacs A. Intensive etravirine PK and HIV-1 viral load in breast milk and plasma in HIV+ women receiving HAART. Poster 891. Presented at: Conference on Retroviruses and Opportunistic Infections. 2014. Boston, MA.
6. Calcagno A, Trentini L, Marinaro L, et al. Transplacental passage of etravirine and maraviroc in a multidrug-experienced HIV-infected woman failing on darunavir-based HAART in late pregnancy. *J Antimicrob Chemother*. 2013;68(8):1938-1939. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23535879.
7. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral pregnancy registry international interim report 1 January 1989–31 January 2018. Wilmington, NC. 2018. Available at: www.APRegistry.com.

Nevirapine (Viramune, NVP)

(Last updated December 7, 2018; last reviewed December 7, 2018)

Available data from the Antiretroviral Pregnancy Registry show no difference between the risk of overall major birth defects for nevirapine and the background rate for major birth defects in a U.S. reference population.

Animal Studies

Carcinogenicity

Nevirapine showed no evidence of mutagenic or clastogenic activity in a battery of *in vitro* and *in vivo* studies. The occurrence of hepatocellular adenomas and carcinomas increased at all doses in male mice and rats and at higher doses in female mice and rats. Systemic exposure at all studied doses was lower than systemic exposure in humans receiving therapeutic nevirapine doses. Given the lack of genotoxic activity of nevirapine, the relevance to humans of hepatocellular neoplasms in nevirapine-treated mice and rats is unknown.[1]

Reproduction/Fertility

Evidence of impaired fertility was seen in female rats receiving nevirapine doses that produced systemic exposures comparable to human therapeutic exposure.[1]

Teratogenicity/Adverse Pregnancy Outcomes

In reproductive studies of rats and rabbits, teratogenic effects of nevirapine have not been observed at systemic exposures approximately equivalent to or 50% greater than the recommended human dose (based on area under the curve [AUC]). In pregnant rats, however, a significant decrease in fetal weight occurred at doses that produced systemic concentrations approximately 50% higher than human therapeutic exposure.[1]

Human Studies in Pregnancy

Pharmacokinetics

The pharmacokinetics (PKs) of nevirapine have been evaluated in pregnant women who received nevirapine as part of antiretroviral therapy (ART) during pregnancy. A study that determined nevirapine PKs in 26 women during pregnancy (which included seven women in their second trimester and 19 women in their third trimester) and again in the same women 4 to 12 weeks after delivery found that pregnancy did not alter nevirapine PK parameters.[2] In contrast, nevirapine clearance was 20% greater, AUC was 28% lower, and maximum plasma concentration was 30% lower in 16 pregnant women than in 13 nonpregnant women, based on nevirapine PK data from a therapeutic drug monitoring program that included 12-hour sampling; the authors of that study also reported high variability in plasma nevirapine concentrations.[3] A Dutch study reported a nonsignificant trend toward lower nevirapine exposure during pregnancy, with steady-state nevirapine concentrations of 5.2 mcg/mL in 45 pregnant women compared to 5.8 mcg/mL in 152 nonpregnant women ($P = 0.08$).[4] An intensive PK study of 59 women with genotype information found that pregnant women who had one or two mutations in CYP2B6 had higher nevirapine clearance than a different group of postpartum women who had one or two mutations in CYP2B6.[5] In fast metabolizers (no mutations), no differences in nevirapine exposure were seen between pregnant women and postpartum women. No dose adjustment during pregnancy is currently recommended for nevirapine.

Placental and Breast Milk Passage

Nevirapine demonstrates rapid and effective placental transfer, achieving near equivalent concentrations in maternal and cord blood (cord-to-maternal-blood ratio ranges from 0.60–1.02).[6,7] Nevirapine has also been shown to be excreted into human breast milk. In a study of 57 Malawian women who received postpartum nevirapine-based therapy, the breast-milk-to-maternal-serum concentration ratio was approximately 0.6; detectable nevirapine concentrations were found in the breastfeeding infants (interquartile range 0.54–1.06 mcg/mL).[8] In data from 15 breastfeeding women who received nevirapine-based therapy in Botswana,

median maternal plasma concentration at 1 month postpartum was 6.71 mcg/mL and median maternal breast milk concentration was 1.83 mcg/mL, for a median maternal breast-milk-to-plasma ratio of 0.27.[9] Infant exposure was measured at 1 month in nine infants; all infants had biologically significant, detectable nevirapine concentrations in their blood, with a median level of 0.37 mcg/mL (and a range of 0.24–1.2 mcg/mL), representing approximately 6% of median maternal value. Similar data were reported in a study of 67 mothers who received nevirapine-based therapy in Kenya; the median concentration of nevirapine in breast milk was 4.55 mcg/mL, with median concentrations in breastfeeding infants of 0.99 mcg/mL, 1.03 mcg/mL, and 0.73 mcg/mL at 2, 6, and 14 weeks postpartum, respectively.[10] An additional study in 122 Nigerian mother/infant pairs found that the median milk-to-plasma nevirapine AUC ratio was 0.95 (with a range of 0.56–1.5). Infant plasma concentrations from exposure through breast milk were 660 ng/mL (with a range of 104–3,090 ng/mL).[5]

Teratogenicity/Adverse Pregnancy Outcomes

In the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposures to nevirapine in humans have been monitored to be able to detect at least a 1.5-fold increase in risk of overall birth defects and a 2-fold increase in cardiovascular and genitourinary defects (the most common classes). No such increase in birth defects has been observed with nevirapine. Among cases of first-trimester nevirapine exposure reported to the Antiretroviral Pregnancy Registry, the prevalence of birth defects was 2.80% (32 of 1,142 births; 95% CI, 1.92% to 3.93%) compared with a total prevalence of 2.72% in the U.S. population, based on Centers for Disease Control and Prevention surveillance.[11] Similarly, the French Perinatal Cohort reported no association between nevirapine and birth defects with 71% power to detect a 1.5-fold increase.[12]

Safety

Severe, life-threatening, and (in some cases) fatal hepatotoxicity—including fulminant and cholestatic hepatitis, hepatic necrosis, hepatic failure, and severe, life-threatening hypersensitivity skin reactions, including Stevens-Johnson syndrome—has been reported in patients with HIV receiving nevirapine in combination with other drugs for treatment of HIV disease and in a small number of individuals receiving nevirapine as part of ART for postexposure prophylaxis of nosocomial or sexual exposure to HIV.[13] In general, in controlled clinical trials, clinical hepatic events, regardless of severity, occurred in 4.0% of patients (with a range of 0% to 11.0%) who received nevirapine; however, the risk of nevirapine-associated liver failure or hepatic mortality has been lower, ranging from 0.04% to 0.40%.[1,14] The greatest risk of severe rash or hepatic events occurs during the first 6 to 18 weeks of therapy, although the risk of toxicity continues past this period and monitoring should continue at frequent intervals.

Incidence of severe nevirapine-associated skin rash has been reported to be 5.5 times to 7.3 times more common in women than men and cases have been reported in pregnant women.[15-17] Other studies have found that hepatic adverse events with systemic symptoms (often rash) were 3.2-fold more common in women than men.[14] Several studies suggest that the degree of risk of hepatic toxicity varies with CD4 T lymphocyte (CD4) cell count. In a summary analysis of data from 17 clinical trials of nevirapine therapy, women with CD4 cell counts >250 cells/mm^3 were 9.8 times more likely to experience symptomatic, often rash-associated, nevirapine-related hepatotoxicity than women with lower CD4 cell counts.[14] Higher CD4 cell counts have also been associated with increased risk of severe nevirapine-associated skin rash.[16] Rates of hepatotoxicity and rash similar to those in U.S. studies have been seen in international cohorts of nonpregnant women, although not all studies have reported an association between rates of hepatotoxicity and rash and CD4 cell counts >250 cells/mm^3.[18] In a study of 359 nonpregnant women randomized to receive nevirapine-based therapy in sub-Saharan Africa, higher nevirapine exposure was associated with development of severe skin toxicity, and baseline CD4 cell counts ≥250 cells/mm^3 were associated with nevirapine-related liver toxicity and drug discontinuation.[19] Some researchers have suggested that genetic variation in drug metabolism polymorphisms (e.g., CYP2B6 variants), TRAF proteins, and immune human leukocyte antigen loci may be associated with higher risk of nevirapine-associated adverse events and that the relationship between genetic variants and adverse events may vary by race.[20-23] Published literature indicates that rash and hyperbilirubinemia have been seen in infants exposed to nevirapine through breastmilk.[1]

Although fatal cases of hepatic failure have been reported in pregnant women with HIV who were receiving nevirapine as part of an ART regimen, it is uncertain whether pregnancy increases the risk of hepatotoxicity in women receiving nevirapine or other antiretroviral drugs.[24] In a systematic review of 20 studies that included 3,582 pregnant women from 14 countries, the pooled proportion of women experiencing a severe hepatotoxic event was 3.6% (95% CI, 2.4% to 4.8%) and the proportion of women experiencing severe rash was 3.3% (95% CI, 2.1% to 4.5%); overall, 6.2% of women stopped nevirapine due to an adverse event (95% CI, 4.0% to 8.4%).[25] These results were comparable to published frequencies in the general adult population and comparable to frequencies in nonpregnant women within the same cohorts. These data suggest that the frequency of adverse events associated with nevirapine during pregnancy is not higher than the frequency reported for nevirapine in the general population, consistent with data from two multicenter prospective cohorts in which pregnancy was not associated with an increased risk of nevirapine-associated hepatic toxicity.[26,27] In contrast, an analysis of data collected in the United Kingdom and Ireland from 2000 to 2011 evaluated 3,426 women, one-quarter of whom were pregnant, and found that pregnant women taking efavirenz, maraviroc, or nevirapine were at increased risk of liver enzyme elevation.[28]

In the systematic review discussed above, there was a nonsignificant trend toward an increased likelihood of cutaneous events (odds ratio [OR] 1.1; 95% CI, 0.8–1.6) and severe cutaneous adverse events in pregnant women with CD4 cell counts ≥250 cell/mm^3 (OR 1.4, 95% CI, 0.8–2.4).[25] A separate systematic review of 14 studies did report a significant association between increased toxicity risk and initiation of nevirapine-based therapy during pregnancy in women with CD4 cell counts ≥250 cells/mm^3.[29] A small case-control study (6 cases, 30 controls) in South Africa reported that pregnancy increased the chance of developing Stevens-Johnson syndrome (OR 14.28, $P = 0.006$; 95% CI, 1.54–131.82).[30] Nevirapine (as a component of a combination regimen) should be initiated in pregnant women with CD4 cell counts ≥250 cells/mm^3 only if the benefit clearly outweighs the risk. Women with CD4 cell counts <250 cells/mm^3 can receive nevirapine-based regimens, and women who become pregnant while taking nevirapine and who are tolerating their regimens well can continue therapy, regardless of CD4 cell count.

In a chart abstraction study that used data collected at eight government hospitals in Botswana, women receiving ART regimens that contained nevirapine were more likely to experience certain adverse events than women on ART regimens that did not contain nevirapine, including hypertension (30% vs. 16%), severe hypertension (3.3% vs. 1.2%), gestational hypertension (18% vs. 10%), and early gestational hypertension (12% vs. 7%).[31]

Because pregnancy itself can mimic some of the early symptoms of hepatotoxicity (i.e., pregnancy-related nausea and vomiting), health care providers who are caring for women receiving nevirapine during pregnancy should be aware of this potential complication. Frequent and careful monitoring of clinical symptoms and hepatic transaminases (i.e., alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) is necessary, particularly during the first 18 weeks of therapy. Some clinicians measure serum transaminases at baseline, every 2 weeks for the first month, and then monthly for the first 18 weeks; in patients with pre-existing liver disease, monitoring should be performed more frequently when initiating therapy and monthly thereafter.[32] Transaminase levels should be checked in all women who develop a rash while receiving nevirapine. Patients who develop suggestive clinical symptoms accompanied by elevation in serum transaminase levels (ALT and/or AST) or who have asymptomatic but severe transaminase elevations should stop nevirapine and not receive the drug in the future.

Additional Information

In a nonrandomized parallel-group study of etonogestrel exposure in women who were taking concomitant ART, nevirapine had no effect on etonogestrel levels, in contrast to efavirenz.[33]

Excerpt from Table 10[a]

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations	Use in Pregnancy
Nevirapine (NVP) *Viramune* *Viramune XR (Extended Release)* **Note:** Generics are available for some formulations	NVP (Viramune) *Tablets:* • 200 mg[d] *Oral Suspension:* • 50 mg/5 mL Viramune XR *Tablets:* • 100 mg • 400 mg[d]	Standard Adult Dose: • 200 mg once-daily Viramune (immediate release) for 14 days (lead-in period); thereafter, 200 mg twice daily or 400 mg (Viramune XR tablet) once daily, without regard to food. • Repeat lead-in period if therapy is discontinued for >7 days. • In patients who develop mild-to-moderate rash without constitutional symptoms during lead-in period, continue lead-in dosing until rash resolves, but administer for ≤28 days total. PK in Pregnancy: • PK of immediate release tablets is not significantly altered in pregnancy. • No data are available on extended release formulations in pregnancy. Dosing in Pregnancy: • No change in dose indicated.	High placental transfer to fetus.[b] No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects and 2-fold increase in cardiovascular and genitourinary defects. Increased risk of symptomatic, often rash-associated, and potentially fatal liver toxicity among women with CD4 cell counts ≥250/mm^3 when first initiating therapy; pregnancy does not appear to increase risk. NVP should be initiated in pregnant women with CD4 cell counts ≥250 cells/mm^3 only if benefit clearly outweighs risk because of potential increased risk of life-threatening hepatotoxicity in women with high CD4 cell counts. Elevated transaminase levels at baseline may increase the risk of NVP toxicity. Women who become pregnant while taking NVP-containing regimens and who are tolerating their regimens well can continue therapy, regardless of CD4 cell count.

[a] Individual ARV drug dosages may need to be adjusted in patients with renal or hepatic insufficiency (for details, see the Adult and Adolescent Guidelines, Appendix B, Table 8).

[b] Placental transfer categories are determined by mean or median cord blood/maternal delivery plasma drug ratio:

High: >0.6 **Moderate:** 0.3–0.6 **Low:** <0.3

[d] Generic formulation available

Key to Acronyms: ARV = antiretroviral; CD4 = CD4 T lymphocyte; NVP = nevirapine; PK = pharmacokinetic

References

1. Nevirapine [package insert]. Food and Drug Administration. 2017. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/020636s048,020933s038lbl.pdf.
2. Capparelli EV, Aweeka F, Hitti J, et al. Chronic administration of nevirapine during pregnancy: impact of pregnancy on pharmacokinetics. *HIV Med*. 2008;9(4):214-220. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18366444.
3. von Hentig N, Carlebach A, Gute P, et al. A comparison of the steady-state pharmacokinetics of nevirapine in men, nonpregnant women and women in late pregnancy. *Br J Clin Pharmacol*. 2006;62(5):552-559. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17061962.
4. Nellen JF, Damming M, Godfried MH, et al. Steady-state nevirapine plasma concentrations are influenced by pregnancy. *HIV Med*. 2008;9(4):234-238. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18366447.
5. Olagunju A, Bolaji O, Neary M, Back D, Khoo S, Owen A. Pregnancy affects nevirapine pharmacokinetics: evidence from a CYP2B6 genotype-guided observational study. *Pharmacogenet Genomics*. 2016;26(8):381-389. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27195527.
6. Else LJ, Taylor S, Back DJ, Khoo SH. Pharmacokinetics of antiretroviral drugs in anatomical sanctuary sites: the fetal compartment (placenta and amniotic fluid). *Antivir Ther*. 2011;16(8):1139-1147. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22155898.
7. Benaboud S, Ekouevi DK, Urien S, et al. Population pharmacokinetics of nevirapine in HIV-1-infected pregnant women and their neonates. *Antimicrob Agents Chemother*. 2011;55(1):331-337. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20956588.
8. Palombi L, Pirillo MF, Andreotti M, et al. Antiretroviral prophylaxis for breastfeeding transmission in Malawi: drug

concentrations, virological efficacy and safety. *Antivir Ther*. 2012;17(8):1511-1519. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22910456.

9. Shapiro RL, Rossi S, Ogwu A, et al. Therapeutic levels of lopinavir in late pregnancy and abacavir passage into breast milk in the Mma Bana Study, Botswana. *Antivir Ther*. 2013;18(4):585-590. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23183881.
10. Mirochnick M, Thomas T, Capparelli E, et al. Antiretroviral concentrations in breast-feeding infants of mothers receiving highly active antiretroviral therapy. *Antimicrob Agents Chemother*. 2009;53(3):1170-1176. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19114673.
11. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral Pregnancy Registry international interim report for 1 January 1989–31 July 2018. Wilmington, NC: Registry Coordinating Center. 2018. Available at: http://www.apregistry.com/.
12. Sibiude J, Mandelbrot L, Blanche S, et al. Association between prenatal exposure to antiretroviral therapy and birth defects: an analysis of the French perinatal cohort study (ANRS CO1/CO11). *PLoS Med*. 2014;11(4):e1001635. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24781315.
13. Patel SM, Johnson S, Belknap SM, Chan J, Sha BE, Bennett C. Serious adverse cutaneous and hepatic toxicities associated with nevirapine use by non-HIV-infected individuals. *J Acquir Immune Defic Syndr*. 2004;35(2):120-125. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14722442.
14. Stern JO, Robinson PA, Love J, Lanes S, Imperiale MS, Mayers DL. A comprehensive hepatic safety analysis of nevirapine in different populations of HIV infected patients. *J Acquir Immune Defic Syndr*. 2003;34 Suppl 1:S21-33. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14562855.
15. Mazhude C, Jones S, Murad S, Taylor C, Easterbrook P. Female sex but not ethnicity is a strong predictor of non-nucleoside reverse transcriptase inhibitor-induced rash. *AIDS*. 2002;16(11):1566-1568. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12131201.
16. Bersoff-Matcha SJ, Miller WC, Aberg JA, et al. Sex differences in nevirapine rash. *Clin Infect Dis*. 2001;32(1):124-129. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11118391.
17. Knudtson E, Para M, Boswell H, Fan-Havard P. Drug rash with eosinophilia and systemic symptoms syndrome and renal toxicity with a nevirapine-containing regimen in a pregnant patient with human immunodeficiency virus. *Obstet Gynecol*. 2003;101(5 Pt 2):1094-1097. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12738113.
18. Peters PJ, Stringer J, McConnell MS, et al. Nevirapine-associated hepatotoxicity was not predicted by CD4 count >/=250 cells/muL among women in Zambia, Thailand and Kenya. *HIV Med*. 2010;11(10):650-660. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20659176.
19. Dong BJ, Zheng Y, Hughes MD, et al. Nevirapine pharmacokinetics and risk of rash and hepatitis among HIV-infected sub-Saharan African women. *AIDS*. 2012;26(7):833-841. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22301417.
20. Yuan J, Guo S, Hall D, et al. Toxicogenomics of nevirapine-associated cutaneous and hepatic adverse events among populations of African, Asian, and European descent. *AIDS*. 2011;25(10):1271-1280. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21505298.
21. Carr DF, Chaponda M, Jorgensen AL, et al. Association of human leukocyte antigen alleles and nevirapine hypersensitivity in a malawian HIV-infected population. *Clin Infect Dis*. 2013;56(9):1330-1339. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23362284.
22. Ciccacci C, Rufini S, Mancinelli S, et al. A pharmacogenetics study in Mozambican patients treated with nevirapine: full resequencing of TRAF3IP2 gene shows a novel association with SJS/TEN susceptibility. *Int J Mol Sci*. 2015;16(3):5830-5838. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25775161.
23. Carr DF, Chaponda M, Cornejo Castro EM, et al. CYP2B6 c.983T>C polymorphism is associated with nevirapine hypersensitivity in Malawian and Ugandan HIV populations. *J Antimicrob Chemother*. 2014;69(12):3329-3334. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25147095.
24. Lyons F, Hopkins S, Kelleher B, et al. Maternal hepatotoxicity with nevirapine as part of combination antiretroviral therapy in pregnancy. *HIV Med*. 2006;7(4):255-260. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16630038.
25. Ford N, Calmy A, Andrieux-Meyer I, Hargreaves S, Mills EJ, Shubber Z. Adverse events associated with nevirapine use in pregnancy: a systematic review and meta-analysis. *AIDS*. 2013. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23299174.
26. Ouyang DW, Brogly SB, Lu M, et al. Lack of increased hepatotoxicity in HIV-infected pregnant women receiving nevirapine compared with other antiretrovirals. *AIDS*. 2010;24(1):109-114. Available at: http://www.ncbi.nlm.nih.gov/

pubmed/19926957.

27. Ouyang DW, Shapiro DE, Lu M, et al. Increased risk of hepatotoxicity in HIV-infected pregnant women receiving antiretroviral therapy independent of nevirapine exposure. *AIDS*. 2009;23(18):2425-2430. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19617813.

28. Huntington S, Thorne C, Anderson J, et al. Does pregnancy increase the risk of ART-induced hepatotoxicity among HIV-positive women? *J Int AIDS Soc*. 2014;17(4 Suppl 3):19486. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25393995.

29. Bera E, Mia R. Safety of nevirapine in HIV-infected pregnant women initiating antiretroviral therapy at higher CD4 counts: a systematic review and meta-analysis. *S Afr Med J*. 2012;102(11 Pt 1):855-859. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23116743.

30. Dube N, Adewusi E, Summers R. Risk of nevirapine-associated Stevens-Johnson syndrome among HIV-infected pregnant women: the Medunsa National Pharmacovigilance Centre, 2007 - 2012. *S Afr Med J*. 2013;103(5):322-325. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23971123.

31. Zash R, Williams P, Jacobson D, et al. Increased risk of hypertension in pregnancy among women on nevirapine-based regimens. Poster 803. Presented at: Conference on Retroviruses and Opportunistic Infections. 2018. Boston, MA.

32. Kontorinis N, Dieterich DT. Toxicity of non-nucleoside analogue reverse transcriptase inhibitors. *Semin Liver Dis*. 2003;23(2):173-182. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12800070.

33. Chappell CA, Lamorde M, Nakalema S, et al. Efavirenz decreases etonogestrel exposure: a pharmacokinetic evaluation of implantable contraception with antiretroviral therapy. *AIDS*. 2017;31(14):1965-1972. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28692531.

Rilpivirine (Edurant, RPV)

(Last updated December 7, 2018; last reviewed December 7, 2018)

The Antiretroviral Pregnancy Registry shows no difference between the overall risk of birth defects for rilpivirine and the background rate for major birth defects, which is 2.7% in the Metropolitan Atlanta Congenital Defects Program reference population.[1]

Animal Studies

Carcinogenicity

Rilpivirine was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests. Rilpivirine was not carcinogenic in rats when administered at doses that resulted in drug exposure 3 times higher than seen in humans at the recommended dose of rilpivirine 25 mg once daily. Hepatocellular neoplasms were observed in both male and female mice at doses resulting in exposures 21 times that of human therapeutic exposure; the observed hepatocellular findings in mice may be rodent-specific.[1]

Reproduction/Fertility

No effect on fertility was observed when rilpivirine was tested in rats at maternal doses up to 400 mg/kg/day, resulting in systemic drug exposure equivalent to 40 times the recommended human dose.[1]

Teratogenicity/Adverse Pregnancy Outcomes

No evidence of embryonic or fetal toxicity or an effect on reproductive function was observed in rat and rabbit dams treated with rilpivirine during pregnancy and lactation. Exposures were 15 and 70 times higher in pregnancy and lactation, respectively, than exposure in humans at the recommended dose of rilpivirine 25 mg once daily.[1]

Placental and Breast Milk Passage

Studies in lactating rats and their offspring indicate that rilpivirine is present in rat milk.[1]

Human Studies in Pregnancy

Pharmacokinetics

A study presenting pharmacokinetic (PK) and safety data from 32 pregnant women with HIV during pregnancy and postpartum found median rilpivirine area under the curve (AUC) and trough concentrations were about 20% to 30% lower in the second and third trimesters than in the postpartum period. Median trough rilpivirine concentrations were significantly lower at 14 visits where the women had detectable HIV-1 RNA (30 ng/mL) than at 62 visits where they had undetectable HIV-1 RNA (63 ng/mL). Ninety percent of women had trough concentrations above the protein-adjusted EC_{90} for rilpivirine. PK exposure was highly variable in this study.[2] Another study in 16 pregnant women with HIV similarly found that exposure was approximately 50% lower in the third trimester than in the postpartum period, with 4 of the 16 women having troughs below the target levels during pregnancy.[3] These authors recommended therapeutic drug monitoring in the third trimester, and attention to ensure that rilpivirine doses are taken with meals. A third study that compared rilpivirine exposure during pregnancy and postpartum noted approximately 30% decreases in total rilpivirine exposure and 22% to 25% decreases in unbound rilpivirine during pregnancy in 15 women.[4] Cervicovaginal fluid rilpivirine concentrations were described in a study of 24 women taking rilpivirine daily during pregnancy and postpartum, which showed cervicovaginal rilpivirine steady-state concentrations similar to those seen in plasma in the same women. The rilpivirine cervicovaginal fluid to plasma AUC ratio was higher during pregnancy than postpartum.[5] While rilpivirine plasma concentration is reduced during pregnancy, higher-than-standard doses have not been studied. Insufficient data are available to recommend a dosing change in pregnancy. With standard dosing, viral loads should be monitored more frequently.

Placental and Breast Milk Passage

One of the PK and safety studies described above included rilpivirine delivery concentration data from 21 mother-infant pairs, with median (range) cord blood rilpivirine plasma concentration of 29.2 ng/mL (<10.0

to 101.5 ng/mL), maternal delivery plasma rilpivirine concentration of 55.2 ng/mL (<10.0 to 233.8 ng/mL) and cord blood/maternal plasma ratio of 0.55 (0.3 to 0.8).[2] Osiyemi et al. found that the median ratio of cord blood to maternal plasma concentration of total rilpivirine in 8 women was 0.55 (range: 0.43-0.98).[4] Similarly, Schalkwijk et al. found a median (range) cord blood-to-maternal plasma ratio of 0.5 (0.35–0.81) in 5 women.[3] An *ex vivo* human cotyledon perfusion model also showed that rilpivirine crosses the placenta with fetal transfer rates ranging from 17% to 37%.[6,7] No data exist on whether rilpivirine is excreted in breast milk in humans.

