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)

Visit the https://clinicalinfo.hiv.gov/en/guidelines website to access the most up-to-date guideline.

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How to Cite the Perinatal Guidelines:

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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 HIVinfo website (LINK).

What's New in the Guidelines

(Last updated February 10, 2021; last reviewed February 10, 2021)

Text and references throughout the guidelines were updated to include new data and publications where relevant. These changes are highlighted in yellow in the PDF version of the guidelines. Major section revisions are summarized below.

February 10, 2021

The Panel has begun to make revisions in language to be more inclusive for the care of transgender and non-binary people who are pregnant or trying to conceive. Revisions are limited to a few sections at present, but this is an effort that will continue in future updates.

Recommendations for the Use of Antiretroviral Drugs During Pregnancy

- The Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission (the Panel) recommends dolutegravir (DTG) as a *Preferred* antiretroviral (ARV) drug throughout pregnancy and now also recommends DTG as a *Preferred* ARV for women who are trying to conceive. This decision was based on updated data showing that that the increased risk of neural tube defects (NTDs) associated with the use of DTG is very small and the advantages of DTG which include once-daily dosing, being generally well tolerated, and producing rapid, durable viral load suppression, which is important for maternal health and the prevention of perinatal HIV transmission.
- With this change, the Panel has removed DTG-specific recommendations, but added content about balancing the risks and benefits of specific ARV drugs in the face of limited data. The Panel continues to emphasize the importance of counseling and informed decision making regarding the use of DTG and all ARV drugs during pregnancy and for people who are trying to conceive and has revised the Counseling Guide in Appendix C, accordingly.
- Lopinavir/ritonavir, formerly classified as an *Alternative* ARV is now *Not Recommended Except in Special Circumstances* based on data about increased risks of preterm delivery and small for gestational age infants (see Antiretroviral Drug Regimens and Maternal and Neonatal Outcome) as well as requirements for twice daily dosing and potential nausea and vomiting.
- The Panel recommends tenofovir alafenamide (TAF) as an *Alternative* nucleoside reverse transcriptase inhibitor for ARV therapy regimens now that additional data about the use and safety of TAF in pregnancy has become available.
- The Panel has revised language about its recommendations about cobicistat containing ARV regimens that pose a risk for low drug levels and viral rebound in the second and third trimesters to point out that some health care providers and their patients may choose to continue with frequent viral load monitoring, rather than switching to a new regimen.
- Fostemsavir, a new ARV, has been classified as for use in pregnancy.
- Revisions have been made to the sections listed below, and those published in December 2020, to incorporate the Panel's updated recommendations about ARV drugs during pregnancy and for women who are trying to conceive.
  - Pregnant People with HIV Who Have Never Received Antiretroviral Drugs (Antiretroviral Naive)
  - Table 4. What to Start: Initial Combination Regimens for Antiretroviral-Naive Pregnant Women
  - Pregnant Women with HIV Who Are Currently Receiving Antiretroviral Therapy
  - Acute HIV
  - Appendix C: Antiretroviral Counseling Guide for Health Care Providers

December 29, 2020

Introduction

- The Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission (the Panel) has added a new guidelines section, HIV Pre-Exposure Prophylaxis (PrEP) to

Reduce the Risk of Acquiring HIV During Periconception, Antepartum, and Postpartum Periods.

- The Panel has begun to make revisions in language and content in the guidelines to address the care of transgender and non-binary people who are pregnant or trying to conceive, an effort that will continue in future updates.

Maternal HIV Testing and Identification of Perinatal HIV Exposure

- Bulleted recommendations have been updated to point out that repeat HIV testing is recommended for pregnant women with a sexually transmitted infection or with signs and symptoms of acute HIV infection **(AIII)** and that expedited HIV testing during labor is recommended for those who are at increased risk of HIV infection and were not retested in the third trimester **(AIII)**.
-

HIV Pre-Exposure Prophylaxis (PrEP) to Reduce the Risk of Acquiring HIV During Periconception, Antepartum, and Postpartum Periods