Teratogenicity/Adverse Pregnancy Outcomes

Among cases of first-trimester exposures to rilpivirine reported to the Antiretroviral Pregnancy Registry, the prevalence of birth defects was 1.01% (3 of 297 births; 95% CI, 0.21% to 2.92%), whereas the total prevalence rate for the U.S. population is 2.7% based on Centers for Disease Control and Prevention surveillance.[8]

Excerpt from Table 10[a]

Note: When using FDCs, refer to other sections in Appendix B and Table 10 for information about the dosing and safety of individual drug components of the FDC during pregnancy.

Generic Name (Abbreviation) *Trade Name*	**Formulation**	**Dosing Recommendations**	**Use in Pregnancy**
Rilpivirine (RPV) *Edurant* (RPV/FTC/TDF) *Complera* (RPV/DTG) *Juluca* (RPV/FTC/TAF) *Odefsey*	RPV (Edurant) *Tablets:* • 25 mg RPV/FTC/TDF (Complera): • RPV 25 mg plus FTC 200 mg plus TDF 300 mg tablet RPV/DTG (Juluca): • RPV 25 mg plus DTG 50 mg tablet RPV/FTC/TAF (Odefsey): • RPV 25 mg plus FTC 200 mg plus TAF 25 mg tablet	Standard Adult Dose *RPV (Edurant):* • RPV 25 mg once daily with food *RPV/FTC/TDF (Complera):* • 1 tablet once daily with food *RPV/DTG (Juluca):* • 1 tablet once daily with food *RPV/FTC/TAF (Odefsey):* • 1 tablet once daily with food PK in Pregnancy: • RPV PK highly variable during pregnancy. RPV AUC and trough concentration reduced 20% to 50% lower in pregnancy than postpartum. While most pregnant women exceeded target exposure, those with detectable viral loads had lower RPV troughs. Dosing in Pregnancy: • While RPV plasma concentration is reduced during pregnancy, higher-than-standard doses have not been studied. Insufficient data are available to recommend a dosing change in pregnancy. With standard dosing, viral loads should be monitored more frequently. For guidance about use of combination products in pregnancy, please see the specific sections on other components (i.e., DTG, FTC, TAF, TDF).	Moderate to high placental transfer to fetus.[b] No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects). Two-drug regimens (e.g., RPV/DTG FDC) are not recommended in pregnancy.

[a] Individual ARV drug dosages may need to be adjusted in patients with renal or hepatic insufficiency (for details, see the Adult and Adolescent Guidelines, Appendix B, Table 8).

[b] Placental transfer categories—Mean or median cord blood/maternal delivery plasma drug ratio:

High: >0.6 **Moderate:** 0.3–0.6 **Low:** <0.3

Key to Acronyms: AUC = area under the curve; DTG = dolutegravir; FDC = fixed-dose combination; FTC = emtricitabine; PK = pharmacokinetic; RPV = rilpivirine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

References

1. Rilpivirine [package insert]. Food and Drug Administration. 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/202022s011lbl.pdf.
2. Tran AH, Best BM, Stek A, et al. Pharmacokinetics of rilpivirine in HIV-infected pregnant women. *J Acquir Immune Defic Syndr*. 2016. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26918544.
3. 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. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28595298.
4. Osiyemi O, Yasin S, Zorrilla C, et al. Pharmacokinetics, antiviral activity, and safety of rilpivirine in pregnant women with HIV-1 infection: results of a phase 3b, multicenter, open-label study. *Infect Dis Ther*. 2018;7(1):147-159. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29335895.
5. Eke AC, Chakhtoura N, Kashuba A, et al. Rilpivirine plasma and cervicovaginal concentrations in women during pregnancy and postpartum. *J Acquir Immune Defic Syndr*. 2018;78(3):308-313. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29528944.
6. Mandelbrot L, Duro D, Belissa E, Peytavin G. Erratum for Mandelbrot et al., placental transfer of rilpivirine in an *ex vivo* human cotyledon perfusion model. *Antimicrob Agents Chemother*. 2015;59(9):5869. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26276897.
7. Mandelbrot L, Duro D, Belissa E, Peytavin G. Placental transfer of rilpivirine in an *ex vivo* human cotyledon perfusion model. Antimicrob Agents Chemother. 2015;59(5):2901-2903. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25691637.
8. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral pregnancy registry international interim report for 1 January 1989–31 January 2018. Wilmington, NC: Registry Coordinating Center. 2018. Available at: http://www.apregistry.com/.

Protease Inhibitors

Glossary of Terms for Supplement
Carcinogenic: Producing or tending to produce cancer • Some agents, such as certain chemicals or forms of radiation, are both mutagenic and clastogenic. • Genetic mutations and/or chromosomal damage can contribute to cancer formation.
Clastogenic: Causing disruption of or breakages in chromosomes
Genotoxic: Damaging to genetic material such as DNA and chromosomes
Mutagenic: Inducing or capable of inducing genetic mutation
Teratogenic: Interfering with fetal development and resulting in birth defects

For information regarding the protease inhibitor (PI) class of drugs and potential metabolic complications during pregnancy and pregnancy outcome, see Combination Antiretroviral Drug Regimens and Pregnancy Outcome.

Atazanavir (Reyataz, ATV)

(Last updated December 7, 2018; last reviewed December 7, 2018)

According to the Food and Drug Administration, available human and animal data suggest that atazanavir does not increase the risk of major birth defects overall compared to the background rate.[1]

Animal Studies

Carcinogenicity

In *in vitro* and *in vivo* assays, atazanavir shows evidence of clastogenicity but not mutagenicity. Two-year carcinogenicity studies in mice and rats were conducted with atazanavir. In female mice, the incidence of benign hepatocellular adenomas increased at systemic exposures that were 2.8- to 2.9-fold higher than those seen in humans who received the recommended therapeutic dose (atazanavir 300 mg boosted with ritonavir 100 mg once daily). There was no increase in the incidence of tumors in male mice at any dose and no significant increase in the incidence of neoplasms in rates at systemic exposures up to 1.1-fold (in males) or 3.9-fold (in females) higher than those seen in humans who received the recommended therapeutic dose.[1]

Reproduction/Fertility

No effect of atazanavir on reproduction or fertility in male and female rodents was seen at area under the curve (AUC) levels that were 0.9-fold (in males) and 2.3-fold (in females) higher than the exposures achieved in humans who received the recommended therapeutic dose.[1]

Teratogenicity/Adverse Pregnancy Outcomes

In animal reproduction studies, there was no evidence of teratogenicity in offspring born to animals that had systemic atazanavir exposure levels (AUC) 0.7 times (in rabbits) and 1.2 times (in rats) those observed in humans who received the recommended therapeutic dose. In developmental toxicity studies in rats, maternal dosing that produced systemic atazanavir exposure 1.3 times the human exposure resulted in maternal toxicity in weight loss or suppression of weight gain in the offspring. However, offspring were unaffected at lower maternal doses that produced systemic drug exposures equivalent to those observed in humans who received the recommended therapeutic dose.[1] A more recent study demonstrated an association between maternal protease inhibitor (PI) use (including atazanavir) and lower progesterone levels, which correlated with lower birthweight in mice.[2,3]

Placental and Breast Milk Passage

Atazanavir is excreted in the milk of lactating rats. Maternal atazanavir use in rats was associated with neonatal growth restriction that reversed after weaning.[1]

Human Studies in Pregnancy

Pharmacokinetics

Several studies have investigated the pharmacokinetics (PKs) and virologic outcomes of using atazanavir/ritonavir (ATV/r) during pregnancy.[4] Overall, most pregnant women achieved undetectable HIV RNA at the time of delivery.[1,5-9] In a retrospective study that measured trough atazanavir concentrations at a median of 30 weeks' gestation in 19 pregnant women (including 14 who were in the third trimester of pregnancy) who received atazanavir 300 mg and ritonavir 100 mg once daily, all but two women had a trough atazanavir concentration >100 ng/mL.[10] In studies that evaluated full PK profiles of atazanavir when administered daily as 300 mg with 100 mg ritonavir during pregnancy, atazanavir AUC was lower during pregnancy than the AUC reported in other studies of nonpregnant adults with HIV infection.[5,7,8,11,12] In one of the studies, there was no difference between atazanavir AUC during pregnancy and postpartum, but AUC at both times was lower than that of nonpregnant historic controls with HIV infection.[7] In the other studies, atazanavir AUC was lower during pregnancy than it was in the same patients postpartum and in nonpregnant control populations.[5,6,8,11,12] Intracellular atazanavir levels in women taking atazanavir 300 mg given with ritonavir 100 mg appear to be stable throughout pregnancy.[13]

ATV/r combined with tenofovir disoproxil fumarate (TDF) and emtricitabine provides a complete, once-a-day antiretroviral therapy (ART) regimen for pregnant women. However, the atazanavir AUC of pregnant women in the third trimester who received concomitant TDF was 30% lower than the atazanavir AUC of women who were not receiving concomitant TDF, an effect similar to that seen in nonpregnant adults.[8,11] The increase in atazanavir AUC postpartum relative to that in the third trimester was similar for women taking concomitant TDF and for those not taking concomitant TDF.[8] On the other hand, a smaller PK study demonstrated that concomitant TDF did not result in lower atazanavir AUC or higher risk of trough concentration <0.15 mg/L (the target for treatment-naive patients) in pregnant women in their third trimester.[14] In a therapeutic drug monitoring (TDM) study of 103 women (mostly African) in Paris, there was no difference in the risk of atazanavir trough concentration <0.15 mg/L between women who did and women who did not take concomitant TDF.[9]

In studies that investigated a dose of atazanavir 400 mg with ritonavir 100 mg once daily during pregnancy,[5,6] pregnant women receiving the increased dose without TDF had an atazanavir AUC equivalent to that seen in historic nonpregnant controls with HIV infection who received standard-dose atazanavir without TDF. Pregnant women who received the increased atazanavir dose with TDF had an atazanavir AUC equivalent to that seen in nonpregnant patients with HIV infection who received standard-dose atazanavir with TDF.[5,6] Although some experts recommend an increased dose of atazanavir for all women during the second and third trimesters, the package insert recommends the use of an increased dose of atazanavir in the second and third trimesters only for antiretroviral (ARV)-experienced pregnant women who are also receiving either TDF or an H2-receptor antagonist. TDM of atazanavir in pregnancy may also be useful.[15] For additional details about interactions between concomitant medications, please see Drug-Drug Interactions in the Adult and Adolescent Guidelines.

The combination of atazanavir and cobicistat has not been directly studied in pregnant women; however, limited data from studies of cobicistat as a pharmacoenhancer for other ARV drugs in pregnant women suggest that cobicistat exposure is substantially reduced in pregnancy[16,17] (see Cobicistat section). Thus, there are insufficient data to make a recommendation about the use of atazanavir/cobicistat in pregnant women.

Placental and Breast Milk Passage

In studies of women receiving ATV/r combination therapy during pregnancy, cord blood atazanavir concentration averaged 13% to 21% of maternal serum levels at delivery.[1,7,8]

In a study of three women, the median ratio of breast milk atazanavir concentration to plasma atazanavir concentration was 13%.[18]

Teratogenicity/Adverse Pregnancy Outcomes

In a multicenter, U.S. cohort of children who were exposed to HIV but who did not contract HIV, first-trimester atazanavir exposure was associated with increased odds of congenital anomalies of the skin (adjusted odds ratio [aOR] = 5.24; $P = 0.02$) and the musculoskeletal system (aOR = 2.55; $P = 0.007$).[19] On the other hand, there was no association between first-trimester atazanavir exposure and birth defects in a French cohort, although this study had <50% power to detect an aOR of 1.5.[20] The Antiretroviral Pregnancy Registry has monitored sufficient numbers of first-trimester exposures to atazanavir in humans to be able to detect at least a 1.5-fold increase in risk of overall birth defects, and no such increase in birth defects has been observed with atazanavir. The prevalence of birth defects with first-trimester atazanavir exposure was 2.2% (28 of 1,279 births; 95% CI, 1.5% to 3.2%) compared with a 2.7% total prevalence in the U.S. population, based on Centers for Disease Control and Prevention surveillance.[21]

Please see Combination Antiretroviral Drug Regimens and Maternal and Neonatal Outcomes for a discussion of the potential association between the use of boosted PIs and preterm delivery.

Other Safety Data

Elevation in indirect (unconjugated) bilirubin that can be attributed to atazanavir-related inhibition of hepatic uridine diphosphate glucuronosyltransferase (UGT) enzyme occurs frequently during treatment with atazanavir, including during pregnancy.[22] It is unknown whether elevated maternal indirect bilirubin throughout pregnancy has any effects on the fetus. Dangerous or pathologic postnatal elevations in bilirubin have not been reported in infants born to mothers who received atazanavir during pregnancy.[1,5,7,8,10,23-25] In some studies, neonatal bilirubin elevations that require treatment with phototherapy occur more frequently after prenatal atazanavir exposure. However, decisions to use phototherapy frequently are subjective and guidelines for phototherapy vary across countries, making it difficult to compare the severity of hyperbilirubinemia between patients within a study and across different studies.[23,24] Elevated neonatal bilirubin in neonates exposed to atazanavir is not associated with UGT-1 genotypes that are associated with decreased UGT function.[25]

In an evaluation of neurodevelopmental outcomes in 374 infants ages 9 to 15 months who were exposed to HIV but who did not contract HIV, the adjusted mean scores on the language and social-emotional domains of the Bayley-III test were significantly lower for infants with perinatal exposure to atazanavir than for infants exposed to other drugs.[26,27] In a study of language assessments among 792 children (ages 1 to 2 years) who were exposed to HIV but who did not contract HIV, children with atazanavir exposure had an increased risk of late language emergence at age 12 months (aOR = 1.83; 95% CI, 1.10–3.04) compared to children without atazanavir exposure, but the association was not significant at 24 months.[28]

Hypoglycemia (glucose <40 mg/dL) that could not be attributed to maternal glucose intolerance, difficult delivery, or sepsis has been reported in three of 38 atazanavir-exposed infants with glucose samples collected during the first day of life. All three hypoglycemic infants' glucose samples were adequately collected and processed in a timely fashion.[1] This finding of infant hypoglycemia is similar to a prior report in which two of 14 infants exposed to PIs (nelfinavir, saquinavir, and indinavir) developed hypoglycemia during the first day of life; both infants with hypoglycemia had been exposed to nelfinavir.[29]

Excerpt from Table 10[a]

Note: When using FDCs, refer to other sections in Appendix B and Table 10 for information about the dosing and safety of individual drug components of the FDC during pregnancy.

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations	Use in Pregnancy
Atazanavir (ATV) *Reyataz* **Note:** Generic available for some formulations. **Note:** ATV must be combined with low-dose RTV boosting in pregnancy. (ATV/COBI) *Evotaz*	ATV (Reyataz) *Capsules*: • 100 mg (generic product only) • 150 mg[d] • 200 mg[d] • 300 mg[d] *Oral Powder:* • 50 mg packet ATV/COBI (Evotaz): • ATV 300 mg plus COBI 150 mg tablet	Standard Adult Doses *ARV-Naive Patients* *Without RTV Boosting:* • ATV 400 mg once daily with food; ATV without RTV boosting **is not recommended** when used with TDF, H2-receptor antagonists, PPIs, or during pregnancy. *With RTV Boosting:* • ATV 300 mg plus RTV 100 mg once daily with food • When combined with EFV in ARV-naive patients: ATV 400 mg plus RTV 100 mg once daily with food *ARV-Experienced Patients:* • ATV 300 mg plus RTV 100 mg once daily with food • Do not use with PPIs or EFV *If Combined with an H2-Receptor Antagonist:* ATV 300 mg plus RTV 100 mg once daily with food *If Combined with an H2-Receptor Antagonist and TDF:* • ATV 400 mg plus RTV 100 mg once daily with food Powder Formulation: • Oral powder is taken with RTV once daily with food at the same recommended adult dose as the capsules. ATV/COBI (Evotaz): • 1 tablet once daily with food PK in Pregnancy *ATV (Reyataz):* • ATV concentrations reduced during pregnancy; further reduced when given concomitantly with TDF or H2-receptor antagonist. *ATV/COBI (Evotaz):* • No PK studies in human pregnancy. • For guidance about use of combination products in pregnancy, please see the specific sections on other components (i.e., COBI). Dosing in Pregnancy *ATV (Reyataz):* • Use of unboosted ATV **is not recommended** during pregnancy. • Use of ATV **is not recommended** for ARV-experienced pregnant women taking TDF **and** an H2-receptor antagonist. • Use of an increased dose (ATV 400 mg plus RTV 100 mg once daily with food) during the second and third trimesters results in plasma ATV concentrations equivalent to those seen in nonpregnant adults on standard dosing. Although some experts recommend increased ATV dosing in all women during the second and third trimesters, the package insert recommends increased ATV dosing only for ARV-experienced pregnant women in the second and third trimesters who are also receiving either TDF or an H2-receptor antagonist. *ATV/COBI (Evotaz):* • Insufficient data to make dosing recommendation in pregnancy (see Cobicistat section).	Low placental transfer to fetus.[b] No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects). Must be given as low-dose RTV-boosted regimen in pregnancy. Effect of *in utero* ATV exposure on infant indirect bilirubin levels is unclear. Nonpathologic elevations of neonatal hyperbilirubinemia have been observed in some, but not all, clinical trials to date. Oral powder (but **not** capsules) contains phenylalanine, which can be harmful to patients with phenylketonuria. ATV/COBI **is not recommended** for use in pregnancy. For women who become pregnant while taking ATV/COBI, consider switching to a more effective, recommended regimen. If an ATV/COBI regimen is continued, doses should be administered with food; viral load should be monitored frequently.

Excerpt from Table 10[a]

[a] Individual ARV drug dosages may need to be adjusted in patients with renal or hepatic insufficiency (for details, see the Adult and Adolescent Guidelines, Appendix B, Table 8).

[b] Placental transfer categories are determined by mean or median cord blood/maternal delivery plasma drug ratio:

High: >0.6 **Moderate:** 0.3–0.6 **Low:** <0.3

[d] Generic formulation available

Key to Acronyms: ARV = antiretroviral; ATV = atazanavir; COBI = cobicistat; EFV = efavirenz; FDC = fixed-dose combination; PK = pharmacokinetic; PPI = proton pump inhibitor; RTV = ritonavir; TDF = tenofovir disoproxil fumarate

References

1. Atazanavir [package insert]. 2017. Food and Drug Administration. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021567s041,206352s006lbl.pdf.
2. Papp E, Mohammadi H, Loutfy MR, et al. HIV protease inhibitor use during pregnancy is associated with decreased progesterone levels, suggesting a potential mechanism contributing to fetal growth restriction. *J Infect Dis*. 2014. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25030058.
3. Powis KM, Shapiro RL. Protease inhibitors and adverse birth outcomes: is progesterone the missing piece to the puzzle? *J Infect Dis*. 2015;211(1):4-7. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25030057.
4. Eley T, Bertz R, Hardy H, Burger D. Atazanavir pharmacokinetics, efficacy and safety in pregnancy: a systematic review. *Antivir Ther*. 2013;18(3):361-375. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23676668.
5. Conradie F, Zorrilla C, Josipovic D, et al. Safety and exposure of once-daily ritonavir-boosted atazanavir in HIV-infected pregnant women. *HIV Med.* 2011;12(9):570-579. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21569187.
6. Kreitchmann R, Best BM, Wang J, et al. Pharmacokinetics of an increased atazanavir dose with and without tenofovir during the third trimester of pregnancy. *J Acquir Immune Defic Syndr*. 2013;63(1):59-66. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23392467.
7. Ripamonti D, Cattaneo D, Maggiolo F, et al. Atazanavir plus low-dose ritonavir in pregnancy: pharmacokinetics and placental transfer. *AIDS*. 2007;21(18):2409-2415. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18025877.
8. Mirochnick M, Best BM, Stek AM, et al. Atazanavir pharmacokinetics with and without tenofovir during pregnancy. *J Acquir Immune Defic Syndr*. 2011;56(5):412-419. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21283017.
9. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25599649.
10. Natha M, Hay P, Taylor G, et al. Atazanavir use in pregnancy: a report of 33 cases. Presented at: 14th Conference on Retoviruses and Opportunistic Infections. 2007. Los Angeles, CA.
11. Taburet AM, Piketty C, Chazallon C, et al. Interactions between atazanavir-ritonavir and tenofovir in heavily pretreated human immunodeficiency virus-infected patients. *Antimicrob Agents Chemother*. 2004;48(6):2091-2096. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15155205.
12. Colbers A, Molto J, Ivanovic J, et al. A comparison of the pharmacokinetics of darunavir, atazanavir and ritonavir during pregnancy and post-partum. Abstract 1013. Presented at: 19th Conference on Retroviruses and Opportunistic Infections. 2012. Seattle, WA.
13. Foca E, Calcagno A, Bonito A, et al. Atazanavir intracellular concentrations remain stable during pregnancy in HIV-infected patients. *J Antimicrob Chemother*. 2017;72(11):3163-3166. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28961777.
14. Colbers A, Hawkins D, Hidalgo-Tenorio C, et al. Atazanavir exposure is effective during pregnancy regardless of tenofovir use. *Antivir Ther*. 2015;20(1):57-64. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24992294.
15. Else LJ, Jackson V, Brennan M, et al. Therapeutic drug monitoring of atazanavir/ritonavir in pregnancy. *HIV Med.* 2014;15(10):604-610. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24825070.
16. Best B, Caparelli E, Stek A, et al. Elvitegravir/cobicistat pharmacokinetics in pregnancy and postpartum. Presented at: Conference on Retroviruses and Opportunistic Infections. 2017. Seattle, WA.

17. Crauwels HM, Osiyemi O, Zorilla C, Bicer C, Brown K. Pharmacokinetics of total and unbound darunavir in HIV-1–infected pregnant women receiving a darunavir/cobicistat-based regimen. Presented at: 8th International Workshop on HIV & Women. 2018. Boston, Massachusetts. Available at: http://www.natap.org/2018/CROI/HIV&Women2018DRVcPKPregnancyPoster_JUV-63244_FINAL.PDF.

18. Spencer L, Neely M, Mordwinkin N, et al. Intensive pharmacokinetics of zidovudine, lamivudine, and atazanavir and HIV-1 viral load in breast milk and plasma in HIV+ women receiving HAART. Presented at: 16th Conference on Retroviruses and Opportunistic Infections. 2009. Montreal, Canada.

19. Williams PL, Crain MJ, Yildirim C, et al. Congenital anomalies and *in utero* antiretroviral exposure in human immunodeficiency virus-exposed uninfected infants. *JAMA Pediatr*. 2015;169(1):48-55. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25383770.

20. Sibiude J, Mandelbrot L, Blanche S, et al. Association between prenatal exposure to antiretroviral therapy and birth defects: an analysis of the French perinatal cohort study (ANRS CO1/CO11). *PLoS Med*. 2014;11(4):e1001635. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24781315.

21. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral pregnancy registry international interim report for 1 January 1989–31 January 2018. Wilmington, NC: Registry Coordinating Center. 2018. Available at: http://www.apregistry.com/.

22. 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.

23. Mandelbrot L, Mazy F, Floch-Tudal C, et al. Atazanavir in pregnancy: impact on neonatal hyperbilirubinemia. *Eur J Obstet Gynecol Reprod Biol*. 2011;157(1):18-21. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21492993.

24. Atrio JM, Sperling RS, Posada R, Rodriguez Caprio G, Chen KT. Maternal atazanavir usage in HIV-infected pregnant women and the risk of maternal and neonatal hyperbilirubinemia. *J Acquir Immune Defic Syndr*. 2013;63(5):e158-159. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23970241.

25. Eley T, Huang SP, Conradie F, et al. Clinical and pharmacogenetic factors affecting neonatal bilirubinemia following atazanavir treatment of mothers during pregnancy. *AIDS Res Hum Retroviruses*. 2013;29(10):1287-1292. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23782005.

26. 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.

27. 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.

28. 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.

29. Dinsmoor MJ, Forrest ST. Lack of an effect of protease inhibitor use on glucose tolerance during pregnancy. *Infect Dis Obstet Gynecol*. 2002;10(4):187-191. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12648312.

Darunavir (Prezista, DRV)

(Last reviewed December 7, 2018; last updated December 7, 2018)

Available data from the Antiretroviral Pregnancy Registry show no increase in the rate of overall birth defects with first-trimester darunavir exposure compared to control populations. The Antiretroviral Pregnancy Registry has monitored a sufficient number of first-trimester exposures to rule out a more than two-fold increase in the rate of birth defects.[1]

Animal Studies

Carcinogenicity

Darunavir was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests. A dose-related increase in the incidence of hepatocellular adenomas and carcinomas was observed in both male and female mice and rats, as well as an increase in thyroid follicular cell adenomas in male rats. The observed hepatocellular findings in rodents are considered to be of limited relevance to humans. Repeated administration of darunavir to rats caused hepatic microsomal enzyme induction and increased thyroid hormone elimination, which predispose rats, but not humans, to thyroid neoplasms. At the highest tested doses, the systemic exposures to darunavir (based on area under the curve [AUC]) were between 0.4-fold and 0.7-fold (in mice) and 0.7-fold and one-fold (in rats) the exposures observed in humans receiving the recommended therapeutic doses (600 mg/100 mg twice daily or 800 mg/100 mg daily).[2]

Reproduction/Fertility

No effects on fertility and early embryonic development were seen in rats receiving darunavir.[2]

Teratogenicity/Adverse Pregnancy Outcomes

No embryotoxicity or teratogenicity was seen in mice, rats, or rabbits with doses (based on AUC) three-fold higher in rats and lower (less than one-fold) in mice and rabbits compared to those obtained in humans receiving recommended darunavir/ritonavir (DRV/r) doses. In a rat prenatal and postnatal development study, a reduction in pup weight gain was observed with breast milk exposure of darunavir administered alone or with ritonavir during lactation. DRV/r is not recommended in pediatric patients <3 years of age due to toxicity and mortality observed in juvenile rats dosed with darunavir up to days 23 to 26 of age.[2]

Placental and Breast Milk Passage

No animal studies of placental passage of darunavir have been reported. Passage of darunavir into breast milk has been noted in rats.[2]

Human Studies in Pregnancy

Pharmacokinetics

Several studies of the pharmacokinetics (PKs) of DRV/r during pregnancy have been completed.[3-7] Compared with postpartum darunavir plasma AUC, darunavir plasma AUC during the third trimester was reduced by 17% to 26% with DRV/r 600 mg/100 mg twice-daily dosing and by 33% to 39% with DRV/r 800 mg/100 mg once-daily dosing.[3-6] Compared with postpartum darunavir trough concentration, trough concentration during the third trimester was reduced by 8% to 12% with DRV/r 600 mg/100 mg twice-daily dosing and by 42% to 58% with DRV/r 800 mg/100 mg once-daily dosing.[4-6] Three studies measured darunavir protein binding during pregnancy. One study found no change in darunavir protein binding during the third trimester. The other two studies reported decreased unbound darunavir concentrations during pregnancy that were not considered clinically significant.[3,5,6] Because of low trough levels with once-daily dosing, twice-daily dosing of darunavir is recommended during pregnancy, especially for antiretroviral-experienced patients. The Food and Drug Administration (FDA) recommends the use of once-daily DRV/r 800 mg/100 mg only for pregnant women who are virally suppressed on a stable, once-daily DRV/r regimen prior to pregnancy and whose adherence or ability to tolerate a regimen may be compromised by a switch to twice-daily DRV/r.[2] Based on review of available evidence, the Panel on Treatment of Pregnant Women with HIV Infection and Prevention

of Perinatal Transmission does not recommend once-daily dosing of DRV/r in pregnancy. An 800-mg darunavir dose administered twice daily did not increase darunavir exposure in pregnant women; use of this increased twice-daily darunavir dose during pregnancy **is not recommended**.[7]

Two studies describing the PK and safety of once-daily darunavir/cobicistat (DRV/c) 800 mg/150 mg during pregnancy have been presented.[8,9] In a study of seven pregnant persons with HIV treated with DRV/c, no drug related adverse events were observed. When PK parameters during the second and third trimesters were compared to postpartum, total darunavir AUC was reduced by 56% and 50% and trough concentration was reduced by 92% and 89%, respectively. Unbound darunavir concentrations were similarly decreased during pregnancy, with AUC 45% and 40% lower and trough concentration 92% and 88% lower during the second and third trimesters than postpartum. Cobicistat exposures were lower during pregnancy, with reductions of 63% and 49% for AUC and 83% and 83% for trough concentration during the second and third trimesters compared to postpartum. Six of seven participants remained virally suppressed during pregnancy. One woman who was not suppressed was assessed to be nonadherent to treatment by pill count. All infants born to study mothers had not contracted HIV.[8] Based on these data, the package insert for the fixed-dose combination of DRV/c was edited to include a statement saying that this product **is not recommended** for use in pregnant women because of substantially lower exposures of darunavir and cobicistat during pregnancy.[10] These findings were confirmed in a larger study of 29 pregnant women who received the DRV/c combination. When PK parameters during the second and third trimesters were compared to postpartum PK parameters in these women, total darunavir AUC was reduced by 33% and 48% and darunavir trough concentrations were reduced by 71% and 75%.[9]

Placental and Breast Milk Passage

In an *ex vivo* human cotyledon perfusion model, the mean fetal transfer rate of darunavir was 15%.[11] In five studies that reported data from between six and 14 subjects each, the median of the ratio of darunavir concentration in cord blood to that in maternal delivery plasma ranged from 13% to 24%.[3-5,8,12] No data are available that describe the breast milk passage of darunavir in humans.

Teratogenicity/Adverse Pregnancy Outcomes

Among cases of first-trimester darunavir exposure reported to the Antiretroviral Pregnancy Registry, prevalence of birth defects was 2.4% (11 of 456 births; 95% CI, 1.2% to 4.3%), which is a sufficient number of first-trimester exposures to conclude that there is no two-fold increase in the risk of overall birth defects compared to control populations.[1]

Excerpt from Table 10[a]

Note: When using FDCs, refer to other sections in Appendix B and Table 10 for information about the dosing and safety of individual drug components of the FDC during pregnancy.

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations	Use in Pregnancy
Darunavir (DRV) *Prezista* **Note:** Must be combined with low-dose RTV or COBI boosting. (DRV/COBI) *Prezcobix* (DRV/COBI/FTC/TAF) *Symtuza*	DRV (Prezista): *Tablet:* • 75 mg • 150 mg • 600 mg • 800 mg *Oral Suspension:* • 100 mg/mL DRV/COBI (Prezcobix): • DRV 800 mg plus COBI 150 mg tablet DRV/COBI/FTC/TAF (Symtuza): • DRV 800 mg plus COBI 150 mg plus FTC 200 mg plus TAF 10 mg tablet	**Standard Adult Doses** ARV-Naive Patients: • DRV 800 mg plus RTV 100 mg once daily with food • DRV 800 mg plus COBI 150 mg once daily with food ARV-Experienced Patients: *If Patient Has No DRV Resistance Mutations:* • DRV 800 mg plus RTV 100 mg once daily with food • DRV 800 mg plus COBI 150 mg once daily with food *If Any DRV Resistance Mutations Are Present:* • DRV 600 mg plus RTV 100 mg twice daily with food *DRV/COBI (Prezcobix):* • 1 tablet once daily with food *DRV/COBI/FTC/TAF (Symtuza):* • 1 tablet once daily with food Dosing in Pregnancy: • The Panel **does not recommend** once-daily dosing with DRV/r during pregnancy or the use of DRV/c during pregnancy. Twice-daily DRV/r dosing (DRV 600 mg plus RTV 100 mg with food) is recommended for all pregnant women. Increased twice-daily DRV dose (DRV 800 mg plus RTV 100 mg with food) during pregnancy does not result in an increase in darunavir exposure and **is not recommended**. PK in Pregnancy: • Decreased exposure in pregnancy with use of DRV/r. • For guidance about use of combination products in pregnancy, please see the specific sections on other components (i.e., COBI, FTC, TAF)	Low placental transfer to fetus.[b] No evidence of teratogenicity in mice, rats, or rabbits. No evidence of human teratogenicity. Must be boosted with low-dose RTV. The Panel **does not recommend** once-daily dosing with DRV/COBI during pregnancy or the use of DRV/COBI during pregnancy. If a DRV/c regimen is continued during pregnancy, viral load should be monitored frequently.

[a] Individual ARV drug dosages may need to be adjusted in patients with renal or hepatic insufficiency (for details, see the Adult and Adolescent Guidelines, Appendix B, Table 8).

[b] Placental transfer categories are determined by mean or median cord blood/maternal delivery plasma drug ratio:

High: >0.6 **Moderate:** 0.3–0.6 **Low:** <0.3

Key to Acronyms: ARV = antiretroviral; COBI = cobicistat; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; FDC = fixed-dose combination; FTC = emtricitabine; PK = pharmacokinetic; RTV = ritonavir; TAF = tenofovir alafenamide

References

1. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral pregnancy registry international interim report 1 January 1989–31 January 2018. Wilmington, NC: Registry Coordinating Center. 2018. Available at: http://www.apregistry.com/.
2. Darunavir [package insert]. Food and Drug Administration. 2017. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021976s045_202895s020lbl.pdf.
3. Zorrilla CD, Wright R, Osiyemi OO, et al. Total and unbound darunavir pharmacokinetics in pregnant women infected with HIV-1: results of a study of darunavir/ritonavir 600/100 mg administered twice daily. *HIV Med*. 2014;15(1):50-56.

Available at: http://www.ncbi.nlm.nih.gov/pubmed/23731450.

4. Stek A, Best BM, Wang J, et al. Pharmacokinetics of once versus twice daily darunavir In pregnant HIV-infected women. *J Acquir Immune Defic Syndr*. 2015. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25950206.
5. Colbers A, Molto J, Ivanovic J, et al. Pharmacokinetics of total and unbound darunavir in HIV-1-infected pregnant women. *J Antimicrob Chemother*. 2015;70(2):534-542. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25326090.
6. Crauwels HM, Kakuda TN, Ryan B, et al. Pharmacokinetics of once-daily darunavir/ritonavir in HIV-1-infected pregnant women. *HIV Med*. 2016;17(9):643-652. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27187894.
7. Stek A, Best B, Capparelli E, et al. Pharmacokinetics of increased dose darunavir during late pregnancy and postpartum. Presented at: 23rd Conference on Retroviruses and Opportunistic Infections. 2016. Boston, MA.
8. Crauwels HM, Osiyemi O, Zorilla C, Bicer C, Brown K. Pharmacokinetics of total and unbound darunavir in HIV-1-infected pregnant women receiving a darunavir/cobicistat-based regimen. Presented at: 8th International Workshop on HIV & Women. 2018. Boston, Massachusetts. Available at: http://www.natap.org/2018/CROI/HIV&Women2018DRVcPKPregnancyPoster_JUV-63244_FINAL.PDF.
9. Momper J, Best B, Wang J, et al. Pharmacokinetics of darunavir boosted with cobicistat during pregnancy and postpartum. Presented at: International AIDS Conference. 2018. Amsterdam, Netherlands.
10. Darunavir/cobicistat [package insert]. Food and Drug Administration. 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/205395s009lbl.pdf.
11. Mandelbrot L, Duro D, Belissa E, Peytavin G. Placental transfer of darunavir in an *ex vivo* human cotyledon perfusion model. *Antimicrob Agents Chemother*. 2014;58(9):5617-5620. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24982090.
12. Courbon E, Matheron S, et al. Efficacy, and pharmacokinetic of darunavir/ritonavir-containing regimen in pregnant HIV+ women. Presented at: 19th Conference on Retroviruses and Opportunistic Infections. 2012. Seattle, WA.

Fosamprenavir (Lexiva, FPV)

(Last updated December 7, 2018; last reviewed December 7, 2018)

Fosamprenavir is classified as Food and Drug Administration Pregnancy Category C. Fosamprenavir **should not** be used during pregnancy.

Animal Studies

Carcinogenicity

Fosamprenavir and amprenavir were neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests. Carcinogenicity studies of fosamprenavir showed an increase in the incidence of hepatocellular adenomas and hepatocellular carcinomas at all doses tested in male mice and at the highest dose tested in female mice. In rats, the incidence of hepatocellular adenomas and thyroid follicular cell adenomas increased in males at all doses and in females at the two highest doses. Repeat dose studies in rats produced effects consistent with enzyme activation, which predisposes rats, but not humans, to thyroid neoplasms. In rats there was an increase in the risk of interstitial cell hyperplasia at higher doses and an increase in the risk of uterine endometrial adenocarcinoma at the highest dose tested. The incidence of endometrial findings was slightly increased over concurrent controls but was within background range for female rats. Thus, the relevance of the incidence of uterine endometrial adenocarcinomas is uncertain. Exposures in the carcinogenicity studies were 0.3 to 0.7 times (in mice) and 0.7 to 1.4 times (in rats) those seen in humans given fosamprenavir 1400 mg twice daily. Exposures were 0.2 to 0.3 times (in mice) and 0.3 to 0.7 times (in rats) those seen in humans given fosamprenavir 1400 mg once daily plus ritonavir 200 mg once daily or 0.1 to 0.3 times (in mice) and 0.3 to 0.6 times (in rats) those seen in humans given fosamprenavir 700 mg plus ritonavir 100 mg twice daily.[1]

Reproduction/Fertility

No impairment of fertility or mating was seen in rats given doses that produced exposures that were three to four times the exposure seen in humans who were given fosamprenavir alone, or exposures that were similar to those seen in humans who received both fosamprenavir and ritonavir. No effect was seen on the development or maturation of sperm in rats at these doses.

Teratogenicity/Adverse Pregnancy Outcomes

Administration of fosamprenavir to pregnant rats and rabbits produced no major effects on embryo-fetal development; however, the incidence of abortion was increased in rabbits that were administered fosamprenavir. Administration of amprenavir to pregnant rabbits was associated with abortions and an increased incidence of minor skeletal variations from deficient ossification of the femur, humerus, and trochlea. Administration of fosamprenavir to pregnant rats at doses that produced twice the exposure typically seen in humans was associated with a reduction in pup survival and body weights. Female offspring had an increased time to successful mating, an increased length of gestation, a reduced number of uterine implantation sites per litter, and reduced gestational body weights compared to controls.

Placental and Breast Milk Passage

Amprenavir is excreted in the milk of lactating rats.

Human Studies in Pregnancy

Pharmacokinetics

Data on the use of fosamprenavir in pregnant women are limited. Fosamprenavir pharmacokinetic (PK) data have been reported in 26 women during pregnancy and postpartum. Following standard dosing with fosamprenavir 700 mg and ritonavir 100 mg twice daily, the fosamprenavir area under the curve and 12-hour trough concentration were somewhat lower during pregnancy and higher postpartum, compared to historical data. Fosamprenavir exposure during pregnancy appeared to be adequate for patients without protease inhibitor resistance mutations.[2] For the postpartum period, potential PK interactions with hormonal contraceptives should be taken into account (see Table 3 in Preconception Counseling and Care).

Placental and Breast Milk Passage

In a small study of women who received fosamprenavir during pregnancy, the median amprenavir concentration in cord blood was 0.27 µg/mL (with a range of 0.09–0.60 µg/mL), and the median ratio of amprenavir concentration in cord blood to that in maternal plasma at the time of delivery was 0.24 (with a range of 0.06–0.93).[2] A second small study in pregnancy yielded a similar mean ratio of amprenavir concentration in cord blood to that in maternal plasma at the time of delivery of 0.27 (95% confidence interval 0.24, 0.30).[3] Whether amprenavir is excreted in human breast milk is unknown.

Teratogenicity/Adverse Pregnancy Outcomes

Two birth defects out of 109 live births with first-trimester exposure and two birth defects out of 36 live births with second- or third-trimester exposure have been reported to the Antiretroviral Pregnancy Registry. These numbers are insufficient to draw conclusions regarding the risk of birth defects.[4]

Excerpt from Table 10[a]

Generic Name (Abbreviation) *Trade Name*	**Formulation**	**Dosing Recommendations**	**Use in Pregnancy**
Fosamprenavir (FPV) *Lexiva (a prodrug of amprenavir)* **Note:** Must be combined with low-dose RTV boosting in pregnancy.	FPV (Lexiva) *Tablets:* • 700 mg *Oral Suspension:* • 50 mg/mL	Standard Adult Doses *FPV (Lexiva)* *ARV-Naive Patients:* • FPV 1400 mg twice daily without food, *or* • FPV 1400 mg plus RTV 100 or 200 mg once daily without food, *or* • FPV 700 mg plus RTV 100 mg twice daily without food *PI-Experienced Patients:* • Once-daily dosing **is not recommended** • FPV 700 mg plus RTV 100 mg twice daily without food *Coadministered with EFV:* • FPV 700 mg plus RTV 100 mg twice daily without food; *or* • FPV 1400 mg plus RTV 300 mg once daily without food PK in Pregnancy: • With RTV boosting, AUC is reduced during the third trimester. However, exposure is greater during the third trimester with boosting than in nonpregnant adults without boosting, and trough concentrations achieved during the third trimester were adequate for patients without PI resistance mutations. Dosing in Pregnancy: • Use of unboosted FPV or once-daily FPV with RTV boosting **is not recommended** during pregnancy. No change is indicated in standard boosted twice-daily dose (FPV 700 mg plus RTV 100 mg twice daily without food).	FPV **should not** be used during pregnancy. Low placental transfer to fetus.[b] Insufficient data to assess for teratogenicity in humans. Increased fetal loss in rabbits, but no increase in defects in rats and rabbits.

[a] Individual ARV drug dosages may need to be adjusted in patients with renal or hepatic insufficiency (for details, see the Adult and Adolescent Guidelines, Appendix B, Table 8).

[b] Placental transfer categories are determined by mean or median cord blood/maternal delivery plasma drug ratio:

High: >0.6 **Moderate:** 0.3–0.6 **Low:** <0.3

Key to Acronyms: ARV = antiretroviral; AUC = area under the curve; EFV = efavirenz; FPV = fosamprenavir; PI = protease inhibitor; PK = pharmacokinetic; RTV = ritonavir

References

1. Fosamprenavir [package insert] Food and Drug Administration. 2017. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021548s040lbledt.pdf.
2. Capparelli EV, Stek A, Best B, et al. Boosted fosamprenavir pharmacokinetics during pregnancy. Presented at: The 17th

Conference on Retroviruses and Opportunistic Infections. 2010. San Francisco, CA.

3. Cespedes MS, Castor D, Ford SL, et al. Steady-state pharmacokinetics, cord blood concentrations, and safety of ritonavir-boosted fosamprenavir in pregnancy. *J Acquir Immune Defic Syndr*. 2013;62(5):550-554. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23314414.
4. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral pregnancy registry international interim report for 1 January 1989–31 January 2018. Wilmington, NC: Registry Coordinating Center. 2018. Available at: http://www.apregistry.com/.

Indinavir (Crixivan, IDV)

(Last updated December 7, 2018; last reviewed December 7, 2018)

Indinavir is classified as Food and Drug Administration Pregnancy Category C. Given the availability of effective alternative antiretroviral (ARV) drugs, indinavir **is not recommended** for use in pregnant women.

Animal Studies

Carcinogenicity

Indinavir is neither mutagenic nor clastogenic in both *in vitro* and *in vivo* assays. No increased incidence of any tumor types occurred during long-term studies in mice. At the highest dose studied in rats (640 mg/kg/day or 1.3-fold higher than systemic exposure at human therapeutic doses), thyroid adenomas were seen in male rats.[1]

Reproduction/Fertility

No effect of indinavir has been seen on reproductive performance, fertility, or embryo survival in rats.[1]

Teratogenicity/Adverse Pregnancy Outcomes

There has been no evidence of teratogenicity or treatment-related effects of indinavir on embryonic/fetal survival or fetal weights in rats, rabbits, or dogs at exposures comparable to, or slightly greater than, therapeutic human exposure. Developmental toxicity in rats, which manifested as an increase in supernumerary and cervical ribs, was observed at doses comparable to those administered to humans. No treatment-related external or visceral changes were observed in rats. No treatment-related external, visceral, or skeletal changes were seen in rabbits (fetal exposure was limited, approximately 3% of maternal levels) or dogs (fetal exposure approximately 50% of maternal levels). Indinavir was administered to rhesus monkeys during the third trimester (at doses up to 160 mg/kg twice daily) and to neonatal rhesus monkeys (at doses up to 160 mg/kg twice daily). When administered to neonates, indinavir caused an exacerbation of the transient physiologic hyperbilirubinemia seen in this species after birth; serum bilirubin values were approximately four-fold greater than those seen in controls receiving indinavir 160 mg/kg twice daily. A similar exacerbation did not occur in neonates after *in utero* exposure to indinavir during the third trimester. In rhesus monkeys, fetal plasma drug levels were approximately 1% to 2% of maternal plasma drug levels approximately 1 hour after maternal dosing with indinavir at 40, 80, or 160 mg/kg twice daily.[1]

Placental and Breast Milk Passage

Significant placental passage of indinavir occurs in rats and dogs, but only limited placental transfer occurs in rabbits. Indinavir is excreted in the milk of lactating rats at concentrations slightly greater than maternal levels.[1]

Human Studies in Pregnancy

Pharmacokinetics

The optimal dosing regimen for use of indinavir in pregnant patients has not been established. Two studies of the pharmacokinetics (PKs) of unboosted indinavir (800 mg taken 3 times/day) during pregnancy demonstrated significantly lower indinavir plasma concentrations during pregnancy than postpartum.[2,3] Use of unboosted indinavir is not recommended in pregnant patients with HIV because of the substantially lower antepartum concentrations and the limited experience in this patient population.

Several studies have investigated the use of indinavir/ritonavir (IDV/r) during pregnancy. In an intensive PK study of 26 pregnant Thai women receiving IDV/r 400/100 mg twice daily, indinavir plasma concentrations were significantly lower during pregnancy than postpartum. The median trough indinavir concentration was 0.13 µg/mL; 24% of subjects had trough concentrations below 0.10 µg/mL, the target trough concentration used in therapeutic drug monitoring programs; and 81% of subjects had RNA viral loads <50 copies/mL at delivery.[4] In a study of pregnant French women receiving IDV/r 400 mg/100 mg twice a day, the median

indinavir trough concentration was 0.16 µg/mL, 18% of subjects had trough concentrations below 0.12 µg/mL, and 93% of subjects had HIV RNA levels <200 copies/mL at delivery.[5] In a small study of two patients who received IDV/r 800 mg/200 mg twice daily, third-trimester indinavir area under the curve exceeded that for historical non-pregnant controls.[6] The available data are insufficient to allow for definitive dosing recommendations for use of IDV/r during pregnancy.

Placental and Breast Milk Passage

Transplacental passage of indinavir was minimal in studies of pregnant women who received unboosted indinavir. In a study of pregnant Thai women receiving IDV/r, median indinavir concentration in cord blood was 0.12 µg/mL, median maternal plasma delivery concentration was 0.96 µg/mL, and the median ratio between indinavir concentrations in cord blood and maternal plasma at delivery was 0.12.[4] In one woman taking IDV/r 600 mg/200 mg twice daily, indinavir concentrations in breast milk were 90% to 540% of plasma concentrations over the first 5 days after delivery.[7]

Teratogenicity/Adverse Pregnancy Outcomes

Although the French Perinatal Cohort reported an association of head and neck birth defects with first trimester exposure to indinavir (3 defects in 350 first-trimester exposures, 0.9%), the Antiretroviral Pregnancy Registry has not observed an increase in birth defects with use of indinavir.[8,9] Among cases of first-trimester indinavir exposure reported to the Antiretroviral Pregnancy Registry, prevalence of birth defects was 2.4% (7 of 289 births; 95% CI, 1.0% to 4.9%) compared with a total prevalence of 2.76% in the U.S. population, according to Centers for Disease Control and Prevention surveillance.[9]

Excerpt from Table 10[a]

Generic Name (Abbreviation) *Trade Name*	**Formulation**	**Dosing Recommendations**	**Use in Pregnancy**
Indinavir (IDV) *Crixivan* **Note:** Must be combined with low-dose RTV boosting in pregnancy	IDV (Crixivan) *Capsules:* • 200 mg • 400 mg	Standard Adult Dose *Without RTV Boosting:* • IDV 800 mg every 8 hours, taken 1 hour before or 2 hours after meals; may be taken with skim milk or a low-fat meal. *With RTV Boosting:* • IDV 800 mg plus RTV 100 mg twice daily without regard to meals PK in Pregnancy: • IDV exposure markedly reduced when administered without RTV boosting during pregnancy. IDV exposure is low with IDV 400 mg/RTV 100 mg dosing during pregnancy; no PK data available on alternative boosted dosing regimens in pregnancy. Dosing in Pregnancy: • Use of unboosted IDV **is not recommended** during pregnancy.	Minimal placental transfer to fetus.[b] No evidence of human teratogenicity in cases reported to the Antiretroviral Pregnancy Registry (can rule out 2-fold increase in overall birth defects). Must be given as low-dose, RTV-boosted regimen in pregnancy. Theoretical concern regarding increased indirect bilirubin levels, which may exacerbate physiologic hyperbilirubinemia in neonates. Minimal placental passage mitigates this concern. Given the available alternative ARVs, IDV **is not recommended** for treatment of pregnant women in the United States.

[a] Individual ARV drug dosages may need to be adjusted in patients with renal or hepatic insufficiency (for details, see the Adult and Adolescent Guidelines, Appendix B, Table 8).

[b] Placental transfer categories are determined by the mean or median cord blood/maternal delivery plasma drug ratio:

High: >0.6 **Moderate:** 0.3–0.6 **Low:** <0.3

Key to Acronyms: ARV = antiretroviral; IDV = indinavir; PK = pharmacokinetic; RTV = ritonavir

References

1. Indinavir [package insert]. Food and Drug Administration. 2016. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020685s078lbl.pdf.
2. Unadkat JD, Wara DW, Hughes MD, et al. Pharmacokinetics and safety of indinavir in human immunodeficiency virus-infected pregnant women. *Antimicrob Agents Chemother*. 2007;51(2):783-786. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17158945.
3. Hayashi S, Beckerman K, Homma M, Kosel BW, Aweeka FT. Pharmacokinetics of indinavir in HIV-positive pregnant women. *AIDS*. 2000;14(8):1061-1062. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10853990.
4. Cressey TR, Best BM, Achalapong J, et al. Reduced indinavir exposure during pregnancy. *Br J Clin Pharmacol*. 2013;76(3):475-483. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23305215.
5. Ghosn J, De Montgolfier I, Cornelie C, et al. Antiretroviral therapy with a twice-daily regimen containing 400 milligrams of indinavir and 100 milligrams of ritonavir in human immunodeficiency virus type 1-infected women during pregnancy. *Antimicrob Agents Chemother*. 2008;52(4):1542-1544. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18250187.
6. Kosel BW, Beckerman KP, Hayashi S, Homma M, Aweeka FT. Pharmacokinetics of nelfinavir and indinavir in HIV-1-infected pregnant women. *AIDS*. 2003;17(8):1195-1199. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12819521.
7. Colebunders R, Hodossy B, Burger D, et al. The effect of highly active antiretroviral treatment on viral load and antiretroviral drug levels in breast milk. *AIDS*. 2005;19(16):1912-1915. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16227801.
8. Sibiude J, Mandelbrot L, Blanche S, et al. Association between prenatal exposure to antiretroviral therapy and birth defects: an analysis of the French perinatal cohort study (ANRS CO1/CO11). *PLoS Med*. 2014;11(4):e1001635. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24781315.
9. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral pregnancy registry international interim report 1 January 1989–31 January 2018. Wilmington, NC: Registry Coordinating Center. 2018. Available at: Available at: http://www. apregistry.com/.

Lopinavir/Ritonavir (Kaletra, LPV/r)

(Last updated December 7, 2018; last reviewed December 7, 2018)

No difference in the risk of overall major birth defects has been shown for lopinavir/ritonavir (LPV/r) compared to the background rate for major birth defects in the United States.