- This new section provides Panel recommendations and summarizes available evidence about the rationale for PrEP and its use and safety in individuals who are trying to conceive or are pregnant, postpartum, or breastfeeding.
- The Panel recommends that health care providers offer and promote oral combination tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) PrEP to individuals who are at risk for HIV and are trying to conceive or are pregnant, postpartum, or breastfeeding **(AII)**. Indications for PrEP include any risk factors for acquiring HIV, such as condomless sex with a partner with HIV whose HIV-RNA level is detectable or unknown, recent sexually transmitted infection, or injection drug use. Because risk factors may be underreported, those who report feeling at risk for HIV acquisition should be counseled on the benefits and risks of and be offered PrEP.
- Providers should counsel individuals about the benefits **(AI)** and risks **(AII)** of PrEP for for their health and their infants and about the importance of daily adherence to oral PrEP in preventing HIV acquisition **(AI)**.
- The section includes recommendations for PrEP initiation and follow-up with links to the Centers for Disease Control and Prevention HIV Pre-Exposure Prophylaxis Guidelines for additional guidance.
- Health care providers are strongly encouraged to register patients who become pregnant while receiving PrEP with the Antiretroviral Pregnancy Registry.

Reproductive Options for Couples When One or Both Partners Have HIV

- Content about PrEP has been shortened and is now linked to the new section, HIV Pre-Exposure Prophylaxis (PrEP) to Reduce the Risk of Acquiring HIV During Periconception, Antepartum, and Postpartum Periods.

General Principles Regarding Use of Antiretroviral Drugs During Pregnancy

- Prenatal care for people with HIV should include assessment of the patient's self-affirmed gender identify, preferred pronouns, use of gender-affirming hormonal therapy, and potential interactions with ARV (see Transgender People with HIV).
- It is important to be aware that COVID-19 may increase the risk of depression, substance use, and intimate partner violence at a time when the frequency of in-person health care services has decreased (see Interim Guidance for COVID-19 and Persons with HIV).

Teratogenicity

- Bulleted recommendations have been revised to reflect additional data and updated Panel recommendations for dolutegravir, which is now a *Preferred* antiretroviral drug for people who are trying to conceive, rather than an *Alternative*.

Antiretroviral Drug Regimens and Maternal and Neonatal Outcomes

- The Panel has added a summary of key points about the outcomes of preterm delivery, low birth weight and small-for-gestational-age infants, stillbirth, and hypertensive disorders of pregnancy.

Monitoring of the Woman and Fetus During Pregnancy

- Information in the bulleted recommendations and the text is now summarized in a new table, Table 6. HIV-Related Laboratory Monitoring Schedule for Pregnant Women with HIV.

Antiretroviral Drug Resistance and Resistance Testing in Pregnancy

- The following guidance from the text has been added as a bulleted recommendation: Phenotypic resistance testing is indicated for treatment-experienced persons on failing regimens who are thought to have multidrug resistance **(BIII)**.
-

Hepatitis B Virus/HIV Coinfection

- Tenofovir alafenamide (TAF) now is included as an option for the treatment of hepatitis B virus and HIV coinfection based on the Panel's updated recommendation of TAF as an *Alternative* non-nucleoside reverse transcriptase inhibitor for the people with HIV who are pregnant or are trying to conceive.

Hepatitis C Virus/HIV Coinfection

- Patients with hepatitis C virus (HCV) should be strongly considered for HCV treatment with direct-acting antiviral agents postpartum **(AI)**.
- The Panel recommends that for patients who have tested positive for HCV, their HCV RNA should be evaluated after delivery to assess for spontaneous clearance of HCV infection, particularly as they are being considered for initiation of HCV therapy postpartum **(BII)**.

Intrapartum Care for Women with HIV

- The former sections on Intrapartum Antiretroviral Therapy/Prophylaxis, Transmission and Mode of Delivery, and Other Intrapartum Management Considerations have been combined into a single section, and Table 7, Intrapartum Care and Recommended Interventions to Prevent Perinatal HIV Transmission for Women with HIV Based on Maternal HIV RNA at the Time of Delivery, has been added to provide easy access to information.
- In the new combined section, some of the Panel's bulleted recommendations have been reorganized according to maternal HIV RNA near the time of delivery, which is defined as ≥34–36 weeks gestation or 4–6 weeks before delivery.
- The Panel has made some additions to the bulleted recommendations to highlight important content from the text clarification. For example, labor should not be induced to prevent perinatal HIV transmission.

Postpartum Follow-Up of Women With HIV

- The Panel recommends that women who desire to breastfeed should receive evidence-based counseling on infant feeding options **(AIII)** (see Counseling and Managing Women with HIV in the United States Who Desire to Breastfeed).