Animal Studies

Carcinogenicity

Neither lopinavir nor ritonavir was found to be mutagenic or clastogenic in a battery of *in vitro* and *in vivo* assays. The LPV/r combination was evaluated for carcinogenic potential by oral gavage administration to mice and rats for ≤104 weeks. Results showed an increased incidence of benign hepatocellular adenomas and increased combined incidence of hepatocellular adenomas plus carcinoma in male and female mice and male rats at doses that produced approximately 1.6 to 2.2 times (mice) and 0.5 times (rats) the human exposure at the recommended therapeutic dose of LPV/r 400 mg/100 mg (based on area under the curve $[AUC]_{0–24hr}$ measurement). Administration of LPV/r did not cause a statistically significant increase in incidence of any other benign or malignant neoplasm in mice or rats.[1]

Reproduction/Fertility

No effects on fertility were observed in male and female rats that received lopinavir in combination with ritonavir at a 2:1 ratio. These rats experienced exposures that were approximately 0.7-fold (lopinavir) and 1.8-fold (ritonavir) the exposures seen in humans at the recommended therapeutic dose.[1]

Teratogenicity/Adverse Pregnancy Outcomes

No evidence exists of teratogenicity with administration of LPV/r to pregnant rats or rabbits. In rats treated with a maternally toxic dosage (LPV/r 100 mg/50 mg/kg/day), embryonic and fetal developmental toxicities (e.g., early resorption, decreased fetal viability, decreased fetal body weight, increased incidence of skeletal variations, and skeletal ossification delays) were observed. Drug exposure in the pregnant rats was 0.7-fold for lopinavir and 1.8-fold for ritonavir the exposures observed in humans at the recommended therapeutic dose. In a perinatal and postnatal study in rats, a decrease in survival of pups between birth and postnatal day 21 occurred with exposure to LPV/r 40 mg/20 mg/kg/day or greater. In rabbits, no embryonic or fetal developmental toxicities were observed with a maternally toxic dose, where drug exposure was 0.6-fold for lopinavir and 1-fold for ritonavir the exposures seen in humans at the recommended therapeutic dose.[1] In a study of pregnant rats receiving chronic administration of zidovudine, lopinavir, and ritonavir, maternal body weight gain was significantly reduced compared to weight gain in rats that received no antiretroviral (ARV) drugs, but no adverse fetal parameters were observed.[2] In pregnant mice, ritonavir, lopinavir and atazanavir were associated with significantly lower progesterone levels than those seen in mice who received no ARV drugs, and the lower progesterone levels directly correlated with lower fetal weight.[3]

Placental and Breast Milk Passage

No information is available on placental transfer of lopinavir in animals.[1]

Human Studies in Pregnancy

Pharmacokinetics

The original capsule formulation of LPV/r has been replaced by a tablet formulation that is heat-stable, has improved bioavailability characteristics, and does not have to be administered with food.[4,5] Pharmacokinetic (PK) studies of standard adult LPV/r doses (400 mg/100 mg twice a day) using either the capsule or tablet formulations in pregnant women have demonstrated a reduction in lopinavir plasma concentrations during pregnancy of around 30% compared with those seen in nonpregnant adults.[6-8] Further reductions in lopinavir exposure by 33% were demonstrated in food-insecure, malnourished pregnant women in Uganda compared to well-nourished, historical pregnant controls. The authors attributed this reduction to decreased bioavailability.[9] Increasing the dose of LPV/r during pregnancy to 600 mg/150 mg (tablets) results in

lopinavir plasma concentrations equivalent to those seen in nonpregnant adults receiving standard doses.[10,11]

Reports of clinical experience suggest that most, but not all, pregnant women receiving standard LPV/r tablet dosing during pregnancy will have trough lopinavir concentrations that exceed 1.0 mcg/mL, the usual trough concentration target used in therapeutic drug monitoring programs for ARV-naive subjects, but not the higher trough concentrations recommended for protease inhibitor (PI)-experienced subjects.[4,7] A population PK study of LPV/r in 154 pregnant women demonstrated that body weight influences lopinavir clearance and volume; larger women (>100 kg) or women who missed a dose were at higher risk for subtherapeutic trough concentrations when taking the standard dose during pregnancy.[12] Another population PK study in 84 pregnant women and 595 nonpregnant adults found no significant difference between lopinavir concentrations observed in pregnant women taking the more bioavailable tablet formulation and those seen in nonpregnant adults taking the original capsule formulation.[13] In one study of 29 women, lopinavir plasma protein binding was reduced during pregnancy, but the resulting increase in free (unbound) drug was insufficient to make up for the reduction in total plasma lopinavir concentration associated with pregnancy.[14] In a study of 12 women, total lopinavir exposure was significantly decreased throughout pregnancy, but unbound AUC and C_{12} did not differ throughout pregnancy, even with an increased dose of LPV/r 500 mg/125 mg. Modeling of these data concluded that standard dosing should be effective during pregnancy with susceptible virus.[15,16] A population PK study found a 39% increase in total lopinavir clearance during pregnancy, but measured unbound lopinavir concentrations in pregnancy were within the range of those simulated in nonpregnant adults.[17] Bonafe et al. randomized 32 pregnant women to receive the standard dose and 31 pregnant women to receive the 600 mg/150 mg dose of LPV/r at gestational ages between 14 and 33 weeks. No differences in adverse events were seen between groups. In women with baseline viral loads >50 copies/mL, 45% of women in the standard dose group had plasma viral loads >50 copies/mL during the last 4 weeks of pregnancy, compared to 10.5% of women in the increased dose group ($P = 0.01$). In women with baseline viral loads <50 copies/mL, no difference was seen between groups in viral load measurements in the last 4 weeks of pregnancy.[18]

These studies have led some experts to support the use of an increased dose of LPV/r in pregnant women with HIV during the second and third trimesters, especially in women who are PI-experienced and women who start treatment during pregnancy with a baseline viral load >50 copies/mL. If standard doses of LPV/r are used during pregnancy, virologic response and lopinavir drug concentrations should be monitored if possible. Instead of using three adult three adult tablets (LPV/r 200 mg/50 mg each) to increase the dose of LPV/r to 600 mg/150 mg during pregnancy, clinicians may consider using two adult tablets and one pediatric LPV/r tablet (100 mg/25 mg) to provide a dose of LPV/r 500 mg/125 mg.[15] Once-daily dosing of LPV/r **is not recommended** in pregnancy because no data exist to address whether drug levels are adequate with such administration.

Placental and Breast Milk Passage

Lopinavir crosses the human placenta; in the P1026s PK study, the average ratio of lopinavir concentration in cord blood to maternal plasma at delivery was 0.20 ± 0.13. In contrast, in a study of plasma and hair drug concentration in 51 mother-infant pairs in Uganda who received LPV/r during pregnancy and breastfeeding, infant plasma levels at delivery and hair levels at age 12 weeks suggested significant *in utero* transfer: 41% of infants had detectable plasma lopinavir concentrations at birth, and mean infant-to-maternal-hair concentrations at 12 weeks postpartum were 0.87 for lopinavir.[19] However, transfer during breastfeeding was not observed, and no infant had detectable plasma lopinavir levels at 12 weeks. Lopinavir concentrations in human breast milk are very low to undetectable, and lopinavir concentrations in breastfeeding infants whose mothers received lopinavir are not clinically significant.[19-23]

Teratogenicity/Adverse Pregnancy Outcomes

The French Perinatal Cohort found no association between birth defects and lopinavir or ritonavir with 85% power to detect a 1.5-fold increase.[24] The Pediatric HIV/AIDS Cohort Study found no association between lopinavir and congenital anomalies.[25] Surveillance data from the United Kingdom and Ireland over a 10-year period showed a 2.9% prevalence of congenital abnormalities (134 children out of 4,609 lopinavir-

exposed pregnancies), comparable to rates of congenital abnormalities in populations without HIV.[26] In the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposures to LPV/r have been monitored for detection of at least a 1.5-fold increase in risk of overall birth defects and a 2-fold increase in the cardiovascular and genitourinary systems. No such increase in birth defects has been observed with LPV/r. Among cases of first-trimester exposure to LPV/r reported to the Antiretroviral Pregnancy Registry, the prevalence of birth defects was 2.1% (30 out of 1,418 births; 95% CI, 1.4% to 3.0%) compared with a prevalence of either 2.7% when using data from the Metropolitan Atlanta Congenital Defects Program (MACDP) or 4.2% when using data from the Texas Birth Defects Registry (TBDR).[27]

In the PROMISE study, LPV/r administered with zidovudine plus lamivudine or with tenofovir disoproxil fumarate plus lamivudine resulted in decreased transmission rates compared to the transmission rates seen with zidovudine alone, but these LPV/r-containing regimens also resulted in increased incidence of low birth weight (<2,500 g).[28] Compared to zidovudine alone, zidovudine plus lamivudine plus LPV/r was associated with increased rates of preterm delivery (<37 weeks). PHACS SMARTT also found an increased rate of preterm birth with PI-based ARV therapy, although not with specific individual drugs.[29] Similarly, a study in China found that PI-based regimens had higher rates of preterm birth than did non-nucleoside reverse transcriptase inhibitor-based regimens.[30] In the United Kingdom/Ireland National Study of HIV in Pregnancy and Childhood, 2,368 out of 6,073 women had taken LPV/r during their pregnancies; LPV/r use was significantly associated with preterm delivery after adjustment for other factors when compared to other boosted-PI regimens or to NNRTI-based regimens.[31] For a more detailed discussion of ARV drug regimens and adverse pregnancy outcomes, please refer to Combination Antiretroviral Drug Regimens and Maternal and Neonatal Outcomes.

Safety

LPV/r oral solution contains 42.4% (volume/volume) alcohol and 15.3% (weight/volume) propylene glycol and is not recommended for use during pregnancy. Reduced hepatic metabolic and kidney excretory function in newborns can lead to accumulation of lopinavir as well as alcohol and propylene glycol, resulting in adverse events (e.g., serious cardiac, renal, metabolic, or respiratory problems).

Preterm babies may be at increased risk because their metabolism and elimination of lopinavir, propylene glycol, and alcohol are further reduced. Post-marketing surveillance has identified 10 neonates (i.e., babies aged <4 weeks), nine of whom were born prematurely, who received LPV/r and experienced life-threatening events.[32] In a separate report comparing 50 newborns exposed to HIV and treated with LPV/r after birth to 108 neonates exposed to HIV and treated with zidovudine alone, elevated concentrations of 17-hydoxyprogesterone and dehydroepiandrosterone-sulfate, consistent with impairment of 21α-hydroxylase activity, were seen only in the infants exposed to lopinavir. All full-term infants were asymptomatic, but three out of eight preterm infants had life-threatening symptoms, including hyponatremia, hyperkalemia, and cardiogenic shock, consistent with adrenal insufficiency.[33] LPV/r oral solution should not be administered to neonates before a postmenstrual age (first day of the mother's last menstrual period to birth, plus the time elapsed after birth) of 42 weeks and a postnatal age of at least 14 days has been attained. Refer to Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV for more information.

Excerpt from Table 10[a]

Generic Name (Abbreviation) *Trade Name*.	**Formulation**	**Dosing Recommendations**	**Use in Pregnancy**
Lopinavir/ Ritonavir (LPV/r) *Kaletra*	LPV/r (Kaletra) *Tablets (Coformulated):* • LPV/r 200 mg/50 mg • LPV/r 100 mg/25 mg *Oral Solution:* • LPV/r 400 mg/100 mg/5 mL	Standard Adult Dose: • LPV/r 400 mg/100 mg twice daily, *or* • LPV/r 800 mg/200 mg once daily *Tablets:* • Take without regard to food. *Oral Solution:* • Take with food. With EFV or NVP (PI-Naive or PI-Experienced Patients): • LPV/r 500 mg/125 mg tablets twice daily without regard to meals (use a combination of 2 LPV 200-mg plus RTV 50-mg tablets and 1 LPV 100-mg plus RTV 25-mg tablet), *or* • LPV/r 520 mg/130 mg oral solution (6.5 mL) twice daily with food PK in Pregnancy: • With twice-daily dosing, LPV exposure is reduced in pregnant women receiving standard adult doses; increasing the dose by 50% results in exposure equivalent to that seen in nonpregnant adults receiving standard doses. • No PK data are available for once-daily dosing in pregnancy. Dosing in Pregnancy: • Once-daily dosing **is not recommended** during pregnancy. • Some experts recommend that an increased dose (i.e., LPV/r 600 mg/150 mg twice daily without regard to meals or LPV/r 500 mg/125 mg twice daily without regard to meals) should be used in the second and third trimesters, especially in PI-experienced pregnant women and women who start treatment during pregnancy with a baseline viral load >50 copies/mL. • If standard dosing is used, monitor virologic response and, if available, LPV drug levels.	Low placental transfer to fetus.[b] No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects). Oral solution contains 42% alcohol and 15% propylene glycol and is not recommended for use in pregnancy. Once-daily LPV/r dosing is not recommended during pregnancy

[a] Individual ARV drug dosages may need to be adjusted in patients with renal or hepatic insufficiency (for details, see the Adult and Adolescent Guidelines, Appendix B, Table 8).

[b] Placental transfer categories are determined by mean or median cord blood/maternal delivery plasma drug ratio:

High: >0.6 **Moderate:** 0.3–0.6 **Low:** <0.3

Key to Acronyms: EFV = efavirenz; LPV = lopinavir; LPV/r = lopinavir/ritonavir; NVP = nevirapine; PI = protease inhibitor; PK = pharmacokinetic; RTV = ritonavir

References

1. Lopinavir/ritonavir (Kaletra) [package insert]. Food and Drug Administration. 2017. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021251s055,021906s050lbl.pdf.
2. Carvalho LP, Simoes RS, Araujo JE, Oliveira Filho RM, Kulay Junior L, Nakamura MU. Highly active antiretroviral therapy during gestation: effects on a rat model of pregnancy. *J Ev Purkyne*. 2014;79(2):128-133. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24874827.
3. Papp E, Mohammadi H, Loutfy MR, et al. HIV protease inhibitor use during pregnancy is associated with decreased progesterone levels, suggesting a potential mechanism contributing to fetal growth restriction. *J Infect Dis*. 2015;211(1):10-18. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25030058.
4. Khuong-Josses MA, Azerad D, Boussairi A, Ekoukou D. Comparison of lopinavir level between the two formulations (soft-gel capsule and tablet) in HIV-infected pregnant women. *HIV Clin Trials*. 2007;8(4):254-255. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17720666.

5. Else LJ, Douglas M, Dickinson L, Back DJ, Khoo SH, Taylor GP. Improved oral bioavailability of lopinavir in melt-extruded tablet formulation reduces impact of third trimester on lopinavir plasma concentrations. *Antimicrob Agents Chemother*. 2012;56(2):816-824. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22106215.

6. 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*.

7. 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.

8. Ramautarsing RA, van der Lugt J, Gorowara M, et al. Thai HIV-1-infected women do not require a dose increase of lopinavir/ritonavir during the third trimester of pregnancy. *AIDS*. 2011;25(10):1299-1303. Available at: *http://www.ncbi.nlm.nih.gov/pubmed/21516029*.

9. Bartelink IH, Savic RM, Mwesigwa J, et al. Pharmacokinetics of lopinavir/ritonavir and efavirenz in food insecure HIV-infected pregnant and breastfeeding women in Tororo, Uganda. *J Clin Pharmacol*. 2014;54(2):121-132. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24038035.

10. 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.

11. 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.

12. Cressey TR, Urien S, Capparelli EV, et al. Impact of body weight and missed doses on lopinavir concentrations with standard and increased lopinavir/ritonavir doses during late pregnancy. *J Antimicrob Chemother*. 2015;70(1):217-224. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25261418.

13. Salem AH, Jones AK, Santini-Oliveira M, et al. No need for lopinavir dose adjustment during pregnancy: a population pharmacokinetic and exposure-response analysis in pregnant and nonpregnant HIV-infected subjects. *Antimicrob Agents Chemother*. 2016;60(1):400-408. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26525798.

14. Aweeka FT, Stek A, Best BM, et al. Lopinavir protein binding in HIV-1-infected pregnant women. *HIV Med*. 2010;11(4):232-238. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20002783.

15. Patterson KB, Dumond JB, Prince HA, et al. Protein binding of lopinavir and ritonavir during 4 phases of pregnancy: implications for treatment guidelines. *J Acquir Immune Defic Syndr*. 2013;63(1):51-58. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23221983.

16. Chen J, Malone S, Prince HM, Patterson KB, Dumond JB. Model-based analysis of unbound lopinavir pharmacokinetics in HIV-infected pregnant women supports standard dosing in the third trimester. *CPT Pharmacometrics Syst Pharmacol*. 2016;5(3):147-157. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27069778.

17. Fauchet F, Treluyer JM, Illamola SM, et al. Population approach to analyze the pharmacokinetics of free and total lopinavir in HIV-infected pregnant women and consequences for dose adjustment. *Antimicrob Agents Chemother*. 2015;59(9):5727-5735. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26149996.

18. Bonafe SM, Costa DA, Vaz MJ, et al. A randomized controlled trial to assess safety, tolerability, and antepartum viral load with increased lopinavir/ritonavir dosage in pregnancy. *AIDS Patient Care STDS*. 2013;27(11):589-595. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24138537.

19. Gandhi M, Mwesigwa J, Aweeka F, et al. Hair and plasma data show that lopinavir, ritonavir, and efavirenz all transfer from mother to infant in utero, but only efavirenz transfers via breastfeeding. *J Acquir Immune Defic Syndr*. 2013;63(5):578-584. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24135775.

20. Rezk NL, White N, Bridges AS, et al. Studies on antiretroviral drug concentrations in breast milk: validation of a liquid chromatography-tandem mass spectrometric method for the determination of 7 anti-human immunodeficiency virus medications. *Ther Drug Monit*. 2008;30(5):611-619. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18758393.

21. Shapiro RL, Rossi S, Ogwu A, et al. Therapeutic levels of lopinavir in late pregnancy and abacavir passage into breast milk in the Mma Bana Study, Botswana. *Antivir Ther*. 2013;18(4):585-590. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23183881.

22. Palombi L, Pirillo MF, Andreotti M, et al. Antiretroviral prophylaxis for breastfeeding transmission in Malawi: drug concentrations, virological efficacy and safety. *Antivir Ther*. 2012;17(8):1511-1519. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22910456.

23. Corbett AH, Kayira D, White NR, et al. Antiretroviral pharmacokinetics in mothers and breastfeeding infants from 6 to 24 weeks post-partum: results of the BAN Study. *Antivir Ther*. 2014;19(6):587-595. Available at: http://www.ncbi.nlm.

nih.gov/pubmed/24464632.

24. Sibiude J, Mandelbrot L, Blanche S, et al. Association between prenatal exposure to antiretroviral therapy and birth defects: an analysis of the French perinatal cohort study (ANRS CO1/CO11). *PLoS Med*. 2014;11(4):e1001635. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24781315.
25. Williams PL, Crain M, Yildirim C, et al. Congenital anomalies and in utero antiretroviral exposure in human immunodeficiency virus-exposed uninfected infants. *JAMA Pediatr*. 2015;169(1):45-55. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25383770.
26. Tookey PA, Thorne C, van Wyk J, Norton M. Maternal and foetal outcomes among 4118 women with HIV infection treated with lopinavir/ritonavir during pregnancy: analysis of population-based surveillance data from the national study of HIV in pregnancy and childhood in the United Kingdom and Ireland. *BMC infectious diseases*. 2016;16:65. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26847625.
27. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral pregnancy registry international interim report for 1 January 1989–31 January 2018. Wilmington, NC: Registry Coordinating Center. 2018. Available at: http://www.apregistry.com/.
28. 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.
29. Van Dyke RB, Chadwick EG, Hazra R, Williams PL, Seage GR, 3rd. The PHACS SMARTT study: assessment of the safety of in utero exposure to antiretroviral drugs. *Front Immunol*. 2016;7:199. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27242802.
30. Wang L, Zhao H, Tao J, et al. Risk factors associated with preterm and low birth weight among infants born to HIV-infected mothers in five tertiary hospitals in China, 2009-2014. *AIDS*. 2016.
31. Favarato G, Townsend CL, Bailey H, et al. Protease inhibitors and preterm delivery: another piece in the puzzle. *AIDS*. 2018;32(2):243-252. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29135577.
32. Boxwell D, Cao K, Lewis L, Marcus K, Nikhar B. Neonatal toxicity of Kaletra oral solution: LPV, ethanol or prophylene glycol? Presented at: 18th Conference on Retroviruses and Opportunistic Infections. 2011. Boston, MA.
33. Simon A, Warszawski J, Kariyawasam D, et al. Association of prenatal and postnatal exposure to lopinavir-ritonavir and adrenal dysfunction among uninfected infants of HIV-infected mothers. *JAMA*. 2011;306(1):70-78. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21730243.

Nelfinavir (Viracept, NFV)

(Last updated December 7, 2018; last reviewed December 7, 2018)

Nelfinavir is classified as Food and Drug Administration Pregnancy Category B. Nelfinavir **should not** be used during pregnancy.

Animal Studies

Carcinogenicity

Nelfinavir was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests. However, incidence of thyroid follicular cell adenomas and carcinomas was increased over baseline in male rats receiving nelfinavir doses of 300 mg/kg/day or higher (which produced exposures that were equal to a systemic exposure observed in humans who received therapeutic doses) and female rats receiving nelfinavir 1000 mg/kg/day (which produced a systemic exposure 3-fold higher than the exposure seen in humans who received therapeutic doses).[1]

Reproduction/Fertility

Nelfinavir has had no observable effect on reproductive performance, fertility, or embryo survival in rats at exposures comparable to human therapeutic exposure.[1] Additional studies in female rats indicated that exposure to nelfinavir from mid-pregnancy through lactation had no effect on the survival, growth, and development of the offspring to weaning. Maternal exposure to nelfinavir also did not affect subsequent reproductive performance of the offspring.

Teratogenicity/Adverse Pregnancy Outcomes

No evidence of teratogenicity has been observed in pregnant rats at exposures that were comparable to human exposure and in rabbits with exposures that were significantly less than human exposure.[1]

Human Studies in Pregnancy

Pharmacokinetics

A Phase 1/2 safety and pharmacokinetic (PK) study (PACTG 353) of nelfinavir administered in combination with zidovudine and lamivudine was conducted in pregnant women with HIV and their infants.[2] In the first nine pregnant women enrolled in the study, nelfinavir administered at a dose of 750 mg three times daily produced drug exposures that were variable and generally lower than those reported in nonpregnant adults with both twice-daily and three-times-daily dosing. Therefore, the study was modified to evaluate an increased dose of nelfinavir given twice daily (1250 mg twice daily), which resulted in adequate levels of the drug in pregnancy. However, in two other small studies of women given nelfinavir 1250 mg twice daily during the second and third trimesters, drug concentrations in both those trimesters were somewhat lower than those seen in nonpregnant women.[3,4]

In a PK study of combination therapy evaluated 25 women at 30 to 36 weeks' gestation and 12 women at 6 to 12 weeks postpartum who received the nelfinavir 625-mg tablet formulation, given as 1250 mg twice daily. Peak nelfinavir levels and area under the curve were lower during the third trimester than postpartum.[5] Only 16% of women (4 of 25) during the third trimester and 8% of women (1 of 12) postpartum had trough values greater than the suggested minimum trough of 800 ng/mL; however, viral load was <400 copies/mL in 96% of women in the third trimester and 86% postpartum.

Placental and Breast Milk Passage

In PACTG 353, transplacental passage of nelfinavir was minimal.[2] In addition, in a study of cord blood samples from 38 women who were treated with nelfinavir during pregnancy, the cord blood nelfinavir concentration was less than the assay limit of detection in 24 women (63%), and the cord blood concentration was low (with a median of 0.35 µg/mL) in the remaining 14 women.[6] Among 20 mother-infant pairs in the Netherlands, the cord blood-to-maternal-plasma ratio for nelfinavir was 0.14 compared to 0.67 for nevirapine and 0.24 for lopinavir.[7]

Nelfinavir also has low breast milk passage. In a PK study conducted in Kisumu, Kenya, concentrations of nelfinavir and its active metabolite, M8, were measured in maternal plasma and breast milk from 26 mothers who received nelfinavir as part of antiretroviral therapy and from plasma samples collected from their 27 infants at birth, 2, 6, 14, and 24 weeks.[8] Peak nelfinavir concentrations were recorded in maternal plasma and breast milk at 2 weeks. Median breast milk-to-plasma ratio was 0.12 for nelfinavir and 0.03 for its active metabolite (i.e., M8). Nelfinavir and M8 concentrations were below the limit of detection in 20 of 28 (71%) infant plasma dried blood spots tested from nine infants over time points from delivery though 24 weeks. Overall transfer to breast milk was low and resulted in nonsignificant exposure to nelfinavir among breastfed infants through age 24 weeks.

Teratogenicity/Adverse Pregnancy Outcomes

In the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposures to nelfinavir have been monitored to be able to detect at least a 1.5-fold increased risk of overall birth defects and a two-fold increased risk of birth defects in the cardiovascular and genitourinary systems. No such increase in birth defects has been observed with exposure to nelfinavir. Among cases of first-trimester nelfinavir exposure reported to the Antiretroviral Pregnancy Registry, prevalence of birth defects was 3.9% (47 of 1,212 births; 95% CI, 2.9% to 5.1%) compared with a 2.7% total prevalence in the U.S. population, based on Centers for Disease Control and Prevention surveillance.[9]

In the U.S. PHACS/SMARTT cohort study, after adjusting for birth cohort and other factors, maternal use of nelfinavir led to no increase in the likelihood of adverse metabolic, growth/development, cardiac, neurological, or neurodevelopmental outcomes.[10]

Excerpt from Table 10[a]

Generic Name (Abbreviation) *Trade Name*	**Formulation**	**Dosing Recommendations**	**Use in Pregnancy**
Nelfinavir (NFV) *Viracept*	NFV (Viracept): *Tablets:* • 250 mg • 625 mg (tablets can be dissolved in a small amount of water) *Powder for Oral Suspension:* • 50 mg/g	Standard Adult Dose: • NFV 1250 mg twice daily, *or* • NFV 750 mg 3 times daily with food PK in Pregnancy: • Lower NFV exposure was observed during the third trimester than postpartum in women receiving NFV 1250 mg twice daily; however, adequate drug levels are generally achieved during pregnancy, although levels are variable in late pregnancy. Dosing in Pregnancy: • NFV 750 mg 3 times daily with food **is not recommended** during pregnancy. No change in standard dose (NFV 1250 mg twice daily with food) indicated.	NFV **should not** be used during pregnancy. Minimal to low placental transfer to fetus.[b] No evidence of human teratogenicity; can rule out 1.5-fold increase in overall birth defects and 2-fold increase in risk of cardiovascular and genitourinary birth defects. Contains aspartame; should not be used in individuals with phenylketonuria.

[a] Individual ARV drug dosages may need to be adjusted in patients with renal or hepatic insufficiency (for details, see the Adult and Adolescent Guidelines, Appendix B, Table 8).

[b] Placental transfer categories are determined by mean or median cord blood/maternal delivery plasma drug ratio:

High: >0.6 **Moderate:** 0.3–0.6 **Low:** <0.3

Key to Acronyms: NFV = nelfinavir; PK = pharmacokinetic

References

1. Nelfinavir [package insert]. 2015.Food and Drug Administration. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/020778s040,020779s061,021503s023lbl.pdf.
2. 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.