Antiretroviral Management of Newborns with Perinatal HIV Exposure of HIV Infection

- In describing infants at high or low risk of perinatal acquisition of HIV and maternal risk factors for perinatal HIV transmission, viral suppression is defined as HIV RNA <50 copies/mL.
- Information about recommended antiretroviral drugs for infants with perinatal exposure to HIV-2 infection is available in Table 9 and HIV-2 Infection and Pregnancy.
- Table 9 has been updated to include dosing of dolutegravir dispersible tablets for oral suspension for HIV therapy, which can replace lopinavir/ritonavir, nevirapine, or raltegravir in infants at least 4 weeks of age and weighing at least 3 kg.

- Information about the two-drug regimen of nevirapine and zidovudine used in NICHD-HPTN 040/PACTG 1043 has been removed from Table 9 but is available in the text (see Two-Drug Antiretroviral Prophylaxis).
- Maraviroc (MVC) was approved recently for infants weighing ≥2 kg and may provide an additional treatment option for newborns of women carrying multidrug resistant HIV-1 that remains CCR5-trophic. However, the lack of data about MVC as prophylaxis or treatment in infants weighing <10 kg and the risk of drug interactions will limit its role for routine use in neonates.

Diagnosis of HIV Infection in Infants and Children

- Maternal HIV viral loads that categorize infants at a high risk of perinatal HIV transmission have been defined at HIV RNA ≥50 copies/mL.
- A statement has been added to clarify that HIV testing at birth might be considered when there are concerns that a newborn at low risk of perinatal HIV transmission may be lost to follow-up without testing.
- Content has been added about the potential for false-positive HIV nucleic acid tests (NATs) with chimeric antigen receptor T cell (CAR-T cell) and lentiviral-based gene therapy.

Initial Postnatal Management of the Neonate Exposed to HIV

- The Panel has added information about hyperbilirubinemia and has added a statement to point out that with appropriate follow-up to support the recommended diagnostic testing schedule, most infants with perinatal HIV exposure do not require trimethoprim-sulfamethoxazole prophylaxis, because HIV can be presumptively excluded by the time their infant ARV regimen is completed (see Diagnosis of HIV Infection in Infants and Children).

Appendix B: Supplement: Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy.

- Table 10: Antiretroviral Drug Use in Pregnant Women with HIV Infection: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy and other sections in Appendix B have been updated with new data for each drug, including new formulations and fixed-dose combination tablets.
- Tenofovir Alafenamide (TAF) now includes data from the Antiretroviral Pregnancy Registry, which has monitored a sufficient number of first-trimester exposures to detect at least a twofold increase in the risk of overall birth defects; no such increase in risks has been observed with TAF.
- Dolutegravir, Elvitegravir, Raltegravir now include supplemental data about central nervous system birth defects from the Antiretroviral Pregnancy Registry.
- A new section was added for Fostemsavir, a drug that has been approved by the Food and Drug Administration for use in adults.

December 15, 2020

Table 5. Situation-Specific Recommendations for Use of Antiretroviral Drugs in Pregnant People and Nonpregnant People Who Are Trying to Conceive

- The Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission (the Panel) recommends dolutegravir (DTG) as a *Preferred* antiretroviral (ARV) drug throughout pregnancy and now also recommends DTG as a *Preferred* ARV for women who are trying to conceive. This decision was based on updated data showing that that the increased risk of neural tube defects (NTDs) associated with the use of DTG is very small and the advantages of DTG which include once-daily dosing, being generally well tolerated, and producing rapid, durable viral load suppression, which is important for maternal health and the prevention of perinatal HIV transmission. The Panel strongly recommends that use of DTG and all ARV drugs be accompanied by appropriate counseling to allow patients and their health care providers to make informed decisions about treatment.
- Lopinavir/ritonavir is now classified as *Not Recommended Except in Special Circumstances*, rather than as an *Alternative* ARV, based on requirements for twice daily dosing, potential nausea and vomiting, and data about increased risks of preterm delivery and small for gestational age infants.

- The Panel now recommends tenofovir alafenamide (TAF) as an *Alternative* nucleoside reverse transcriptase inhibitor for ARV therapy regimens now that additional data about the use and safety of TAF in pregnancy has become available.
- The Panel has revised language about its recommendations for pregnant women who are currently receiving a cobicistat containing ARV regimens that pose a risk for low drug levels and viral rebound in the second and third trimesters to point out that some women may choose to continue with frequent viral load monitoring, rather than switching to a new regimen.
- Fostemsavir, a new ARV, has been classified as for use in pregnancy.
- Upcoming publication of other sections will reflect these changes in the full Guidelines.