3. 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.
4. Fang A, Valluri SR, O'Sullivan MJ, et al. Safety and pharmacokinetics of nelfinavir during the second and third trimesters of pregnancy and postpartum. *HIV Clin Trials*. 2012;13(1):46-59. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22306587.
5. 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.
6. Mirochnick M, Dorenbaum A, Holland D, et al. Concentrations of protease inhibitors in cord blood after in utero exposure. *Pediatr Infect Dis J*. 2002;21(9):835-838. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12352805.
7. van Hoog S, Boer K, Nellen J, Scherpbier H, Godfried MH. Transplacental passage of nevirapine, nelfinavir and lopinavir. *Neth J Med*. 2012;70(2):102-103. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22418759.
8. Weidle PJ, Zeh C, Martin A, et al. Nelfinavir and its active metabolite, hydroxy-t-butylamidenelfinavir (M8), are transferred in small quantities to breast milk and do not reach biologically significant concentrations in breast-feeding infants whose mothers are taking nelfinavir. *Antimicrob Agents Chemother*. 2011;55(11):5168-5171. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21876052.
9. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral pregnancy registry international interim report for 1 January 1989–31 January 2018. Wilmington, NC: Registry Coordinating Center. 2018. Available at: http://www.apregistry.com/.
10. Van Dyke RB, Chadwick EG, Hazra R, Williams PL, Seage GR, 3rd. The PHACS SMARTT study: assessment of the safety of In utero exposure to antiretroviral drugs. *Front Immunol*. 2016;7:199. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27242802.

Saquinavir (Invirase, SQV)

(Last updated December 7, 2018; last reviewed December 7, 2018)

Saquinavir is classified as Food and Drug Administration Pregnancy Category B. Saquinavir **should not** be used during pregnancy.

Animal Studies

Carcinogenicity

Saquinavir was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests. Carcinogenicity studies found no indication of carcinogenic activity in rats and mice given saquinavir for approximately 2 years at doses that produced plasma exposures approximately 29% (in rats) and 65% (in mice) of those obtained in humans who received the recommended clinical dose boosted with ritonavir.[1]

Reproduction/Fertility

Saquinavir has had no observable effects on reproductive performance, fertility, or embryo survival in rats. Because of the limited bioavailability of saquinavir in animals, the maximum plasma exposures achieved in rats were approximately 26% of those obtained in humans who received the recommended clinical dose boosted with ritonavir.[1]

Teratogenicity/Adverse Pregnancy Outcomes

No evidence of embryotoxicity or teratogenicity of saquinavir has been found in rabbits or rats. Because of the limited bioavailability of saquinavir in animals and/or dosing limitations, the plasma exposures (measured as area under the curve [AUC] values) were approximately 29% (in rats) and 21% (in rabbits) of those obtained in humans who received the recommended clinical dose boosted with ritonavir.[1]

Placental and Breast Milk Passage

Placental transfer of saquinavir in rats and rabbits was minimal. Saquinavir is excreted in the milk of lactating rats.[1]

Human Studies in Pregnancy

Pharmacokinetics

Studies have investigated saquinavir pharmacokinetics (PK) during pregnancy using 800 mg to 1200 mg of the original hard-gel capsule formulation and ritonavir 100 mg. Saquinavir exposures were reduced in pregnant adults compared to nonpregnant adults, but the majority of subjects achieved adequate C_{min}.[2-4] The PKs of saquinavir when using the current 500-mg tablets at a dose of saquinavir/ritonavir 1000 mg/100 mg twice daily have been studied in pregnant women in two studies.[5,6] One study performed intensive sampling on pregnant women with HIV at 20 weeks' gestation (n = 16), 33 weeks' gestation (n = 31), and 6 weeks postpartum (n = 9). PK parameters were comparable during pregnancy and postpartum.[5] The second study performed intensive sampling in 14 pregnant women at 24 and 34 weeks' gestation and 6 weeks postpartum. Saquinavir AUC was similar during the second trimester and postpartum. Although there was a 50% reduction in saquinavir AUC during the third trimester compared to postpartum, no participant experienced loss of virologic control and all but one maintained adequate third-trimester trough levels of saquinavir.[7] An observational study analyzed saquinavir concentrations in samples that were collected as part of clinical care between 11 and 13 hours after dosing with the tablet formulation (saquinavir/ritonavir 1000 mg/100 mg) in pregnant women with HIV during the third trimester (n = 20) and at delivery (n = 5). Saquinavir plasma concentrations averaged around 1.15 mg/L and exceeded 0.1 mg/L, the usual trough drug concentration target for saquinavir, in all but one subject.[6]

Placental and Breast Milk Passage

In a Phase 1 study in pregnant women and their infants (PACTG 386), transplacental passage of saquinavir was minimal.[8] In addition, in a study of eight women treated with saquinavir during pregnancy, the cord

blood concentration of saquinavir was less than the assay limit of detection in samples from all of the women in the study.[9] It is not known whether saquinavir is excreted in human milk.

Teratogenicity/Adverse Pregnancy Outcomes

Only 182 cases of first-trimester saquinavir exposure have been reported to the Antiretroviral Pregnancy Registry. Without more data, the prevalence of birth defects among infants exposed to saquinavir cannot be accurately calculated.[10]

Other Safety Information

One study of 42 pregnant women who received antiretroviral therapy that included saquinavir/ritonavir reported abnormal transaminase levels in 13 women (31%) within 2 to 4 weeks of treatment initiation, although the abnormalities were mild (toxicity Grade 1–2 in most women, Grade 3 in one woman).[11] In a study of 62 pregnant women on a regimen that included saquinavir/ritonavir, one severe adverse event occurred (maternal Grade 3 hepatotoxicity).[6]

In the U.S. PHACS/SMARTT cohort study, after adjusting for birth cohort and other factors, maternal use of saquinavir led to no increase in the likelihood of adverse metabolic, growth/development, cardiac, or neurological outcomes. Late language emergence was more likely among saquinavir-exposed infants at 1 year (odds ratio 2.72; 95% CI, 1.09–6.91, $P = 0.03$), but not at 2 years. No significant differences were observed for other neurodevelopmental outcomes.[12]

Excerpt from Table 10[a]

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations	Use in Pregnancy
Saquinavir (SQV) *Invirase* **Note:** Must be combined with low-dose RTV for PK boosting	SQV (Invirase) *Tablet:* • 500 mg *Capsule:* • 200 mg	Standard Adult Dose: • SQV 1000 mg plus RTV 100 mg twice a day with food or within 2 hours after a meal PK in Pregnancy: • Based on limited data, SQV exposure may be reduced in pregnancy, but this effect is not sufficient to warrant a dose change. Dosing in Pregnancy: • No change in dose indicated.	SQV **should not be used** during pregnancy. **Contraindicated** in patients with pre-existing cardiac conduction system disease. Baseline ECG recommended before starting, because PR and/or QT interval prolongations have been observed. Low placental transfer to fetus.[b] Insufficient data to assess for teratogenicity in humans. No evidence of teratogenicity in rats or rabbits. Must be boosted with low-dose RTV.

[a] Individual ARV drug dosages may need to be adjusted in patients with renal or hepatic insufficiency (for details, see the Adult and Adolescent Guidelines, Appendix B, Table 8).

[b] Placental transfer categories are determined by mean or median cord blood/maternal delivery plasma drug ratio:

High: >0.6 **Moderate:** 0.3–0.6 **Low:** <0.3

Key to Acronyms: ECG = electrocardiogram; PK = pharmacokinetic; RTV = ritonavir; SQV = saquinavir

References

1. Saquinavir [package insert]. Food and Drug Administration. 2016. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020628s041,021785s017lbl.pdf.
2. Khan W, Hawkins DA, Moyle G, et al. Pharmacokinetics (PK), safety, tolerability and efficacy of saquinavir hard-gel capsules/ritonavir (SQV/r) plus 2 nucleosides in HIV-infected pregnant women. Presented at: XV International AIDS Conference. 2004. Bangkok, Thailand.
3. Lopez-Cortes LF, Ruiz-Valderas R, Pascual R, Rodriguez M, Marin Niebla A. Once-daily saquinavir-hgc plus low-

dose ritonavir (1200/100 mg) in HIV-infected pregnant women: pharmacokinetics and efficacy. *HIV Clin Trials*. 2003;4(3):227-229. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12815561.

4. Lopez-Cortes LF, Ruiz-Valderas R, Rivero A, et al. Efficacy of low-dose boosted saquinavir once daily plus nucleoside reverse transcriptase inhibitors in pregnant HIV-1-infected women with a therapeutic drug monitoring strategy. *Ther Drug Monit*. 2007;29(2):171-176. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17417070.
5. van der Lugt J, Colbers A, Molto J, et al. The pharmacokinetics, safety and efficacy of boosted saquinavir tablets in HIV type-1-infected pregnant women. *Antivir Ther*. 2009;14(3):443-450. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19474478.
6. Brunet C, Reliquet V, Jovelin T, et al. Effectiveness and safety of saquinavir/ritonavir in HIV-infected pregnant women: INEMA cohort. *Med Mal Infect*. 2012;42(9):421-428. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22938775.
7. Martinez-Rebollar M, Lonca M, Perez I, et al. Pharmacokinetic study of saquinavir 500 mg plus ritonavir (1000/100 mg twice a day) in HIV-positive pregnant women. *Ther Drug Monit*. 2011;33(6):772-777. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22105596.
8. Zorrilla CD, Van Dyke R, Bardeguez A, et al. Clinical response and tolerability to and safety of saquinavir with low-dose ritonavir in human immunodeficiency virus type 1-infected mothers and their infants. *Antimicrob Agents Chemother*. 2007;51(6):2208-2210. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17420209.
9. Mirochnick M, Dorenbaum A, Holland D, et al. Concentrations of protease inhibitors in cord blood after *in utero* exposure. *Pediatr Infect Dis J*. 2002;21(9):835-838. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12352805.
10. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral pregnancy registry international interim report for 1 January 1989–31 January 2018. Wilmington, NC: Registry Coordinating Center. 2018. Available at: http://www.apregistry.com/.
11. Hanlon M, O'Dea S, Clarke S, al e. Maternal hepatotoxicity with boosted saquinavir as part of combination ART in pregnancy. Presented at: 14th Conference on Retoviruses and Opportunistic Infections. 2007. Los Angeles, CA.
12. Van Dyke RB, Chadwick EG, Hazra R, Williams PL, Seage GR, 3rd. The PHACS SMARTT study: assessment of the safety of In utero exposure to antiretroviral drugs. *Front Immunol*. 2016;7:199. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27242802.

Tipranavir (Aptivus, TPV)

(Last reviewed December 7, 2018; last updated December 7, 2018)

Tipranavir is classified as Food and Drug Administration Pregnancy Category C. Tipranavir **should not** be used during pregnancy.

Animal Studies

Carcinogenicity

Tipranavir was neither mutagenic nor clastogenic in a battery of five screening tests, both *in vitro* and, in animals, *in vivo*. Long-term carcinogenicity studies of tipranavir have been conducted in mice and rats. Mice were administered tipranavir doses ranging from 30 to 300 mg/kg/day, with or without ritonavir 40 mg/kg/day; all doses resulted in systemic exposures below those seen in humans receiving the recommended dose. Incidence of benign hepatocellular adenomas, combined adenomas/carcinomas, and hepatocellular carcinoma was increased in both male and female mice receiving tipranavir/ritonavir (TPV/r). The clinical relevance of the carcinogenic findings in mice is unknown. Rats were administered doses ranging from 30 to 300 mg/kg/day tipranavir, with or without ritonavir. No drug-related findings were observed in male rats. At the highest dose of tipranavir (approximately equivalent to exposure in humans at the recommended therapeutic dose), an increased incidence of benign follicular cell adenomas of the thyroid gland was observed in female rats. This finding is probably not relevant to humans, because thyroid follicular cell adenomas are considered a rodent-specific effect secondary to enzyme induction.[1]

Reproduction/Fertility

Tipranavir had no effect on fertility or early embryonic development in rats at exposure levels that are similar to human exposure levels at the recommended clinical dose (TPV/r 500 mg/200 mg administered twice daily).[1]

Teratogenicity/Adverse Pregnancy Outcomes

No teratogenicity was detected in studies of pregnant rats and rabbits with exposure levels that were approximately 1.1-fold and 0.1-fold human exposure levels. Fetal toxicity (decreased ossification and body weights) was observed in rats exposed to 400 mg/kg/day or more of tipranavir (~0.8-fold human exposure). Fetal toxicity was not seen in rats and rabbits at levels of 0.2-fold and 0.1-fold human exposures. In rats, no adverse effects on development occurred at exposure levels of 40 mg/kg/day (~0.2-fold human exposure), but growth inhibition in pups and maternal toxicity were observed at 400 mg/kg/day (~0.8-fold human exposure).[1]

Placental and Breast Milk Passage

No animal studies of placental or breast milk passage of tipranavir have been reported.

Human Studies in Pregnancy

Pharmacokinetics

No studies of tipranavir have been completed in pregnant women or neonates.

Placental and Breast Milk Passage

It is unknown if tipranavir passes through the placenta or breast milk in humans. A single case report described relatively high levels of tipranavir in the third trimester and relatively high placental transfer (0.41), as measured by cord blood.[2]

Teratogenicity/Adverse Pregnancy Outcomes

The five first-trimester exposures to tipranavir that have been monitored to date in the Antiretroviral Pregnancy Registry are insufficient to draw conclusions regarding the risk of birth defects.[3]

Excerpt from Table 10[a]

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations	Use in Pregnancy
Tipranavir (TPV) *Aptivus* **Note:** Must be combined with RTV for PK boosting	TPV (Aptivus) *Capsules:* • 250 mg *Oral Solution:* • 100 mg/mL	Standard Adult Dose: • TPV/r 500 mg/200 mg twice daily *With RTV Tablets:* • Take with food. *With RTV Capsules or Solution:* • Take without regard to food; however, administering with food may help make the dose more tolerable. Dosing in Pregnancy: • Insufficient data to make dosing recommendation PK in Pregnancy: • Limited PK data in human pregnancy	TPV **should not be used** during pregnancy. Moderate placental transfer to fetus reported in 1 patient.[b] Insufficient data to assess teratogenicity in humans. No evidence of teratogenicity in rats or rabbits. Must be given as low-dose, RTV-boosted regimen.

[a] Individual ARV drug dosages may need to be adjusted in patients with renal or hepatic insufficiency (for details, see the Adult and Adolescent Guidelines, Appendix B, Table 8).

[b] Placental transfer categories are determined by mean or median cord blood/maternal delivery plasma drug ratio:

High: >0.6 **Moderate:** 0.3–0.6 **Low:** <0.3

Key to Acronyms: PK = pharmacokinetic; RTV = ritonavir; TPV = tipranavir; TPV/r = tipranavir/ritonavir

References

1. Tipranavir [package insert]. Food and Drug Administration. 2016. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021814s016,022292s009lbl.pdf.
2. Weizsaecker K, Kurowski M, Hoffmeister B, Schurmann D, Feiterna-Sperling C. Pharmacokinetic profile in late pregnancy and cord blood concentration of tipranavir and enfuvirtide. *Int J STD AIDS*. 2011;22(5):294-295. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21571982.
3. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral pregnancy registry international interim report for 1 January 1989–31 January 2018. Wilmington, NC: Registry Coordinating Center. 2018. Available at: http://www.apregistry.com/.

Entry and Attachment Inhibitors

Glossary of Terms for Supplement
Carcinogenic: Producing or tending to produce cancer • Some agents, such as certain chemicals or forms of radiation, are both mutagenic and clastogenic. • Genetic mutations and/or chromosomal damage can contribute to cancer formation.
Clastogenic: Causing disruption of or breakages in chromosomes
Genotoxic: Damaging to genetic material such as DNA and chromosomes
Mutagenic: Inducing or capable of inducing genetic mutation
Teratogenic: Interfering with fetal development and resulting in birth defects

The antiretroviral (ARV) drugs in the entry inhibitor class inhibit viral binding or fusion of HIV to host target cells. When the viral envelope glycoprotein (gp) 120 binds to the CD4 receptor, it induces conformational changes that enable gp120 to interact with a chemokine receptor such as CCR5 or CXCR4 on the host cell. After gp120 binds to the co-receptor, subsequent conformational changes expose the fusion peptide of viral transmembrane gp41. The fusion peptide then inserts into the cell membrane. A helical region of gp41, called HR1, then interacts with a similar helical region, HR2, on gp41. The two helices zip together and mediate the fusion of cellular and viral membranes. Enfuvirtide, which requires subcutaneous (SQ) administration, is a synthetic 36-amino-acid peptide derived from a naturally occurring motif within the HR2 domain of viral gp41. The drug binds to the HR1 region, preventing the HR1-HR2 interaction and the correct folding of gp41 into its secondary structure, thereby inhibiting virus-cell fusion. Maraviroc is a CCR5 co-receptor antagonist that interferes with viral entry at the chemokine co-receptor level.

Ibalizumab-uiyk, a recombinant humanized monoclonal antibody, is a CD4-directed post-attachment HIV-1 inhibitor. Ibalizumab-uiyk blocks HIV from infecting CD4+ T cells by binding to domain 2 of CD4, thereby interfering with post-attachment steps required for viral entry and preventing viral transmission that occurs via cell-cell fusion.

Enfuvirtide (Fuzeon, T-20)

(Last updated December 7, 2018; last reviewed December 7, 2018)

Enfuvirtide is classified as Food and Drug Administration Pregnancy Category B.

Animal Studies

Carcinogenicity

Enfuvirtide was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests. Long-term animal carcinogenicity studies of enfuvirtide have not been conducted.

Reproduction/Fertility

Reproductive toxicity has been evaluated in rats and rabbits. Enfuvirtide produced no adverse effects on the fertility of male or female rats at doses up to 30 mg/kg/day administered SQ (a dose that is 1.6 times the maximum recommended adult human daily dose on a body surface area basis).

Teratogenicity/Adverse Pregnancy Outcomes

Studies in rats and rabbits have shown no evidence of teratogenicity and no effect on reproductive function with enfuvirtide.[1]

Placental and Breast Milk Passage

A study in rats revealed no evidence of harm to the fetus when enfuvirtide was administered in doses up to 27 times the adult human daily dose on a body surface area basis. A separate study in rabbits likewise

revealed no harm to the fetus from enfuvirtide doses that were up to 3.2 times the adult human daily dose. Studies of radiolabeled enfuvirtide administered to lactating rats indicated radioactivity in the milk; however, it is not known if this reflected radiolabeled enfuvirtide or metabolites (amino acid and peptide fragments) of enfuvirtide.[1]

Human Studies in Pregnancy

Pharmacokinetics

Data on the use of enfuvirtide during human pregnancy are limited to case reports of a small number of women treated with the drug.[2-9]

Placental and Breast Milk Passage

In vitro and *in vivo* studies suggest that enfuvirtide does not readily cross the human placenta. Minimal placental passage of enfuvirtide was reported in published studies that included a total of eight peripartum patients and their neonates. These findings were supported by data from an *ex vivo* human placental cotyledon perfusion model.[2,5,10-12]

Teratogenicity/Adverse Pregnancy Outcomes

In the Antiretroviral Pregnancy Registry and in a national cohort of pregnant women with HIV infection in Italy, insufficient numbers of first-trimester exposures to enfuvirtide in humans have been monitored to be able to make a risk determination.[13,14]

Excerpt from Table 10[a]

Generic Name (Abbreviation) *Trade Name.*	Formulation	Dosing Recommendations	Use in Pregnancy
Enfuvirtide (T-20) *Fuzeon*	T-20 (Fuzeon) *Injectible:* • Supplied as lyophilized powder. Each vial contains 108 mg of T-20; reconstitute with 1 mL of sterile water for injection for SQ delivery of approximately 90 mg/1 mL.	T-20 is indicated for advanced HIV disease and must be used in combination with other ARV drugs to which the patient's virus is susceptible, as determined by resistance testing. Standard Adult Dose: • T-20 90 mg (1 mL) twice daily without regard to meals PK in Pregnancy: • No PK data in human pregnancy. Dosing in Pregnancy: • Insufficient data to make dosing recommendation.	Minimal to low placental transfer to fetus.[b] No data on human teratogenicity.

[a] Individual ARV drug dosages may need to be adjusted in patients with renal or hepatic insufficiency (for details, see the Adult and Adolescent Guidelines, Appendix B, Table 8).

[b] Placental transfer categories are determined by mean or median cord blood/maternal delivery plasma drug ratio:

High: >0.6 **Moderate:** 0.3–0.6 **Low:** <0.3

Key to Acronyms: ARV = antiretroviral; PK = pharmacokinetic; SQ = subcutaneous; T-20 = enfuvirtide

References

1. Enfuvirtide [package insert]. Food and Drug Administration. 2015. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/021481s030lbl.pdf.
2. Brennan-Benson P, Pakianathan M, Rice P, et al. Enfurvitide prevents vertical transmission of multidrug-resistant HIV-1 in pregnancy but does not cross the placenta. *AIDS*. 2006;20(2):297-299. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16511429.

3. Cohan D, Feakins C, Wara D, et al. Perinatal transmission of multidrug-resistant HIV-1 despite viral suppression on an enfuvirtide-based treatment regimen. *AIDS*. 2005;19(9):989-990. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15905684.
4. Meyohas MC, Lacombe K, Carbonne B, Morand-Joubert L, Girard PM. Enfuvirtide prescription at the end of pregnancy to a multi-treated HIV-infected woman with virological breakthrough. *AIDS*. 2004;18(14):1966-1968. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15353987.
5. Weizsaecker K, Kurowski M, Hoffmeister B, Schurmann D, Feiterna-Sperling C. Pharmacokinetic profile in late pregnancy and cord blood concentration of tipranavir and enfuvirtide. *Int J STD AIDS*. 2011;22(5):294-295. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21571982.
6. Furco A, Gosrani B, Nicholas S, et al. Successful use of darunavir, etravirine, enfuvirtide and tenofovir/emtricitabine in pregnant woman with multiclass HIV resistance. *AIDS*. 2009;23(3):434-435. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19188762.
7. Sued O, Lattner J, Gun A, et al. Use of darunavir and enfuvirtide in a pregnant woman. *Int J STD AIDS*. 2008;19(12):866-867. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19050223.
8. Madeddu G, Calia GM, Campus ML, et al. Successful prevention of multidrug resistant HIV mother-to-child transmission with enfuvirtide use in late pregnancy. *Int J STD AIDS*. 2008;19(9):644-645. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18725561.
9. Shust GF, Jao J, Rodriguez-Caprio G, et al. Salvage regimens containing darunavir, etravirine, raltegravir, or enfuvirtide in highly treatment-experienced perinatally infected pregnant women. *J Pediatric Infect Dis Soc*. 2014;3(3):246-250. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25844164.
10. Ceccaldi PF, Ferreira C, Gavard L, Gil S, Peytavin G, Mandelbrot L. Placental transfer of enfuvirtide in the *ex vivo* human placenta perfusion model. *Am J Obstet Gynecol*. 2008;198(4):433 e431-432. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18241815.
11. Peters PJ, Polle N, Zeh C, et al. Nevirapine-associated hepatotoxicity and rash among HIV-infected pregnant women in Kenya. *J Int Assoc Physicians AIDS Care (Chic)*. 2012;11(2):142-149. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22020069.
12. Moisan A, Desmoyer A, Bourgeois-Moine A, et al. Placental transfer of antiretroviral drugs in HIV-infected women: a retrospective study from 2002 to 2009. Abstract 1. Presented at: 11th International Workshop on Clinical Pharmacology of HIV Therapy. 2010. Sorrento, Italy.
13. Floridia M, Mastroiacovo P, Tamburrini E, et al. Birth defects in a national cohort of pregnant women with HIV infection in Italy, 2001–2011. *BJOG*. 2013;120(12):1466-1475. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23721372.
14. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral Pregnancy Registry international interim report for 1 January 1989–31 January 2018. Wilmington, NC: Registry Coordinating Center. 2018. Available at: http://www.apregistry.com/.

Ibalizumab-uiyk (Trogarzo, IBA)

(Last updated December 7, 2018, last reviewed December 7, 2018)

There are insufficient human data on the use of ibalizumab during pregnancy to inform a drug-associated risk determination for birth defects and miscarriage.

Animal studies

Carcinogenicity

Carcinogenesis and mutagenesis toxicology studies of ibalizumab have not been conducted.[1]

Reproduction/Fertility

Reproductive toxicology studies of ibalizumab have not been conducted.[1]

Teratogenicity/Adverse Pregnancy Outcomes

Early embryonic development and embryo-fetal development studies with ibalizumab have not been conducted.

Placental and Breast Milk Passage

No animal data on placental or breast milk passage are available for ibalizumab.

Human Studies in Pregnancy

Pharmacokinetics

No pharmacokinetic studies of ibalizumab have been reported in pregnant women.

Placental and Breast Milk Passage

No data are available on placental or breast milk passage of ibalizumab in humans. However, since monoclonal antibodies are transported across the placenta during pregnancy, ibalizumab has the potential to be transmitted from the mother to the developing fetus. Human IgG is also present in human milk, although published data indicate that antibodies in breast milk do not enter the neonatal or infant circulation system in substantial amounts.[1]

Teratogenicity/Adverse Pregnancy Outcomes

No data are available to inform the risk determination for birth defects following exposure to ibalizumab.

Excerpt from Table 10[a]

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations	Use in Pregnancy
Ibalizumab-uiyk (IBA) *Trogarzo*	IBA (Trogarzo): • Solution for IV infusion is available in single-dose vials	Standard Adult Dose • IBA 2000-mg loading dose, followed by IBA 800-mg maintenance doses administered every 2 weeks Dosing in Pregnancy: • Insufficient data are available to make dosing recommendation. PK in Pregnancy: • No PK studies have been reported in human pregnancy.	No data are available, but placental transfer of IBA, a monoclonal antibody, is possible. Insufficient data are available to assess for teratogenicity in humans.

[a] Individual ARV drug dosages may need to be adjusted in patients with renal or hepatic insufficiency (for details, see the Adult and Adolescent Guidelines, Appendix B, Table 8).

Key to Acronyms: ARV = antiretroviral; IBA = ibalizumab; IV = intravenous; PK = pharmacokinetic

References

1. Ibalizumab-uiyk [package insert]. Food and Drug Administration. 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761065lbl.pdf.

Maraviroc (Selzentry, MVC)

(Last updated December 7, 2018; last reviewed December 7, 2018)

The limited data available on the use of maraviroc during pregnancy are not sufficient to assess any potential drug-associated risk of birth defects.