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Members of the Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission

(Last updated: December 29, 2020; Last reviewed December 29, 2020)

Revisions to the December 24, 2019 *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).

Members of the Panel	
Elaine J. Abrams, MD	Columbia University, New York, NY
Jean Anderson, MD	Johns Hopkins University School of Medicine, Baltimore, MD
Martina L. Badell, MD	Emory University School of Medicine, Atlanta, GA
Brookie M. Best, PharmD, MAS	University of California, San Diego, La Jolla, CA Rady Children's Hospital—San Diego, San Diego, CA
Danielle Campbell, MPH	Los Angeles Women's HIV/AIDS Task Force, Los Angeles, CA
Rana Chakraborty, MD, MS, PhD[a]	Mayo Clinic College of Medicine, Rochester, MN
Susan E. Cohn, MD, MPH	Northwestern University Feinberg School of Medicine, Chicago, IL
Susan Cu-Uvin, MD	Alpert School of Medicine, Brown University, Providence, RI
Patricia M. Flynn, MD	St. Jude Children's Research Hospital, Memphis, TN
Jennifer Jao, MD, MPH	Northwestern University Feinberg School of Medicine, Chicago, IL
Susana Keeshin, MD	University of Utah, Salt Lake City, UT
Gweneth B. Lazenby, MD, MSCR	Medical University of South Carolina, Charleston, SC
Judy Levison, MD, MPH	Baylor College of Medicine, Houston, TX
Lynn Matthews, MD, MPH	University of Alabama at Birmingham, Birmingham, AL
Lynne M. Mofenson, MD	Elizabeth Glaser Pediatric AIDS Foundation, Washington, DC
Florence Momplaisir, MD, MSPH	University of Pennsylvania, Philadelphia, PA
Fatima Y. Prioleau, MA	Brooklyn, NY
Lisa Rahangdale, MD, MPH	University of North Carolina School of Medicine, Chapel Hill, NC
Rachel K. Scott, MD, MPH	MedStar Washington Hospital Center, MedStar Health Research Institute, Washington, DC Georgetown University, Washington, DC
Jeanne Sheffield, MD	Johns Hopkins University School of Medicine, Baltimore, MD
William R. Short, MD, MPH	University of Pennsylvania, Philadelphia, PA
Fatoumatta Sissoho	Windsor Mill, MD
Stephen A. Spector, MD	University of California, San Diego, La Jolla, CA Rady Children's Hospital—San Diego, San Diego, CA
Rodney Wright, MD, MS	Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY
Rebecca Zash, MD	Harvard Medical School, Boston, MA

[a] American Academy of Pediatrics Committee on Pediatric AIDS liaison

Panel Chair/Executive Secretary	
Nahida Chakhtoura, MD, MsGH	National Institutes of Health, Bethesda, MD

Panel Co-Chairs	
Andrea Ciaranello, MD, MPH	Massachusetts General Hospital, Harvard Medical School, Boston, MA
Mark Mirochnick, MD	Boston Medical Center, Boston University School of Medicine, Boston, MA

Ex Officio Members	
Isabelle Boucoiran, MD, MSc[b]	Society of Obstetricians and Gynaecologists of Canada, Montreal, Quebec, Canada
Fatima Kakkar, MPH[c]	Centre Hospitalier Universitaire Sainte-Justine, Montreal, Quebec, Canada
Lealah Pollock, MD, MS	National Perinatal HIV Hotline, San Francisco, CA

[b] Society of Obstetricians and Gynaecologists of Canada liaison

[c] Canadian Pediatric & Perinatal AIDS Research Group liaison

Members from the United States Government	
Athena P. Kourtis, MD, PhD, MPH	Centers for Disease Control and Prevention, Atlanta, GA
Steve Nesheim, MD	Centers for Disease Control and Prevention, Atlanta, GA
George K. Siberry, MD, MPH	United States Agency for International Development (USAID), Washington, DC
Prabha Viswanathan, MD	Food and Drug Administration, Silver Spring, MD
D. Heather Watts, MD	Office of the Global AIDS Coordinator and Health Diplomacy, Washington, DC

Panel Consultant	
Deborah Storm, MSN, PhD	Fairfield, CA. Formerly François-Xavier Bagnoud Center, School of Nursing, Rutgers, The State University of New Jersey, Newark, NJ (retired November 1, 2016)

Panel Coordinator	
Maria Nkwanzi, MPH	The Scientific Consulting Group, Gaithersburg, MD

Financial Disclosure List for Members of the Health and Human Services Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission (Reporting Period: December 2019 to December 2020)

Name	Panel Status	Company	Relationship
Abrams, Elaine J.	M	None	N/A
Anderson, Jean	M	Gilead	Stockholder
Badell, Martina L.	M	None	N/A
Best, Brookie M.	M	PPD	DSMB
		C&R Research, Inc.	DSMB
Boucoiran, Isabelle	ExOM	None	N/A
Campbell, Danielle	M	None	N/A
Chakhtoura, Nahida	ES	None	N/A
Chakraborty, Rana	M	None	N/A
Ciaranello, Andrea	CC	None	N/A
Cohn, Susan E.	M	None	N/A
Cu-Uvin, Susan	M	AIDS Malignancy Consortium	DSMB
		Clinical Care Options	Speaker
		DC Health (Washington, DC DOH)	Speaker
		UpToDate	Section Writer
Flynn, Patricia M.	M	Merck	Safety Monitoring Committee
Jao, Jennifer	M	None	N/A
Kakkar, Fatima	ExOM	None	N/A
Keeshin, Susana	M	None	N/A
Kourtis, Athena P.	HHS	None	N/A
Lazenby, Gweneth B.	M	None	N/A
Levison, Judy	M	None	N/A
Matthews, Lynn	M	Gilead	Research Support
Mirochnick, Mark	CC	ViiV	Research Support
		Merck	Research Support
		Gilead	Research Support
Mofenson, Lynne M.	M	None	N/A
Momplaisir, Florence	M	None	N/A
Nesheim, Steve	HHS	None	N/A
Pollock, Lealah	ExOM	None	N/A
Prioleau, Fatima Y.	M	None	N/A
Rahangdale, Lisa	M	None	N/A
Scott, Rachel K.	M	Gilead	Research Support
Sheffield, Jeanne	M	None	N/A
Short, William R.	M	ViiV	Consultant
		Janssen	Consultant
Siberry, George K.	M	None	N/A
Sissoho, Fatoumatta	M	None	N/A
Spector, Stephen A.	M	J&J	Stockholder

Name	Panel Status	Company	Relationship
Storm, Deborah	C	Merck	Stockholder
		Eli Lilly and Company	Stockholder
		Roche	Stockholder
Viswanathan, Prabha	HHS	None	N/A
Watts, D. Heather	HHS	None	N/A
Wright, Rodney	M	None	N/A
Zash, Rebecca	M	None	N/A

Key: DSMB = Data Safety Monitoring Board; C= Consultant; 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 29, 2020; last reviewed December 29, 2020)

Recommendations regarding HIV screening in pregnancy, treatment of pregnant women with HIV infection, and the use of antiretroviral (ARV) drugs to prevent perinatal transmission of HIV have evolved considerably in the United States since the mid-1990s, reflecting changes in both the epidemic and the science of prevention and treatment. Current recommendations for universal prenatal HIV counseling and testing,[1] antiretroviral therapy (ART) for all pregnant women 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 have resulted in a dramatic decrease in the rate of perinatal transmission of HIV to 1% or less in the United States and Europe.[2] In 2016, only 44 infants were born with HIV infection in the United States; the estimated incidence of perinatally acquired HIV infection was 1.1 out of 100,000 live births.[3]

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.[4] However, incomplete implementation of routine antenatal HIV testing and other recommended interventions remains a barrier to achieving this goal.[5,6] Laws that promote universal HIV testing for pregnant women vary by jurisdiction, and prenatal testing coverage is higher in states with stronger regulations for testing all pregnant women.[7,8] Testing coverage is also poorer for pregnant women in subgroups that are perceived by health care providers to be at low risk of HIV acquisition (e.g., women who are married, white, non-Hispanic, or multiparous).[9,10] To address such challenges, many states and the District of Columbia have developed additional effective strategies to advance progress toward eliminating perinatal HIV transmission.[11] To further support HIV prevention and reduction of perinatal HIV transmission, the Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission (the Panel) has now added guidance about the use of HIV pre-exposure prophylaxis in women at risk of HIV infection who are trying to conceive, pregnant, postpartum or breastfeeding, see HIV Pre-exposure Prophylaxis (PrEP) to Reduce the Risk of Acquiring HIV During Periconception, Antepartum, and Postpartum Periods.

Every year, approximately 5,000 women with HIV give birth in the United States.[12] In addition to primary prevention of HIV infection in women, the best way to prevent HIV infection in infants is to focus on appropriate overall medical care for women with HIV; this includes comprehensive reproductive health care, 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 that a woman receives ART that maximally suppresses viral replication as early as possible during pregnancy or, ideally, prior to conception.