Animal Studies

Carcinogenicity

Maraviroc was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests. Long-term carcinogenicity studies of maraviroc in rats showed no drug-related increases in tumor incidence at exposures approximately 11 times those observed in humans at the therapeutic dose.

Reproduction/Fertility

Reproductive toxicity has been evaluated in rats and rabbits. Maraviroc produced no adverse effects on the fertility of male or female rats at doses with exposures (area under the curve [AUC]) up to 20-fold higher than those seen in humans given the recommended 300-mg, twice-daily dose.

Teratogenicity/Adverse Pregnancy Outcomes

In animal reproduction studies, no evidence of adverse developmental outcomes was observed with maraviroc. During organogenesis in the rat and rabbit, systemic exposures (AUC) to maraviroc were approximately 20 times (in rats) and 5 times (in rabbits) the exposure seen in humans given the recommended 300-mg, twice-daily dose. In the rat prenatal and postnatal development study, maternal maraviroc AUC was approximately 14 times the exposure seen in humans given the recommended 300-mg, twice-daily dose.[1]

Placental and Breast Milk Passage

A study in rhesus macaques showed that single-dose maraviroc had poor placental transfer and rapid clearance from infant monkeys' blood.[2] Studies in lactating rats indicate that maraviroc is extensively secreted into rat milk.[1]

Human Studies in Pregnancy

Pharmacokinetics

A U.S./European study of intensive, steady-state, 12-hour pharmacokinetic profiles in the third trimester, and at least 2 weeks postpartum, included 18 women taking maraviroc as part of clinical care.[3] Sixty-seven percent of the women in the study were taking maraviroc 150 mg BID with a protease inhibitor; 11% took maraviroc 300 mg BID and 22% took an alternative regimen. The geometric mean ratios for third-trimester AUC versus postpartum AUC were 0.72 and 0.70 for maximum maraviroc concentration. Despite an overall 30% decrease in maraviroc AUC during pregnancy and a 15% decrease in C_{trough}, C_{trough} exceeded the minimum target concentration of 50 ng/mL in all participants except for one woman who had a C_{trough} below 50 ng/mL during both pregnancy and postpartum. These data suggest that the standard adult dose adjusted for concomitant antiretroviral (ARV) drugs seems appropriate in pregnancy. A review of drug interactions between ARV drugs and oral contraceptives found that it is safe to co-administer oral contraceptives with maraviroc.[4]

Placental and Breast Milk Passage

An *ex vivo* human placental cotyledon perfusion model demonstrated minimal placental passage of maraviroc.[5] In a study in humans of six mother and infant pairs, the median ratio of cord blood to maternal plasma drug concentrations was 0.33 (0.03–0.56).[3,6] Whether maraviroc is secreted into human milk is unknown.

Teratogenicity/Adverse Pregnancy Outcomes

The 27 cases of first-trimester exposure that have been monitored to date in the Antiretroviral Pregnancy

Registry and other available first-trimester exposure data are insufficient to make a risk determination regarding birth defects.[7,8]

Other Safety Information

A retrospective study from an English-Irish cohort of 857 pregnant women showed an increased rate of hepatotoxicity among the 492 women who started ARV therapy during pregnancy.[9] Maraviroc was one of three drugs that was associated with an increased risk of liver enzyme elevation during pregnancy, with an aHR of 4.19 (1.34–13.1, $P = 0.01$), along with efavirenz and nevirapine. In a model using human placental BeWo cells, maraviroc inhibited transplacental passage of two fluorescent organic cations, suggesting that it might influence placental drug transfer and cause drug-drug interactions.[10]

Excerpt from Table 10[a]

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations	Use in Pregnancy
Maraviroc (MVC) *Selzentry*	MVC (Selzentry) *Tablets:* • 150 mg • 300 mg	Standard Adult Dose: • MVC 300 mg twice daily with or without food • MVC should only be used for patients with CCR5-tropic virus (and no X4-tropic virus). Dose Adjustments: • Increase to MVC 600 mg BID when used with potent CYP3A inducers: EFV, ETR, and rifampin. • Decrease to MVC 150 mg BID when used with CYP3A inhibitors: all PIs except TPV/r, itraconazole. PK in Pregnancy: • A PK study in human pregnancy demonstrated a 20% to 30% overall decrease in AUC, but C_{trough} exceeded the recommended minimal concentration of 50 ng/mL. Dosing in Pregnancy: • Standard adult dosing adjusted for concomitant ARV use appears appropriate.	No evidence of teratogenicity in rats or rabbits; insufficient data to assess for teratogenicity in humans. MVC placental passage category should be moderate.[b]

[a] Individual ARV drug dosages may need to be adjusted in patients with renal or hepatic insufficiency (for details, see the Adult and Adolescent Guidelines, Appendix B, Table 8).

[b] Placental transfer categories are determined by mean or median cord blood/maternal delivery plasma drug ratio:

High: >0.6 **Moderate:** 0.3–0.6 **Low:** <0.3

Key to Acronyms: ARV = antiretroviral; AUC = area under the curve; BID = twice daily; CYP3A = cytochrome P450 3A4; EFV = efavirenz; ETR = etravirine; MCV = maraviroc; PI = protease inhibitor; PK = pharmacokinetic; TPV/r = tipranavir/ritonavir

References

1. Maraviroc [package insert]. Food and Drug Administration. 2016. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/208984_022128s017lbl.pdf.
2. Winters MA, Van Rompay KK, Kashuba AD, Shulman NS, Holodniy M. Maternal-fetal pharmacokinetics and dynamics of a single intrapartum dose of maraviroc in rhesus macaques. *Antimicrob Agents Chemother*. 2010;54(10):4059-4063. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20696881.
3. 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.
4. Tittle V, Bull L, Boffito M, Nwokolo N. Pharmacokinetic and pharmacodynamic drug interactions between antiretrovirals and oral contraceptives. *Clin Pharmacokinet*. 2015;54(1):23-34. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25331712.
5. Vinot C, Gavard L, Treluyer JM, et al. Placental transfer of maraviroc in an *ex vivo* human cotyledon perfusion model and influence of ABC transporter expression. *Antimicrob Agents Chemother*. 2013;57(3):1415-1420. Available at: http://

www.ncbi.nlm.nih.gov/pubmed/23295922.

6. Colbers A, Best B, et al. A Comparison of the pharmacokinetics of maraviroc during pregnancy and postpartum. Abstract 931. Presented at: 20th Conference on Retroviruses and Opportunistic Infections. 2013. Atlanta, GA.
7. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral pregnancy registry international interim report for 1 January 1989–31 January 2018. Wilmington, NC: Registry Coordinating Center. 2018. Available at: http://www.apregistry.com/.
8. Floridia M, Mastroiacovo P, Tamburrini E, et al. Birth defects in a national cohort of pregnant women with HIV infection in Italy, 2001–2011. *BJOG*. 2013;120(12):1466-1475. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23721372.
9. Huntington S, Thorne C, Anderson J, et al. Does pregnancy increase the risk of ART-induced hepatotoxicity among HIV-positive women? *J Int AIDS Soc*. 2014;17(4 Suppl 3):19486. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25393995.
10. Nabekura T, Kawasaki T, Kamiya Y, Uwai Y. Effects of antiviral drugs on organic anion transport in human placental BeWo cells. *Antimicrob Agents Chemother*. 2015;59(12):7666-7670. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26416870.

Integrase Inhibitors

Glossary of Terms for Supplement
Carcinogenic: Producing or tending to produce cancer • Some agents, such as certain chemicals or forms of radiation, are both mutagenic and clastogenic. • Genetic mutations and/or chromosomal damage can contribute to cancer formation.
Clastogenic: Causing disruption of or breakages in chromosomes
Genotoxic: Damaging to genetic material such as DNA and chromosomes
Mutagenic: Inducing or capable of inducing genetic mutation
Teratogenic: Interfering with fetal development and resulting in birth defects

This class of antiretroviral (ARV) drugs inhibits integrase, the viral enzyme that catalyzes the two-step process that inserts HIV DNA into the genome of the human cell. Integrase catalyzes a preparatory step that excises two nucleotides at both ends of one strand of HIV DNA and a final "strand transfer" step that inserts the viral DNA into the exposed regions of cellular DNA. The integrase inhibitor drug class targets this second step of the integration process. Integration is required for the stable maintenance of the viral genome as well as for efficient viral gene expression and replication. Integrase also affects reverse transcription and viral assembly. Host cells lack the integrase enzyme. Because HIV integrase represents a distinct therapeutic target, integrase inhibitors would be expected to maintain activity against HIV that is resistant to other classes of ARV drugs.

Bictegravir (BIC)

(Last updated December 7, 2018; last reviewed December 7, 2018)

There are insufficient human data on the use of bictegravir in pregnancy to inform a drug-associated risk determination for birth defects and miscarriage.

Animal Studies

Carcinogenicity

Bictegravir was not genotoxic or mutagenic *in vitro*.[1]

Reproduction/Fertility

Bictegravir did not affect fertility, reproductive performance, or embryonic viability in male and female rats at exposures (area under the curve [AUC]) that were 29 times higher than those seen in humans receiving the recommended dose.[1]

Teratogenicity/Adverse Pregnancy Outcomes

No adverse embryo-fetal effects were observed in rats and rabbits at bictegravir exposures (AUC) of up to approximately 36 times (rats) and 0.6 times (rabbits) the exposures seen in humans receiving the recommended dose. Spontaneous abortion, increased clinical signs (e.g., fecal changes, thin body, and cold-to-touch), and decreased body weight were observed at a maternally toxic dose in rabbits (i.e., 1000 mg/kg/day; approximately 1.4 times higher than human exposure at the recommended dose).[1]

Placental and Breast Milk Passage

No data on placental passage are available for bictegravir. In a pre/postnatal development study conducted in rats, bictegravir was detected in the plasma of nursing rat pups on postnatal day 10, likely due to the presence of bictegravir in milk.[1]

Human Studies in Pregnancy

Pharmacokinetics

No pharmacokinetic studies of bictegravir have been reported in pregnant women.

Placental and Breast Milk Passage

No data are available on the placental or breast milk passage of bictegravir in humans.

Teratogenicity/Adverse Pregnancy Outcomes

No data are available to inform the risk determination for birth defects following bictegravir exposure.

Excerpt from Table 10[a]

Note: When using FDCs, refer to other sections in Appendix B and Table 10 for information about the dosing and safety of individual drug components of the FDC during pregnancy.

Generic Name (Abbreviation) *Trade Name*	**Formulation**	**Dosing Recommendations**	**Use in Pregnancy**
Bictegravir/ Emtricitabine/ Tenofovir Alafenamide (BIC/FTC/TAF) *Biktarvy* **Note:** BIC is not available as a single-entity formulation.	BIC/FTC/TAF (Biktarvy): • BIC 50 mg plus FTC 200 mg plus TAF 25 mg tablet	Standard Adult Dose • 1 tablet once daily with or without food Dosing in Pregnancy: • There is insufficient data to make a dosing recommendation. PK in Pregnancy: • No PK studies have been reported in human pregnancy. • For guidance about use of combination products in pregnancy, please see the specific sections on other components (i.e., FTC, TAF).	No data are available on placental transfer of BIC. Insufficient data to assess for teratogenicity in humans. No evidence of teratogenicity in rats or rabbits. To maximize BIC absorption, doses should not be administered within 2 hours of ingestion of any preparation containing minerals such as iron or calcium, including prenatal vitamins.

[a] Individual ARV drug dosages may need to be adjusted in patients with renal or hepatic insufficiency (for details, see the Adult and Adolescent Guidelines, Appendix B, Table 8).

Key to Acronyms: ARV = antiretroviral; BIC = bictegravir; FTC = emtricitabine; FDC = fixed-dose combination; PK = pharmacokinetic; TAF = tenofovir alafenamide

References

1. Bicitegravir/emtricitabine/tenofovir alafendamide fumarate (Biktarvy) [package insert]. Food and Drug Administration. 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210251s000lbl.pdf.

Dolutegravir (Tivicay, DTG)

(Last updated December 12, 2019; last reviewed December 12, 2019)

Animal Studies

Carcinogenicity

Dolutegravir (DTG) has not been shown to be genotoxic or mutagenic *in vitro*. No carcinogenicity was detected in 2-year, long-term studies in mice at DTG exposures that were up to 14-fold higher than the exposures achieved in humans with systemic exposure to the recommended dose. In addition, no carcinogenicity was detected in rats at DTG exposures up to 10-fold higher in males and 15-fold higher in females than the exposures seen in humans who received the recommended dose.[1]

Reproduction/Fertility

DTG did not affect fertility in male and female rats and rabbits at doses that produced exposures (based on area under the curve [AUC]) that were approximately 27-fold higher than that achieved in humans who received the recommended dose.[1]

Teratogenicity/Adverse Pregnancy Outcomes

Studies of DTG in rats and rabbits have shown no evidence of developmental toxicity, teratogenicity, or effects on reproductive function.[1]

Placental and Breast Milk Passage

Studies in rats have demonstrated that DTG crosses the placenta and is excreted into breast milk.[1]

Human Studies in Pregnancy

Pharmacokinetics

DTG pharmacokinetics (PK) in human pregnancy have been reported in three studies and a series of case reports.[2-8] In a safety and PK study of 29 pregnant women in the United States, DTG plasma concentrations were lower during pregnancy than postpartum, with DTG AUC reduced by 21% during pregnancy. Although trough concentrations were reduced by 34% during the third trimester compared to postpartum, trough concentrations during pregnancy were well above 0.064 μg/mL, the 90% effective concentration for DTG. DTG was well tolerated by these pregnant women. During the third trimester, HIV-1 RNA was below 50 copies/mL in 27 of 29 participants, and no infants acquired HIV.[7]

In contrast, PK sampling during pregnancy and the early postpartum period of 17 African women who were receiving DTG showed a small reduction in DTG C_{max} and no differences in C_{24h} and $AUC_{0\text{-}24h}$ when geometric mean ratios in pregnancy were compared to the postpartum period. However, postpartum sampling was performed at a median of 10 days postpartum, when maternal physiology had likely not yet returned to the nonpregnant state.[8] In a smaller study of five European pregnant women, DTG was well tolerated and the reduction in plasma exposures during pregnancy was similar to that observed in the U.S. study described above.[6] In the case reports, DTG was used safely and effectively in individual pregnant women and plasma exposures were adequate.[2-5]

Placental and Breast Milk Passage

Placental transfer of DTG in an *ex vivo* perfusion model was high, with a mean fetal-to-maternal concentration ratio of 0.6.[9] In two *in vivo* PK studies, the median DTG cord blood-to-maternal-plasma concentration ratios were 1.21 and 1.25.[7,8] High placental transfer of DTG has also been reported in several of the case reports.[2,4,5] In 17 breastfeeding mothers, the median ratio of DTG in breast milk to maternal plasma was 0.03. Their infants had a median maximum DTG concentration of 66.7 ng/mL (range 21–654 ng/mL) and a median minimum concentration of 60.9 ng/mL (range 16.3–479 ng/mL) at a median age of 10 days (range 7–18 days). The geometric mean ratio of infant plasma to maternal plasma DTG concentrations in these 17 mother-infant pairs was 0.03.[8]

Teratogenicity/Adverse Pregnancy Outcomes

Among live births that have been reported to the Antiretroviral Pregnancy Registry as of January 31, 2019, the overall birth defect rate for infants with first-trimester exposure to DTG is 3.6% (11 infants out of 302 live births).[10] There has been one neural tube defect (NTD) among the 248 infants with periconception exposure to DTG that have been reported to the Antiretroviral Pregnancy Registry.[10] In the U.S. PK study in pregnant women discussed above, birth abnormalities were reported in seven of 29 infants: three with normal variants; one with total anomalous pulmonary venous return (DTG was initiated at 16 weeks gestation); one with a polycystic right kidney (DTG was initiated at 11 weeks gestation); one with an isolated left renal cyst (DTG was initiated at 12 weeks gestation); and one with jitteriness and chin tremors (DTG was initiated at 28 weeks gestation).[7] DTG was initiated at 28 weeks gestation or later in the PK study in African women discussed above, and no congenital anomalies were observed among 28 live births.[8] In two reviews of clinical experience with pregnant women who received DTG, birth defects were noted in four infants born to 81 European women, in two infants born to 66 women from the United States, and in no infants born to 116 women from Botswana who received DTG during the first trimester.[11-13]

In July 2019, a report from a National Institutes of Health-funded surveillance study of birth outcomes among pregnant women in Botswana who were receiving antiretroviral therapy found that DTG exposure at the time of conception was associated with a slightly higher rate of NTDs than other types of antiretroviral drug exposure (0.3% vs. 0.1%).[14] Unlike in the United States, there is no folate fortification of food in Botswana, and it is unknown how folate levels may affect the possible association between periconceptual DTG exposure and NTDs. The Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission recommends the use of DTG as part of a *Preferred* regimen in all pregnant women at any gestational age and as part of an *Alternative* regimen in women who are trying to conceive. Decisions about DTG use should be made after discussing the risks and benefits of using DTG with the patient. This discussion should include the potential risk of NTDs, as well as the benefits of the DTG-containing regimen and the risks and benefits of alternative regimens (see Appendix D: Dolutegravir Counseling Guide for Health Care Providers). For additional information, please contact the National Perinatal HIV Hotline (1-888-448-8765) and see Updated Guidance About the Use of Dolutegravir in Pregnancy in Recommendations for Use of Antiretroviral Drugs During Pregnancy and Teratogenicity.

Excerpt from Table 10

Note: When using FDC tablets, refer to other sections in Appendix B and Table 10 for information about the dosing and safety of individual drug components of the FDC tablet during pregnancy.

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations[a]	Use in Pregnancy
Dolutegravir (DTG) *Tivicay* (DTG/3TC) *Dovato* (DTG/RPV) *Juluca* (DTG/ABC/3TC) *Triumeq*	**DTG (Tivicay):** • DTG 50 mg tablet **DTG/3TC (Dovato):** • DTG 50 mg/3TC 300 mg tablet **DTG/RPV (Juluca):** • DTG 50 mg/RPV 25 mg tablet **DTG/ABC/3TC (Triumeq):** • DTG 50 mg/ABC 600 mg/3TC 300 mg tablet	**Standard Adult Doses** *In ARV-Naive or ARV-Experienced (but INSTI-Naive) Patients* DTG (Tivicay): • One tablet once daily, without regard to food DTG/3TC (Dovato): • One tablet once daily, without regard to food DTG/RPV (Juluca): • One tablet once daily with food DTG/ABC/3TC (Triumeq): • One tablet once daily, without regard to food *In ARV-Naive or ARV-Experienced (but INSTI-Naive) Patients Who Are Also Receiving EFV, FPV/r, TPV/r, or Rifampin* DTG (Tivicay): • One tablet twice daily, without regard to food *In INSTI-Experienced Patients* DTG (Tivicay): • One tablet twice daily, without regard to food **Pregnancy** *PKs in Pregnancy:* • AUC may be decreased during the third trimester compared with postpartum, but exposures during pregnancy are well above those needed to inhibit viral replication. *Dosing in Pregnancy:* • No change in dose indicated. • For guidance about the use of combination products in pregnancy, please see the specific sections on other components (i.e., ABC, 3TC, RPV).	High placental transfer to fetus.[b] No evidence of teratogenicity in rats or rabbits. In pregnancy surveillance data from Botswana, there was a slightly increased risk of NTDs in infants born to women who initiated DTG prior to pregnancy and who were receiving it at the time of conception. DTG may be used as part of a *Preferred* regimen in all pregnant women at all gestational ages and as part of an *Alternative* regimen in women who are trying to conceive. Clinicians should discuss the risks and benefits of DTG use with the patient. For more information, see Updated Guidance About the Use of Dolutegravir in Pregnancy in Recommendations for Use of Antiretroviral Drugs During Pregnancy. To maximize DTG absorption, doses should not be administered within 2 hours of ingesting any preparation that contains minerals such as iron or calcium, including prenatal vitamins.

[a] Individual ARV drug doses may need to be adjusted in patients with renal or hepatic insufficiency (for details, see the Adult and Adolescent Antiretroviral Guidelines, Appendix B, Table 10).

[b] Placental transfer categories are determined by mean or median cord blood/maternal delivery plasma drug ratio:

High: >0.6 **Moderate:** 0.3–0.6 **Low:** <0.3

Key: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; AUC = area under the curve; DTG = dolutegravir; EFV = efavirenz; FDC = fixed-dose combination; FPV/r = fosamprenavir/ritonavir; INSTI = integrase strand transfer inhibitor; NTD = neural tube defect; PK = pharmacokinetic; RPV = rilpivirine; TPV/r = tipranavir/ritonavir

References

1. Dolutegravir [package insert]. Food and Drug Administration. 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/204790s024lbl.pdf.
2. 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.
3. Pinnetti C, Tintoni M, Ammassari A, et al. Successful prevention of HIV mother-to-child transmission with dolutegravir-based combination antiretroviral therapy in a vertically infected pregnant woman with multiclass highly drug-resistant HIV-1. *AIDS*. 2015;29(18):2534-2537. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26372490.
4. Lewis JM, Railton E, Riordan A, Khoo S, Chaponda M. Early experience of dolutegravir pharmacokinetics in pregnancy: high maternal levels and significant foetal exposure with twice-daily dosing. *AIDS*. 2016;30(8):1313-1315. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27128333.
5. Schalkwijk S, Feiterna-Sperling C, Weizsacker K, et al. Substantially lowered dolutegravir exposure in a treatment-experienced perinatally HIV-1-infected pregnant woman. *AIDS*. 2016;30(12):1999-2001. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27428578.
6. Bollen P, Colbers A, Schalkwijk S, et al. A comparison of the pharmacokinetics of dolutegravir during pregnancy and postpartum. Presented at: 18th International Workshop on Clinical Pharmacology of Antiviral Therapy. 2017. Chicago, IL.
7. 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.
8. 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.
9. Schalkwijk S, Greupink R, Colbers AP, et al. Placental transfer of the HIV integrase inhibitor dolutegravir in an *ex vivo* human cotyledon perfusion model. *J Antimicrob Chemother*. 2016;71(2):480-483. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26538508.
10. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral Pregnancy Registry international interim report for 1 January 1989–31 January 2019. Wilmington, NC: Registry Coordinating Center. 2019. Available at: http://www.apregistry.com.
11. Thorne C, Favarato G, Peters H, et al. Pregnancy and neonatal outcomes following prenatal exposure to dolutegravir. Presented at: International AIDS Society Conference. 2017. Paris, France.
12. 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.
13. Grayhack C, Sheth A, Kirby O, et al. Evaluating outcomes of mother-infant pairs using dolutegravir for HIV treatment during pregnancy. *AIDS*. 2018;32(14):2017-2021. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29944472.
14. 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.

Elvitegravir (EVG)

(Last updated December 7, 2018; last reviewed December 7, 2018)

There are insufficient human data on the use of elvitegravir during pregnancy to determine the drug-associated risk for birth defects and miscarriage.

Animal Studies

Carcinogenicity

Elvitegravir was not genotoxic or mutagenic *in vitro*. No carcinogenicity was detected in long-term studies in mice and rats at exposures up to 14-fold and in rats at exposures up to 27-fold that achieved with human systemic exposure at the recommended dose.[1]

Reproduction/Fertility

Elvitegravir did not affect fertility in male and female rats at approximately 16- and 30-fold higher exposures than those seen in humans receiving standard doses. Fertility was normal in the offspring of these rats.[1]

Teratogenicity/Adverse Pregnancy Outcomes

Studies have shown no evidence of teratogenicity and no effect on reproductive function in rats and rabbits receiving elvitegravir.[1]

Placental and Breast Milk Passage

No data are available describing placental transfer of elvitegravir in nonhuman primates. Studies in rats have demonstrated that elvitegravir is secreted in breast milk.[1]

Human Studies in Pregnancy

Pharmacokinetics

A study with pharmacokinetic (PK) and safety data from 30 pregnant women with HIV who received a fixed-dose combination of elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate (TDF) has been published. Compared to postpartum, elvitegravir area under the curve (AUC) was 24% lower in the second trimester and 44% lower in the third trimester while elvitegravir trough concentration (C_{24}) was 81% lower in the second trimester and 89% lower in the third trimester. Cobicistat AUC was 54% to 57% lower and C_{24h} was 72% to 76% lower in the second and third trimesters compared with postpartum. Elvitegravir AUC failed to reach the exposure target of 23 mcg•hr/mL (the 10th percentile for nonpregnant adults) in 50% of women during the second trimester and 55% of women during the third trimester, compared with 12% of women postpartum. Plasma HIV RNA at delivery was less than 50 copies/mL in 19 of 25 women (76%) for whom data were available.[2] A smaller study of the PK of elvitegravir administered with cobicistat in seven pregnant women found reductions of 33% in AUC and 65% in C_{trough} during the third trimester compared with postpartum. One of the seven women had detectable plasma HIV RNA at delivery.[3] Two case reports of elvitegravir and cobicistat PK, safety, and efficacy in individual pregnant women found similar reductions in elvitegravir and cobicistat exposure during pregnancy although viral loads in both women remained undetectable throughout pregnancy.[4,5] One case report measured unbound elvitegravir concentrations and found an unbound fraction of 0.3% during pregnancy compared to 0.5% at 6 months postpartum.[5] In order to maximize absorption, elvitegravir should be administered with a meal and should not be administered within 2 hours of intake of preparations containing minerals such as iron or calcium, including prenatal vitamins.[6]

Placental and Breast Milk Passage

Placental passage of elvitegravir has been evaluated in three studies. The largest study of elvitegravir PK and safety observed that elvitegravir crossed the placenta well with a median cord to maternal plasma ratio of 91%. Median elvitegravir elimination half-life in neonates was 7.6 hours, similar to that in non-pregnant adults. Cobicistat concentrations were low in cord blood and were not detected in the plasma of any neonates.[2] Similar results were seen in the 2 smaller series of women from the United States and Europe and in several case reports.[4,5] No data are available on human breast milk transfer of elvitegravir.

Teratogenicity/Adverse Pregnancy Outcomes

In the Antiretroviral Pregnancy Registry, insufficient numbers of first-trimester exposures to elvitegravir in humans have been monitored to be able to make a risk determination.[7] In the largest PK and safety study that included data on 26 live born infants, congenital anomalies were reported in two infants: one infant with amniotic band syndrome, microcephaly, and intrauterine growth restriction and one infant with ulnar postaxial polydactyly (supernumerary digit).[2] In a study of the safety and efficacy of the elvitegravir, cobicistat, emtricitabine, and TDF combination product in adult women with HIV, there were 10 infants born to the women in the study and none had birth defects.[8]

Excerpt from Table 10[a]

Note: When using FDCs, refer to other sections in Appendix B and Table 10 for information about the dosing and safety of individual drug components of the FDC during pregnancy.

Generic Name (Abbreviation) *Trade Name*	**Formulation**	**Dosing Recommendations**	**Use in Pregnancy**
Elvitegravir (EVG) **Note:** As of October 2017, Vitekta (i.e., EVG as a single-entity formulation) is no longer available (EVG/COBI/FTC/TAF) *Genvoya* (EVG/COBI/FTC/TDF) *Stribild*	EVG/COBI/FTC/TAF (Genvoya): • EVG 150 mg plus COBI 150 mg plus FTC 200 mg plus TAF 10 mg tablet EVG/COBI/FTC/TDF (Stribild): • EVG 150 mg plus COBI 150 mg plus FTC 200 mg plus TDF 300 mg tablet	Standard Adult Dose (Genvoya and Stribild): • 1 tablet once daily with food Dosing in Pregnancy: • Insufficient data to make dosing recommendation PK in Pregnancy: • PK studies in women who received EVG/c demonstrated significant reduction in EVG plasma exposure during pregnancy.	Evidence of high placental transfer of EVG and low transfer of COBI.[b] Insufficient data to assess for teratogenicity in humans. No evidence of teratogenicity in rats or rabbits. EVG/COBI **is not recommended** for use in pregnancy. For women who become pregnant while taking EVG/c, consider switching to a more effective, recommended regimen. If an EVG/COBI regimen is continued, doses should not be administered within 2 hours of ingestion of any preparation containing minerals such as iron or calcium, including prenatal vitamins.

[a] Individual ARV drug dosages may need to be adjusted in patients with renal or hepatic insufficiency (for details, see the Adult and Adolescent Guidelines, Appendix B, Table 8).

[b] Placental transfer categories—Mean or median cord blood/maternal delivery plasma drug ratio:

High: >0.6 **Moderate:** 0.3–0.6 **Low:** <0.3

Key to Acronyms: COBI = cobicistat; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FDC = fixed-dose combination; FTC = emtricitabine; PK = pharmacokinetic; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TDM = therapeutic drug monitoring

References

1. Elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (Stribild) [package insert]. Food and Drug Administration. 2017. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/203100s030lbl.pdf.
2. Momper J, Best BM, Wang J, et al. Elvitegravir/cobicistat pharmacokinetics in pregnant and postpartum women with HIV. AIDS. 2018. In Press.
3. Colbers A, Schalkwijk S, Konopnicki D, Rockstroh J, Burger D. Elvitegravir pharmacokinetics during pregnancy and postpartum. Abstract 17. Presented at: 19th International Workshop on Clinical Pharmacology of Antiviral Therapy. 2018. Baltimore, Maryland. Available at: http://www.natap.org/2018/Pharm/Pharm_11.htm.
4. Schalkwijk S, Colbers A, Konopnicki D, et al. First reported use of elvitegravir and cobicistat during pregnancy. *AIDS*. 2016;30(5):807-808. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26913711.
5. Marzolini C, Decosterd L, Winterfeld U, et al. Free and total plasma concentrations of elvitegravir/cobicistat during pregnancy and postpartum: a case report. *Br J Clin Pharmacol*. 2017;83(12):2835-2838. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28512794.
6. Genvoya [package insert]. Food and Drug Administration. 2017. Available at: https://www.gilead.com/~/media/files/pdfs/medicines/hiv/genvoya/genvoya_pi.pdf?la=en.
7. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral pregnancy registry international interim report

for 1 January 1989–31 January 2018. Wilmington, NC: Registry Coordinating Center. 2018. Available at: http://www.apregistry.com/.

8. Squires KE, Kityo C, Hodder S, et al. The safety and efficacy of E/C/F/TDF In treatment-naïve women with HIV-1 infection (WAVES Study): week 96 results. Presented at: 7th International Workshop on HIV & Women. 2017. Seattle, WA. Available at: http://regist2.virology-education.com/2017/7hivwomen/22_Squires.pdf.

Raltegravir (Isentress, RAL)

(Last updated December 7, 2018; last reviewed December 7, 2018)

Raltegravir has been evaluated in a limited number of women during pregnancy, and available human and animal data suggest that raltegravir does not increase the risk of major birth defects overall compared to the background rate.[1]

Animal Studies

Carcinogenicity

Raltegravir was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests. Long-term carcinogenicity studies of raltegravir in mice did not show any carcinogenic potential at systemic exposures 1.8-fold (in females) or 1.2-fold (in males) greater than human exposure at the recommended dose. Treatment-related squamous cell carcinoma of the nose/nasopharynx was observed in female rats dosed with raltegravir 600 mg/kg/day for 104 weeks. This dose produced exposures that were three-fold higher than exposures seen in humans who received the recommended adult dose. These tumors were possibly the result of local irritation and inflammation due to local deposition and/or aspiration of drug in the mucosa of the nose/nasopharynx during dosing. No tumors of the nose/nasopharynx were observed in rats with systemic exposures that were 1.7-fold (in males) or 1.4-fold (in females) greater than the exposure observed in humans who received the recommended dose.[1]

Reproduction/Fertility

Raltegravir produced no adverse effects on the fertility of male or female rats at doses up to 600 mg/kg/day, which provided exposures that were up to three-fold higher than the exposures seen in humans who received the recommended adult human dose.

Teratogenicity/Adverse Pregnancy Outcomes

Studies in rats and rabbits revealed no evidence of treatment-related effects on embryonic/fetal survival or fetal weights from raltegravir administered in doses that produced systemic exposures approximately three-fold to four-fold higher than the exposures seen in humans who received the recommended adult human daily dose. In rabbits, no treatment-related external, visceral, or skeletal changes were observed. However, treatment-related increases in the incidence of supernumerary ribs were seen in rats given raltegravir at 600 mg/kg/day (which produced exposures that were three-fold higher than the exposure seen in humans who received the recommended daily dose).[1]

Placental and Breast Milk Passage

Placental transfer of raltegravir was demonstrated in both rats and rabbits. In pregnant rats given a dose of raltegravir 600 mg/kg/day, mean fetal blood concentrations were approximately 1.5-fold to 2.5-fold higher than the concentrations in maternal plasma at 1 hour and 24 hours post-dose, respectively. However, in rabbits, the mean drug concentration in fetal plasma was approximately 2% of the mean maternal plasma concentration at both 1 hour and 24 hours following a maternal dose of 1,000 mg/kg/day.[1]

Raltegravir is secreted in the milk of lactating rats. At a maternal dose of raltegravir 600 mg/kg/day, mean drug concentrations in milk are about three-fold higher than the drug concentrations in maternal plasma. No effects in rat offspring were attributable to raltegravir exposure through breast milk.[1]

Human Studies in Pregnancy

Pharmacokinetics

Raltegravir pharmacokinetics (PK) were evaluated in 42 women during pregnancy in the IMPAACT P1026s study. Raltegravir PKs in these women showed extensive variability; variability is also seen in nonpregnant individuals. Median raltegravir area under the curve (AUC) was reduced by approximately 50% during pregnancy. No significant difference was seen between the third trimester and postpartum trough concentrations. Plasma HIV RNA levels were under 400 copies/mL in 92% of women at delivery. Given the high rates of virologic suppression and the lack of a clear relationship between raltegravir concentration and

virologic effect in nonpregnant adults, no change in dosing was recommended during pregnancy.[2] In a study of 22 women with paired third-trimester and postpartum data from the PANNA Network, the geometric mean ratios of third trimester/postpartum values were $AUC_{0\text{-}12hr}$ 0.71 (0.53–0.96), C_{max} 0.82 (0.55–1.253), and C_{12hr} 0.64 (0.34–1.22). One patient was below the target C_{12hr} in the third trimester, and no patients were below the threshold postpartum. No change in dosing during pregnancy was recommended based on these data.[3]

In a single-center, observational study of pregnant women who were started on raltegravir as part of intensification of an antiretroviral (ARV) regimen or part of triple-ARV regimens, the raltegravir C_{12hr} in the second and third trimester were similar to historical data in a nonpregnant population, and the cord blood/maternal plasma raltegravir concentration ratio was 1.03.[4]

In the P1097 study of washout PKs in 21 neonates born to women who received ongoing raltegravir during pregnancy, raltegravir elimination was highly variable and extremely prolonged in some infants (median $t_{1/2}$ 26.6 hours; range 9.3–184 hours).[3] In a case report of an infant born at 30 weeks' gestation after the mother had received three doses of raltegravir, the cord blood level of raltegravir was 145 ng/mL; the level at age 2 days was 106 ng/mL, and at age 1 month the level was 29 ng/mL, still above the IC_{95} of 15 ng/mL.[5] In a report of 14 infants who were exposed to raltegravir *in utero*, the infants had no adverse effects and raltegravir levels were within therapeutic range.[6]

Caution is advised when raltegravir is coadministered with atazanavir, a uridine diphosphate glucuronosyltransferase UGTA1 inhibitor, because this combination results in elevated levels of raltegravir according to the results of a study in healthy, nonpregnant adult women.[7]

Placental and Breast Milk Passage

An *ex vivo* study of term placentas from normal pregnancies reported high bidirectional transfer of raltegravir across the placenta.[8]

In vivo human studies have confirmed that raltegravir readily crosses the placenta. In the IMPAACT P1026s study, the ratio of cord blood to maternal plasma raltegravir concentration was 1.5.[2] In the P1097 study, the median cord blood/maternal delivery plasma raltegravir concentration ratio was 1.48 (with a range of 0.32–4.33), and in the PANNA study it was 1.21.[3,9] Other case reports have shown cord blood/maternal blood drug level ratios of 1.00 to 1.06.[10-12] In a series of three cases with preterm deliveries at 29 to 33 weeks' gestation (in two of these cases, raltegravir was added to the maternal ARV regimen shortly before anticipated preterm delivery), cord blood-to-maternal-plasma ratios ranged from 0.44 to 1.88.[13]

Whether raltegravir is secreted in human breast milk is unknown.

Teratogenicity/Adverse Pregnancy Outcomes

As of January 31, 2018, nine cases of birth defects have been reported among the 291 infants with first-trimester exposure to raltegravir that are included in the Antiretroviral Pregnancy Registry. The prevalence of birth defects among exposed infants was 3.09% (95% CI, 1.42–5.79), compared with a 2.8% total prevalence in the U.S. population, based on Centers for Disease Control and Prevention surveillance.[14,15]

In a retrospective study of 497 women in the French Perinatal Cohort who received raltegravir during pregnancy, there were similar rates of birth defects among infants born to women who were on raltegravir in the first trimester and those born to women who initiated raltegravir in the second or third trimester (5.7% vs. 3.5%, $P = 0.29$). No specific pattern of birth defects emerged during the study.[15]

Safety

In the P1026s study and the PANNA study, raltegravir was well tolerated, with no treatment-related serious adverse events in pregnant women. All infants had reached a gestational age of ≥36 weeks at delivery.[2,3] In multiple case reports and case series that involved four, five, and 14 pregnant women who were treated with raltegravir in combination with two or three other ARV drugs due to persistent viremia or late presentation, raltegravir was well tolerated and led to rapid reduction in HIV RNA levels.[16-22]

However, in one case report, 10-fold to 23-fold increases in maternal liver transaminases were reported after

initiation of raltegravir. Resolution occurred when raltegravir was discontinued.[23] Drug levels were not measured.

One case of drug reaction has been reported with eosinophilia and systemic symptoms syndrome with extensive pulmonary involvement in a postpartum woman. The drug reaction resolved with discontinuation of raltegravir. Such reactions have been reported in nonpregnant adults receiving raltegravir, and these reactions should be taken into consideration when making a differential diagnosis of fever in women on raltegravir during pregnancy or the postpartum period.[24] In a study of 155 nonpregnant adults with HIV (mean age 49.2 years) who initiated raltegravir-containing therapy, skeletal muscle toxicity occurred in 23.9% of participants and isolated creatine kinase (CK) elevation was reported in 21.3% of participants. These instances of CK elevation were Grade 1 or 2 and self-limiting. Fewer than 3% of patients complained of myalgia or muscle weakness. Skeletal muscle toxicity and CK elevation were significantly associated with prior use of zidovudine, higher baseline CK levels, and a higher body mass index.[25]

Because raltegravir is highly protein bound to albumin, there is concern about displacement of bilirubin from albumin in the neonate, which could potentially increase the risk of neonatal hyperbilirubinemia. In an *in vitro* study of the effect of raltegravir on bilirubin-albumin binding, raltegravir had minimal effect on bilirubin-albumin binding at concentrations of 5 μM and 10 μM, caused a small but statistically significant increase in unbound bilirubin at 100 μM, and caused potentially harmful increases at 500 μM and 1,000 μM.[26] These data suggest that the effect of raltegravir on neonatal bilirubin binding is unlikely to be clinically significant at the typical peak concentrations reached in adults with the usual dosing (adult concentrations with standard raltegravir doses had a geometric mean C_{max} of 4.5 μM, a median C_{max} of 6.5 μM, and a maximum observed C_{max} of 10.2 μM).[26] In the P1097 study, one of 19 infants (5.3%) received phototherapy for treatment of hyperbilirubinemia, but this was judged to be unrelated to maternal raltegravir use.[9] In a retrospective study of 31 pregnant women who received a standard dose of raltegravir as part of a standard antiretroviral therapy regimen or as part of an intensification regimen late in pregnancy (at a median gestational age of 34 weeks), mild elevation of transaminases in 35% of neonates was reported.[27]

Raltegravir chewable tablets contain phenylalanine.

Excerpt from Table 10[a]

Generic Name (Abbreviation) *Trade Name*	**Formulation**	**Dosing Recommendations**	**Use in Pregnancy**
Raltegravir (RAL) *Isentress* *Isentress HD*	RAL (Isentress) *Film-Coated Tablets:* • 400 mg *Chewable Tablets:* • 25 mg • 100 mg RAL (Isentress HD) *Film-Coated Tablets:* • 600 mg	Standard Adult Doses: • RAL 400-mg, film-coated tablets twice daily without regard to food • Two RAL 600-mg, film-coated tablets (1200 mg) once daily for ARV-naive patients or patients who are already virologically suppressed on an initial regimen of RAL 400 mg twice daily without regard to food • Chewable and oral suspension doses are not interchangeable with either film-coated tablets or each other *With Rifampin:* • Two RAL 400-mg, film-coated tablets (800 mg) twice daily without regard to food PK in Pregnancy: • Decreased drug concentrations in third trimester not of sufficient magnitude to warrant a change in dosing. Dosing in Pregnancy: • No change in dose is indicated. • Once-daily dosing (i.e., two RAL 600-mg, film-coated tablets) **should not be used** in pregnant women until more information is available.	High placental transfer to fetus.[b] No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects). Case report of markedly elevated liver transaminases with RAL use in late pregnancy. Severe, potentially life-threatening, and fatal skin and HSRs have been reported in nonpregnant adults. Chewable tablets contain phenylalanine. To maximize RAL absorption, doses should not be administered within 2 hours of ingestion of any preparation containing minerals such as iron or calcium, including prenatal vitamins.

Excerpt from Table 10[a]

[a] Individual ARV drug doses may need to be adjusted in patients with renal or hepatic insufficiency (for details, see the Adult and Adolescent Guidelines, Appendix B, Table 8).

[b] Placental transfer categories are determined by mean or median cord blood/maternal delivery plasma drug ratio:

High: >0.6 **Moderate:** 0.3–0.6 **Low:** <0.3

Key to Acronyms: ARV = antiretroviral; BIC = bictegravir; HSR = hypersensitivity reaction; PK = pharmacokinetic; RAL = raltegravir

References

1. Raltegravir [package insert]. Food and Drug Administration. 2017. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/022145s036,203045s013,205786s004lbl.pdf.
2. 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.
3. Blonk M, Colbers A, Hidalgo-Tenorio C, et al. Raltegravir in HIV-1 infected pregnant women: pharmacokinetics, safety and efficacy. *Clin Infect Dis*. 2015. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25944344.
4. Belissa E, Benchikh A, Charpentier C, et al. Raltegravir plasma concentrations on HIV-1 infected pregnant women. Presented at: Conference on Retroviruses and Opportunistic Infections. 2015. Seattle, WA.
5. Clavel-Osorio C, Cazassus F, Stegmann S, Huc-Anais P, Lecam D, Peytavin G. One-month transplacental pharmacokinetics of raltegravir in a premature newborn after short-course treatment of the HIV-1-infected mother. *Antimicrob Agents Chemother*. 2013;57(12):6393-6394. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24080650.
6. Trahan MJ, Lamarre V, Metras ME, Lapointe N, Kakkar F. Raltegravir for the prevention of mother-to-child transmission of HIV. Presented at: International AIDS Society. 2015. Vancouver, CA.
7. Krishna R, East L, Larson P, et al. Atazanavir increases the plasma concentrations of 1200 mg raltegravir dose. *Biopharm Drug Dispos*. 2016;37(9):533-541. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27696440.
8. Vinot C, Treluyer JM, Giraud C, Gavard L, Peytavin G, Mandelbrot L. Bidirectional transfer of raltegravir in an *ex vivo* human cotyledon perfusion model. *Antimicrob Agents Chemother*. 2016;60(5):3112-3114. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26833154.
9. Clarke DF, Acosta EP, Rizk ML, et al. Raltegravir pharmacokinetics in neonates following maternal dosing. *J Acquir Immune Defic Syndr*. 2014;67(3):310-315. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25162819.
10. 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.
11. Croci L, Trezzi M, Allegri MP, et al. Pharmacokinetic and safety of raltegravir in pregnancy. *Eur J Clin Pharmacol*. 2012. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22382989.
12. 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.
13. Hegazi A, Mc Keown D, Doerholt K, Donaghy S, Sadiq ST, Hay P. Raltegravir in the prevention of mother-to-child transmission of HIV-1: effective transplacental transfer and delayed plasma clearance observed in preterm neonates. *AIDS*. 2012;26(18):2421-2423. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23151500.
14. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral pregnancy registry international interim report for 1 January 1989–31 January 2018. Wilmington, NC: Registry Coordinating Center. 2018. Available at: http://www.apregistry.com/.
15. Sibiude J, Warszawski J, Blanchard S, et al. Evaluation of the risk of birth defects among children exposed to raltegravir in utero in the ANRS-French perinatal cohort EPF. Presented at: International AIDS Society; 2017; Paris, France.
16. Taylor N, Touzeau V, Geit M, et al. Raltegravir in pregnancy: a case series presentation. *Int J STD AIDS*. 2011;22(6):358-360. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21680678.
17. Cha A, Shaikh R, Williams S, Berkowitz LL. Rapid reduction in HIV viral load in late pregnancy with raltegravir:

a case report. *J Intern Assoc Provid AIDS Care*. 2013;12(5):312-314. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23695227.

18. De Hoffer L, Di Biagio A, Bruzzone B, et al. Use of raltegravir in a late presenter HIV-1 woman in advanced gestational age: case report and literature review. *J Chemother*. 2013;25(3):181-183. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23783144.
19. Westling K, Pettersson K, Kaldma A, Naver L. Rapid decline in HIV viral load when introducing raltegravir-containing antiretroviral treatment late in pregnancy. *AIDS Patient Care STDS*. 2012;26(12):714-717. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23101466.
20. Nobrega I, Travassos AG, Haguihara T, Amorim F, Brites C. Short communication: use of raltegravir in late-presenting HIV-infected pregnant women. *AIDS Res Hum Retroviruses*. 2013;29(11):1451-1454. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23731224.
21. Adeyemo A, Wood C, Govind A. Achieving rapid reduction of HIV-1 viral load in HIV-positive pregnant women close to term - an obstetric/medical emergency: a review of three cases. *Int J STD AIDS*. 2013;24(7):591-592. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23970779.
22. Maliakkal A, Walmsley S, Tseng A. Critical review: review of the efficacy, safety, and pharmacokinetics of raltegravir in pregnancy. *J Acquir Immune Defic Syndr*. 2016;72(2):153-161. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27183177.
23. Renet S, Closon A, Brochet MS, Bussieres JF, Boucher M. Increase in transaminase levels following the use of raltegravir in a woman with a high HIV viral load at 35 weeks of pregnancy. *Journal Obstet Gynaecol Can*. 2013;35(1):68-72. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23343800.
24. Yee BE, Nguyen NH, Lee D. Extensive pulmonary involvement with raltegravir-induced DRESS syndrome in a postpartum woman with HIV. *BMJ Case Rep*. 2014;2014. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24798353.
25. Calza L, Danese I, Colangeli V, et al. Skeletal muscle toxicity in HIV-1-infected patients treated with a raltegravir-containing antiretroviral therapy: a cohort study. *AIDS Res Hum Retroviruses*. 2014;30(12):1162-1169. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25369244.
26. Clarke DF, Wong RJ, Wenning L, Stephenson DK, Mirochnick M. Raltegravir in vitro effect on bilirubin binding. *Pediatr Infect Dis J*. 2013. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23470680.
27. Cecchini DM, Martinez MG, Morganti LM, Rodriguez CG. Antiretroviral therapy containing raltegravir to prevent mother-to-child transmission of HIV in infected pregnant women. *Infect Dis Rep*. 2017;9(2):7017. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28663779.

Glossary of Terms for Supplement
Carcinogenic: Producing or tending to produce cancer • Some agents, such as certain chemicals or forms of radiation, are both mutagenic and clastogenic. • Genetic mutations and/or chromosomal damage can contribute to cancer formation.
Clastogenic: Causing disruption of or breakages in chromosomes
Genotoxic: Damaging to genetic material such as DNA and chromosomes
Mutagenic: Inducing or capable of inducing genetic mutation
Teratogenic: Interfering with fetal development and resulting in birth defects

Cobicistat (Tybost, COBI)

(Last updated December 7, 2018, last reviewed December 7, 2018)

Cobicistat has insufficient data on human use in pregnancy to inform a drug-associated risk determination for birth defects or miscarriage.

Animal Studies

Carcinogenicity

At cobicistat exposures 7 times and 16 times the human systemic exposure, no increases in tumor incidence were seen in male and female mice. In rats, an increased incidence of follicular cell adenomas and/or carcinomas in the thyroid gland was observed at doses up to twice the typical human exposure. The follicular cell findings are considered rat-specific and not relevant to humans.[1]

Reproduction/Fertility

No effect has been seen on fertility in male or female rats.[1]

Teratogenicity/Adverse Pregnancy Outcomes

Studies in pregnant rats and rabbits have shown no evidence of teratogenicity, even with cobicistat exposures that were 1.4 times higher than the recommended human exposure in rats and 3.3 times higher than the recommended human exposure in rabbits.[1]

Placental and Breast Milk Passage

No information is available on placental passage of cobicistat. Studies in rats have shown that cobicistat is secreted in breast milk.[2]

Human Studies in Pregnancy

Pharmacokinetics

Cobicistat pharmacokinetics (PKs) have been described in pregnant and postpartum women who were taking concomitant elvitegravir and darunavir. In a study of 30 pregnant women who were receiving elvitegravir/cobicistat, the area under the curve (AUC) for cobicistat was 44% lower in the second trimester and 59% lower in the third trimester than during the postpartum period. Trough cobicistat concentrations (24 hours post-dose) were 60% lower in the second trimester and 76% lower in the third trimester than during the postpartum period. Trough cobicistat concentrations were below the assay quantitation limit (<10 ng/mL) in 65% of women during the second trimester, 73% of women during the third trimester, and 24% of postpartum women.

The pharmaco-enhancing effect of cobicistat on elvitegravir was impacted during pregnancy; elvitegravir AUC was reduced by 44% and trough concentrations were reduced by 89% in the third trimester when compared to postpartum AUC and trough concentrations. Elvitegravir apparent oral clearance during

pregnancy and postpartum was negatively associated with cobicistat AUC.[3] Study results reported in two conference abstracts have described decreases of similar magnitudes in cobicistat and darunavir exposures among pregnant women.[4,5] In one of these abstracts, cobicistat AUC was decreased by 63% in the second trimester and 49% in the third trimester compared to AUC postpartum. Trough cobicistat concentrations decreased by 83% in both the second and third trimesters.

The pharmaco-enhancing effect of cobicistat on darunavir was also impacted during pregnancy; AUC based on total darunavir concentrations was 56% (in the second trimester) and 50% (in the third trimester) lower than AUC postpartum, and AUC based on unbound concentrations was 45% and 40% lower, respectively. The effect on darunavir trough concentrations was more pronounced, with both total and unbound concentrations showing essentially identical decreases of 92% (in the second trimester) and 88% to 89% (in the third trimester) compared to postpartum. One of six women in this study experienced virologic failure during the third trimester, and virologic failure continued through the postpartum period.[4] Because of these substantial reductions in drug exposures during pregnancy, use of elvitegravir/cobicistat or darunavir/cobicistat **is not recommended** during pregnancy.[6,7]

A study reported in a recent conference abstract evaluated tenofovir alafenamide (TAF) exposure when TAF was administered as a daily 10-mg dose with cobicistat 150 mg and found no differences between TAF exposure during pregnancy and TAF exposure in the same women postpartum. The authors concluded that no dose adjustment is needed during pregnancy for TAF when it is coadministered with cobicistat.[8] However, TAF 10 mg with cobicistat is only available in fixed-dose combination products that also include either dolutegravir or elvitegravir, which are not recommended for use during pregnancy.

Placental and Breast Milk Passage

A study in 10 pregnant women receiving elvitegravir/cobicistat found a median cord blood to maternal delivery plasma cobicistat concentration ratio of 0.09. This study also found measurable concentrations of cobicistat in placental tissue and cord blood peripheral blood mononuclear cells (PBMC), with a cord/maternal PBMC ratio of 0.49.[9] In another study, seven pregnant women who received elvitegravir/cobicistat had quantifiable cobicistat concentrations that were detectable in plasma at delivery. The median ratio for cord blood to maternal delivery plasma cobicistat concentration was 0.09. In 27 neonates born to mothers who were receiving elvitegravir/cobicistat, cobicistat was below the assay quantitation limit of 10 ng/mL in all washout PK samples taken between 2 hours and 9 days post-delivery.[3] No data are available on breast milk passage of cobicistat in humans.

Teratogenicity/Adverse Pregnancy Outcomes

In the Antiretroviral Pregnancy Registry, five birth defects have been reported out of 204 live births to mothers with first-trimester exposure to cobicistat. The number of first-trimester exposures to cobicistat in humans is insufficient to be able to make a risk determination.[2]

Excerpt from Table 10[a] (page 1 of 2)

Note: When using FDCs, refer to other sections in Appendix B and Table 10 for information about the dosing and safety of individual drug components of the FDC during pregnancy.

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations	Use in Pregnancy
Cobicistat (COBI) *Tybost* (ATV/COBI) *Evotaz* (EVG/COBI/FTC/TAF) *Genvoya* (DRV/COBI) *Prezcobix* (EVG/COBI/FTC/TDF) *Stribild* (DRV/COBI/FTC/TAF) *Symtuza*	COBI (Tybost) *Tablet:* • COBI 150 mg ATV/COBI (Evotaz): • ATV/COBI 300 mg/50 mg tablet EVG/COBI/FTC/TAF (Genvoya): • EVG 150 mg plus COBI 150 mg plus FTC 200 mg plus TAF 10 mg tablet DRV/COBI (Prezcobix): • DRV/COBI 800 mg/150 mg tablet EVG/COBI/FTC/TDF (Stribild): • EVG 150 mg plus COBI 150 mg plus FTC 200 mg plus TDF 300 mg tablet DRV/COBI/FTC/TAF (Symtuza): • DRV 800 mg plus COBI 150 mg plus FTC 200 mg plus TAF 10 mg tablet	Standard Adult Doses *COBI (Tybost):* • As an alternative PK booster with ATV or DRV: 1 tablet (150 mg) once daily with food *ATV/COBI (Evotaz):* • 1 tablet once daily with food *EVG/COBI/FTC/TAF (Genvoya):* • 1 tablet once daily with food *DRV/COBI (Prezcobix):* • 1 tablet once daily with food *EVG/COBI/FTC/TDF (Stribild):* • 1 tablet once daily with food *DRV/COBI/FTC/TAF (Symtuza):* • 1 tablet once daily with food PK in Pregnancy: • Based on limited data, COBI exposure and pharmaco-enhancing effect on DRV and EVG are markedly reduced in pregnancy. • No data are available on the pharmaco-enhancing effect of COBI on ATV. • When coadministered with COBI, TAF exposure is not significantly different between pregnancy and the postpartum period. Dosing in Pregnancy: • While COBI exposure is markedly reduced during pregnancy, higher than standard doses have not been studied. The Panel recommends RTV as the preferred pharmaco-enhancer for PIs and INSTIs during pregnancy until more data are available on COBI activity during pregnancy. • For guidance about the use of combination products in pregnancy, please see the specific sections on other components (i.e., FTC, TAF, TDF, ATV, DRV, EVG).	Low placental transfer to fetus.[b] Insufficient data to assess for teratogenicity in humans. No evidence of teratogenicity in rats or rabbits. Use of COBI-boosted ATV, DRV, or EVG **is not recommended** in pregnancy.

[a] Individual ARV drug doses may need to be adjusted in patients with renal or hepatic insufficiency (for details, see the Adult and Adolescent Guidelines, Appendix B, Table 8).

[b] Placental transfer categories are determined by mean or median cord blood/maternal delivery plasma drug ratio:

High: >0.6 Moderate: 0.3–0.6 Low: <0.3

Key to Abbreviations: ARV = antiretroviral; ATV = atazanavir; COBI = cobicistat; DRV = darunavir; EVG = elvitegravir; FDC = fixed-dose combination; FTC = emtricitabine; INSTIs = integrase strand transfer inhibitors; PIs = protease inhibitors; PK = pharmacokinetic; RTV = ritonavir; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

References

1. Cobicistat [package insert].Food and Drug Administration. 2017. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/203094s007lbl.pdf.
2. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral pregnancy registry international interim report for 1 January 1989–31 January 2018. Wilmington, NC: Registry Coordinating Center. 2018. Available at: http://www.apregistry.com/.

3. 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.
4. Crauwels HM, Osiyemi O, Zorilla C, Bicer C, Brown K. Pharmacokinetics of total and unbound darunavir in HIV-1–infected pregnant women receiving a darunavir/cobicistat-based regimen. Presented at: 8th International Workshop on HIV & Women. 2018. Boston, Massachusetts. Available at: http://www.natap.org/2018/CROI/HIV&Women2018DRVcPKPregnancyPoster_JUV-63244_FINAL.PDF.
5. Momper J, Best B, Wang J, et al. Pharmacokinetics of darunavir boosted with cobicistat during pregnancy and postpartum. Presented at: International AIDS Conference. 2018. Amsterdam, Netherlands.
6. Darunavir/cobicstat (Prezcobix) [package insert]. Food and Drug Administration. 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/205395s009lbl.pdf.
7. Genvoya [package insert]. Food and Drug Administration. 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/207561s000lbl.pdf.
8. 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.
9. Rimawi BH, Johnson E, Rajakumar A, et al. Pharmacokinetics and placental transfer of elvitegravir and dolutegravir, and other antiretrovirals during pregnancy. *Antimicrob Agents Chemother*. 2017. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28348149.

Ritonavir (Norvir, RTV)

(Last updated December 7, 2018; last reviewed December 7, 2018)

Available data from the Antiretroviral Pregnancy Registry show no difference between the rate of overall birth defects in infants born to mothers who are taking ritonavir and the background rate of birth defects in a U.S. reference population. The Antiretroviral Pregnancy Registry has monitored a sufficient number of first-trimester exposures to be able to detect at least a 1.5-fold increase in risk of overall birth defects; however, no such increase has been observed. Use of ritonavir oral solution is not recommended during pregnancy, because this formulation contains alcohol and there is no known safe level of alcohol exposure during pregnancy.

Animal Studies

Carcinogenicity

Ritonavir was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests. Carcinogenicity studies in mice and rats have been completed. In male mice, a dose-dependent increase in adenomas of the liver and combined adenomas and carcinomas of the liver was observed at levels of ritonavir 50, 100, or 200 mg/kg/day; based on area under the curve, exposure in male mice at the highest dose was approximately 0.3-fold that seen in male humans at the recommended therapeutic dose. No carcinogenic effects were observed in female mice with exposures 0.6-fold that of female humans at the recommended therapeutic dose. No carcinogenic effects were observed in rats at exposures up to 6% of recommended therapeutic human exposure.[1]

Reproduction/Fertility

No effect of ritonavir has been seen on reproductive performance or fertility in rats at drug exposures 40% (male) and 60% (female) of that achieved with human therapeutic dosing; higher doses were not feasible because of hepatic toxicity in the rodents.[1]

Teratogenicity/Adverse Pregnancy Outcomes

No ritonavir-related teratogenicity has been observed in rats or rabbits. Developmental toxicity, including early resorptions, decreased body weight, ossification delays, and developmental variations such as wavy ribs and enlarged fontanelles, was observed in rats; however, these effects occurred only at maternally toxic dosages (with exposures equivalent to 30% human therapeutic exposures). In addition, a slight increase in cryptorchidism was noted in rats at exposures equivalent to 22% of the human therapeutic dose. In rabbits, developmental toxicity (resorptions, decreased litter size, and decreased fetal weight) was also observed only at maternally toxic doses (1.8 times human therapeutic exposure based on body surface area).[1]

Placental and Breast Milk Passage

Transplacental passage of ritonavir has been observed in rats with fetal tissue-to-maternal-serum ratios >1.0 at 24 hours post-dose in mid- and late-gestation fetuses.

Human Studies in Pregnancy

Pharmacokinetics

A Phase 1/2 safety and pharmacokinetic study (PACTG 354) of ritonavir (500 or 600 mg twice daily) administered in combination with zidovudine and lamivudine to pregnant women living with HIV showed lower levels of ritonavir during pregnancy than postpartum.[2] Ritonavir concentrations are also reduced during pregnancy versus postpartum when the drug is used at a low dose (100 mg) to boost the concentrations of other protease inhibitors.[3,4]

Placental and Breast Milk Passage

In a human placental perfusion model, the clearance index of ritonavir was very low, with little accumulation in the fetal compartment and no accumulation in placental tissue.[5] In a Phase 1 study of pregnant women and their infants (PACTG 354), transplacental passage of ritonavir was minimal, with an average cord blood-to-

maternal-delivery concentration ratio of 5.3%.[2] In a study of cord blood samples from six women treated with ritonavir during pregnancy, the cord blood concentration was less than the assay limit of detection in five of the women and was only 0.38 micrograms/mL in the remaining woman.[6] In contrast, in a study of plasma and hair drug concentration in 51 mother-infant pairs in Uganda receiving lopinavir/ritonavir-based therapy during pregnancy and breastfeeding, infant plasma levels at delivery and hair levels at age 12 weeks suggested *in utero* transfer of ritonavir: 2% of infants had detectable plasma ritonavir concentrations at birth, while mean infant-to-maternal-hair concentration at 12 weeks postpartum was 0.47 for ritonavir.[7] However, transfer during breastfeeding was not observed, with no infant having detectable ritonavir plasma levels at 12 weeks.

Teratogenicity/Adverse Pregnancy Outcomes

In the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposures to ritonavir have been monitored to be able to detect at least a 1.5-fold increase in risk of overall birth defects. No such increase in birth defects has been observed with ritonavir. Among cases of first-trimester ritonavir exposure reported to the Antiretroviral Pregnancy Registry, the prevalence of birth defects was 2.2% (70 of 3,155 births; 95% CI, 1.7% to 2.8%) compared with a total prevalence of 2.7% in the U.S. population, based on Centers for Disease Control and Prevention surveillance.[8]

Excerpt from Table 10[a]

Generic Name (Abbreviation) *Trade Name*	**Formulation**	**Dosing Recommendations**	**Use in Pregnancy**
Ritonavir (RTV) *Norvir*	RTV (Norvir) *Capsules:* • RTV 100 mg *Tablets:* • RTV 100 mg *Oral Solution:* • RTV 80 mg/mL *Powder:* • RTV 100 mg/sachet	Standard Adult Dose as PK Booster for Other PIs: • RTV 100–400 mg per day in 1–2 divided doses (refer to other PIs for specific dosing recommendations.) *Tablet:* • Take with food. *Capsule or Oral Solution:* • To improve tolerability, take with food if possible. PK in Pregnancy: • Lower levels seen during pregnancy than during postpartum. Dosing in Pregnancy: • No dosage adjustment necessary when used as booster.	Low placental transfer to fetus.[b] No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects). Should only be used as low-dose booster for other PIs. Oral solution contains 43% alcohol and is therefore not recommended during pregnancy, because there is no known safe level of alcohol exposure during pregnancy.

[a] Individual ARV drug dosages may need to be adjusted in patients with renal or hepatic insufficiency (for details, see the Adult and Adolescent Guidelines, Appendix B, Table 8).

[b] Placental transfer categories are determined by mean or median cord blood/maternal delivery plasma drug ratio:

High: >0.6 **Moderate:** 0.3–0.6 **Low:** <0.3

Key to Acronyms: PI = protease inhibitor; PK = pharmacokinetic; RTV = ritonavir

References

1. Ritonavir [package insert]. Food and Drug Administration. 2017. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209512s002,022417s020,020659s068lbl.pdf.
2. Scott GB, Rodman JH, Scott WA, et al. Pharmacokinetic and virologic response to ritonavir (RTV) in combination with zidovudine (ZDV) and lamivudine (3TC) in HIV-10-infected pregnant women and their infants. Presented at: 9th Conference on Retroviruses and Opportunistic Infections. 2002. Seattle, WA. Available at: http://www.retroconference.

org/2002/Abstract/13702.htm.

3. 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.
4. Mirochnick M, Best BM, Stek AM, et al. Atazanavir pharmacokinetics with and without tenofovir during pregnancy. *J Acquir Immune Defic Syndr*. 2011;56(5):412-419. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21283017.
5. Casey BM, Bawdon RE. Placental transfer of ritonavir with zidovudine in the ex vivo placental perfusion model. *Am J Obstet Gynecol*. 1998;179(3 Pt 1):758-761. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9757985.
6. Mirochnick M, Dorenbaum A, Holland D, et al. Concentrations of protease inhibitors in cord blood after *in utero* exposure. *Pediatr Infect Dis J*. 2002;21(9):835-838. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12352805.
7. Gandhi M, Mwesigwa J, Aweeka F, et al. Hair and plasma data show that lopinavir, ritonavir, and efavirenz all transfer from mother to infant in utero, but only efavirenz transfers via breastfeeding. *J Acquir Immune Defic Syndr*. 2013;63(5):578-584. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24135775.
8. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral pregnancy registry international interim report for 1 January 1989–31 January 2018. Wilmington, NC: Registry Coordinating Center. 2018. Available at http://www.apregistry.com/.

Antiretroviral Pregnancy Registry (Last updated March 28, 2014; last reviewed March 28, 2014)

The Antiretroviral Pregnancy Registry (APR) is an epidemiologic project to collect observational, non-experimental data on antiretroviral (ARV) drug exposure during pregnancy for the purpose of assessing the potential teratogenicity of these drugs. Registry data will be used to supplement animal toxicology studies and assist clinicians in weighing the potential risks and benefits of treatment for individual patients. The registry is a collaborative project of the pharmaceutical manufacturers with an advisory committee of obstetric and pediatric practitioners.

It is strongly recommended that health care providers who are treating HIV-infected pregnant women and their newborns report cases of prenatal exposure to ARV drugs (either alone or in combination) to the APR. The registry does not use patient names and birth outcome follow-up is obtained from the reporting physician by registry staff.

Referrals should be directed to:

Antiretroviral Pregnancy Registry

Research Park

1011 Ashes Drive

Wilmington, NC 28405

Telephone: 1–800–258–4263

Fax: 1–800–800–1052

http://www.APRegistry.com

Appendix D: Dolutegravir Counseling Guide for Health Care Providers (Last updated December 12, 2019; last reviewed December 12, 2019)

This counseling guide represents the most recent guidance by the Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission (the Panel) based on all currently available data. It replaces all prior statements regarding the safety of dolutegravir (DTG) in pregnant women and women who are trying to conceive.

Use of Dolutegravir in Pregnant Women and Women Who Are Trying to Conceive[a]

In 2018, preliminary data from a study in Botswana identified an increased risk of infant neural tube defects (NTDs) in women who were taking DTG when they became pregnant. This observation led numerous organizations, including the Panel, to advise avoiding the use DTG in women who are trying to conceive or who are already in the first trimester[b] of pregnancy. In July 2019, the results from an analysis of NTDs in a larger number of pregnancies were published. The updated data showed that the risk of infant NTDs is lower than previously reported in preliminary data, but there was still a small but significant increase in the risk of infant NTDs among women who were taking DTG when they became pregnant compared to women who conceived on a regimen that did not contain DTG. An increased risk of infant NTDs has not been found in women who initiate DTG during pregnancy.

Because updated data indicate that the increased risk of NTDs associated with the use of DTG is small, and because DTG has the advantages of once-daily dosing, being generally well tolerated, and producing rapid, durable viral load suppression, which is important for the prevention of perinatal HIV transmission, **the Panel now recommends DTG as a *Preferred* antiretroviral (ARV) drug throughout pregnancy, and as an *Alternative* ARV drug in women who are trying to conceive**. The Panel strongly recommends that use of DTG be accompanied by appropriate counseling to allow patients and their health care providers to make joint decisions about treatment. This counseling guide summarizes considerations that should be addressed when counseling pregnant women and women who are trying to conceive about the use of DTG. For more information, see Updated Guidance about the Use of Dolutegravir in Pregnancy in Recommendations for Use of Antiretroviral Drugs During Pregnancy, Table 6, Table 7, and Pregnant Women Living with HIV Who Are Currently Receiving Antiretroviral Therapy.

General Counseling Considerations for Pregnant Women and Women Who Are Trying to Conceive

- In the United States, the background risk of NTDs in the general population is 0.07% (7 per 10,000 pregnancies). The Centers for Disease Control and Prevention (CDC) notes that 3,000 pregnancies are affected by infant NTDs every year in the United States.
- DTG exposure at the time of conception was associated with a small but significant increase in the risk of infant NTDs in a birth surveillance study in Botswana. The prevalence of infant NTDs was slightly higher in women who were taking DTG at the time of conception (0.30%, or 30 infants with NTDs per 10,000 deliveries) than in women without HIV infection (0.08%, 8 infants with NTDs per 10,000 deliveries) or in women who initiated DTG later in pregnancy (0.03%, 3 infants with NTDs per 10,000 deliveries). The risk of infant NTDs was higher in women who were taking DTG at the time of conception than in women who were receiving efavirenz (EFV)-based antiretroviral therapy (ART) at the time of conception (0.05%, or 5 infants with NTDs per 10,000 deliveries) for women taking EFV.
- Although data have not shown an increase in the risk of NTDs in infants born to women who initiated DTG during pregnancy, it is important to note that there is a background risk of NTDs regardless of the ART regimen used or a woman's HIV status. With the exception of EFV, there are not enough data to determine the risk of NTDs with periconception use of any of the other currently *Preferred* and

Alternative ARV drugs in the United States. Using the data from Botswana, we can now rule out a three-fold or more increased risk of NTDs associated with periconception use of EFV.

- Before, during, and after pregnancy, clinicians and patients should discuss future childbearing desires and plans, the potential risks and benefits of conceiving while taking specific ARV medications, including DTG, and contraceptive options to prevent unintended pregnancy.
- Folic acid is known to lower the risk of NTDs in the general population. The United States Public Health Service recommends that all pregnant women and women who might conceive take at least 400 mcg of folic acid daily and continue to do so throughout pregnancy. Unlike food in Botswana, food in the United States is routinely fortified with folate. However, there is no established link between the use of DTG and impaired folate metabolism, nor is there any evidence that folate supplementation prevents NTDs that are associated with the use of DTG.
- It is important to help women weigh the available information about the risks of NTDs when using DTG against what is known (or not known) about risks of NTDs associated with other ARV drugs that are recommended for use in pregnancy. To date, systematic birth surveillance data in a sufficiently large number of women to rule out an association between periconception drug exposure and NTDs are available only for EFV, which the Panel recommends as an *Alternative* ARV drug for pregnant women and women who are trying to conceive (see Table 6, Table 7, and Efavirenz).
- It is important to help women consider the available information about other potential risks associated with the use of ARV drugs, such as other birth defects or other adverse pregnancy outcomes (e.g., preterm delivery); see Teratogenicity and Combination Antiretroviral Drug Regimens and Maternal and Neonatal Outcomes for more information.
- Most NTDs occur before the neural tube closes at 4 weeks post-conception, approximately 6 weeks post-last menstrual period, often before a woman realizes she is pregnant. After 6 weeks gestation, the additional risk of NTDs developing is thought to be much less likely.
- Changes in antiretroviral therapy (ART) during pregnancy can lead to increases in viral load that increase the risk of perinatal HIV transmission; this viral rebound may affect choices for future ARV regimens due to the possible development of resistance.
- Pregnant women who are receiving DTG and present to care during the first trimester[b] and women who are trying to conceive should receive counseling about the risks and benefits of continuing DTG or switching to another ARV regimen, as described above. In most cases, the Panel recommends **continuation** of DTG for pregnant women, because:
  - The risk of NTDs is small; *and*
  - Rapid, durable viral load suppression in pregnancy is important to prevent perinatal HIV transmission, and changes in ART may result in loss of viral suppression.
- When assessing the the benefits and risks of switching a patient from DTG to another ARV drug, clinicians and patients should consider factors such as the feasibility of switching to another ARV drug, each drug's tolerability, the ability to maintain viral suppression, the risk of perinatal HIV transmission, and the risk of NTDs.
- Women who are trying to conceive should receive information about the use of specific ARV regimens, including those containing DTG; this will enable them to make informed decisions about ARV regimens before they become pregnant.
- All cases of ARV drug exposure during pregnancy should be reported to the Antiretroviral Pregnancy Registry.

Other Antiretroviral Drugs That Are Recommended for Use in Pregnancy

- Other *Preferred* ARV drug options for women who are initiating ART while pregnant or while trying to conceive include raltegravir,[c] atazanavir/ritonavir, and darunavir/ritonavir. We have a moderate amount of data about pregnancy outcomes and birth defects with each of these drugs and drug combinations. While these data are reassuring, it is important to note that a rigorous, systematic birth surveillance program that includes large numbers of women with periconception exposure like in the Botswana study does not exist for these drugs. Additionally, because of mandatory food folate fortification, the overall risk of NTDs in the United States is low in the general population, and there are currently insufficient DTG periconception exposures reported to the Antiretroviral Pregnancy Registry be able to determine whether there is an increase in the risk of NTDs in the United States.
- EFV, rilpivirine, and lopinavir/ritonavir are recommended as *Alternative* ARV drug options in pregnancy. *Alternative* drugs may have more limited data on use in pregnancy than *Preferred* drugs (e.g., rilpivirine) or may be associated with more pharmacokinetic (PK), dosing, tolerability, drug interaction, or resistance concerns than those in the *Preferred* category, but they are acceptable for use in pregnancy.
- When discussing ARV drug options, it is important to point out that some ARV drugs that are recommended for use in adults and nonpregnant women are not *Preferred* or *Alternative* options for women who are pregnant or who are trying to conceive for the following reasons:
  - Not enough is known about the safety of using some ARV drugs before or during pregnancy, because studies about their use in pregnancy are limited. It is important to emphasize that a lack of data does not indicate the absence or presence of risk. It only means that we do not have all the information about all the possible effects when using these drugs during pregnancy (e.g., bictegravir and tenofovir alafenamide).
  - For some ARV drugs (e.g., cobicistat-boosted regimens), there are PK changes in pregnancy that decrease blood levels of those agents, potentially leading to loss of virologic control and an increased risk of perinatal transmission or adverse effects on maternal HIV infection. With newer ARV drugs, PK and safety data may not be available to guide dosing in pregnancy.
- Regimens that contain atazanavir/cobicistat, darunavir/cobicistat, or elvitegravir/cobicistat **are not recommended** for use in pregnant women because of PK changes that may lead to increased viral loads later in pregnancy. Health care providers should discuss whether to continue the regimen or switch to one that is recommended for use in pregnant women with patients (see Table 7 and Pregnant Women Living with HIV Who Are Currently Receiving Antiretroviral Therapy). If a regimen with PK concerns is continued, it is important that the patient follow the instructions for taking the regimen in order to optimize absorption (e.g., taking certain drugs with or without food, avoiding antacids or divalent cation-containing vitamins). Viral load should be monitored more frequently in these patients (i.e., every 1–2 months).
- If an ARV regimen is changed during pregnancy, drugs in the new regimen should be ARV drugs that are recommended for use in pregnancy (see Table 6 and Table 7) and viral load should be checked 2 to 4 weeks after the switch.
- Recommendations regarding the use of specific ARV agents or ARV regimens often change as more information on the safety, tolerability and PK changes of these drugs in pregnancy becomes available.

Footnotes

[a] Guidance on the care of pregnant women and women who are trying to conceive is also applicable to transgender and nonbinary people of childbearing potential.

[b] The first trimester is less than 14 weeks (up to 13 6/7 weeks) gestational age by last menstrual period.

[c] Raltegravir requires twice-daily dosing during pregnancy and has a lower barrier to resistance than DTG.

Appendix E: Acronyms (Last updated October 26, 2016; last reviewed October 26, 2016)

Acronym/Abbreviation	Full Name
3TC	lamivudine
ABC	abacavir
ACOG	American College of Obstetricians and Gynecologists
ALT	alanine aminotransferase
anti-HBc	anti-hepatitis B core antibody
anti-HBS	hepatitis B surface antibody
AOR	adjusted odds ratio
AP	antepartum
ART	antiretroviral therapy
ARV	antiretroviral
AST	aspartate aminotransferase
ATV	atazanavir
ATV/r	atazanavir/ritonavir
AUC	area under the curve
AZT	zidovudine
BID	twice daily
BMI	body mass index
CBC	complete blood count
CD4	CD4 T lymphocyte
CDC	Centers for Disease Control and Prevention
CI	confidence interval
C_{max}	maximum plasma concentration
C_{min}	minimum plasma concentration
CNS	central nervous system
COBI	cobicistat
CVS	chorionic villus sampling
CYP	cytochrome P
CYP3A4	cytochrome P450 3A4
d4T	stavudine
ddI	didanosine
DMPA	depot medroxyprogesterone acetate
DRV	darunavir
DRV/r	darunavir/ritonavir
DSMB	Data and Safety Monitoring Board

DTG	dolutegravir
EC	enteric coated
ECG	electrocardiogram
EFV	efavirenz
EMS	ethyl methane sulfonate
ETR	etravirine
EVG	elvitegravir
FDA	Food and Drug Administration
FDC	fixed drug combination
FPV	fosamprenavir
FPV/r	fosamprenavir/ritonavir
FTC	emtricitabine
gp	glycoprotein
HAV	hepatitis A virus
HBIG	hepatitis B immune globulin
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HELLP	hemolysis, elevated liver enzymes, and low platelets
HGC	hard gel capsule
HR	hazard ratio
HRSA	Health Resources and Services Administration
HSR	hypersensitivity reaction
IC_{50}	inhibitory concentration 50%
IDV	indinavir
IDV/r	indinavir/ritonavir
IGF	insulin-like growth factor
IgG	Immunoglobulin G
IP	intrapartum
IQR	interquartile range
IRIS	immune reconstitution inflammatory syndrome
IUD	intrauterine device
IV	intravenous/intravenously
LPV	lopinavir
LPV/r	lopinavir/ritonavir
MAC	*Mycobacterium avium* complex
mtDNA	mitochondrial DNA
MVC	maraviroc

NFV	nelfinavir
NIH	National Institutes of Health
NNRTI	non-nucleoside reverse transcriptase inhibitor/non-nucleoside analogue reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor/nucleoside analogue reverse transcriptase inhibitor
NtRTI	nucleotide analogue reverse transcriptase inhibitor
NVP	nevirapine
OC	oral contraceptive
OI	opportunistic infection
OR	odds ratio
The Panel	The Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission
PCP	*Pneumocystis jirovecii* pneumonia
PCR	polymerase chain reaction
PI	protease inhibitor
PK	pharmacokinetic
PO	orally
PP	postpartum
PPI	proton pump inhibitor
PrEP	pre-exposure prophylaxis
PTD	preterm delivery
RAL	raltegravir
RDS	respiratory distress syndrome
RPV	rilpivirine
RR	relative risk
RTV	ritonavir
SD	single dose
SQ	subcutaneous
SQV	saquinavir
SQV/r	saquinavir/ritonavir
STD	sexually transmitted disease
T20	enfuvirtide
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil fumarate
TDM	therapeutic drug monitoring
TID	three times daily
TPV	tipranavir
TPV/r	tipranavir/ritonavir

UGT	uridine diphosphate glucuronosyltransferase
WHO	World Health Organization
ZDV	zidovudine