A critical role of 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 ART. Secondary considerations include characteristics that help promote adherence, such as improved tolerability or convenience (e.g., 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 during 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 of reports to the Antiretroviral Pregnancy Registry, and all available postmarketing surveillance data.

When strong evidence of fetal (or maternal) harm or unacceptable drug exposure exists, 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 must make recommendations for ARV drugs for which there are insufficient PK data in pregnant women and/or inadequate safety information on fetal exposure early in pregnancy or during the periconception period. Policymakers, regulators, clinicians, and community advocates are striving to improve the availability of data on ARV drug exposure and safety in women who are pregnant or breastfeeding, or in women who are of reproductive potential.[13-15]

In the meantime, to ensure that pregnant women are not denied the best available ART—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 regimens to use during pregnancy:

- ARV regimens that are designated as *Preferred* in pregnancy are those that have been shown to be effective and durable in clinical trials in adults. *Preferred* regimens have acceptable toxicity and ease of use, pregnancy-specific PK data to guide dosing, and available data that suggest a favorable risk-benefit balance compared to other ARV options, incorporating outcomes for women, fetuses, or newborns. Some *Preferred* drugs 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.
- Preferred ARV 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 on the use of these regimens in pregnancy are generally favorable, but still limited. Most *Alternative* drugs or regimens are associated with more concerns (or insufficient data) related to PK, dosing, tolerability, formulation, administration, or drug–drug interactions than those in the preferred category, but they are acceptable for use in pregnancy. They may also 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.
- Caution should be used when considering regimens that contain drugs with little or no pregnancy data. These regimens are considered to have for initiation in pregnancy, but no specific data exist that would support a recommendation to discontinue 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 in some situations, 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.
- Some drugs are designated as *Not Recommended* in pregnancy because they have inferior virologic efficacy, because PK data demonstrate low drug levels and a risk of viral rebound during pregnancy, or because they are associated with potentially serious maternal or fetal safety concerns.

The Panel systematically reviews all new information from the Antiretroviral Pregnancy Registry, published studies, and other sources to update the 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 December 2019 *Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States*. The Panel, a working group of the National Institutes of Health (NIH) OARAC, develops these guidelines. The Panel collaborates 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. Health care providers should discuss the information in these guidelines with pregnant women with HIV in order to make collaborative, informed decision-making regarding

the use of ARV drugs during pregnancy, the use of scheduled cesarean delivery to reduce the risk of perinatal transmission of HIV, and the use of ARV drugs in infants who have been exposed to HIV. The guidelines are structured to address the care of all pregnant individuals with HIV and their infants and people who are trying to conceive. Many of the studies that informed these guidelines included only cisgender women and, as a result, data specifically relevant for transgender men and non-binary people who are pregnant are often not available. Most sections of these guidelines, therefore, use the terminology, 'women'. The Panel continues to advocate for greater inclusion of transgender and non-binary people in research, and the Panel recommends a gender-affirmative model of care to ensure that services encompass and address the needs of transgender and non-binary people who are pregnant or trying to conceive, see Transgender People with HIV.

The recommendations in these guidelines are accompanied by discussions of common circumstances that occur in clinical practice and the factors that influence treatment considerations. The Panel recognizes that strategies to prevent perinatal transmission and concepts related to managing HIV in pregnant women are rapidly evolving, and the Panel will continue to consider new evidence and adjust recommendations accordingly. The current guidelines are available on the ClinicalInfo 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 with HIV or who are at risk for HIV and for their children, and it serves as a resource for obtaining expert consultation on individual cases.

The Panel's recommendations are designed to ensure that women receive the full benefit of ART for their own health and to prevent perinatal transmission. However, the Panel recognizes that women have the right 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-infant 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 (see the World Health Organization guidelines for more information).

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 to treat pregnant women with HIV and to prevent perinatal HIV transmission in HIV-exposed infants.
Panel Members	The Panel is composed of approximately 30 voting members who have expertise in managing the care of pregnant women with HIV (e.g., training in obstetrics/gynecology, infectious diseases, or women's health), the pharmacology of ARV drugs during pregnancy, and the interventions for prevention of perinatal transmission (e.g., specialized training in pediatric HIV infection). The Panel also includes 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 (HRSA), and the National Institutes of Health (NIH). Members who do not represent U.S. government agencies are selected by Panel members after an open call for nominations. Each member serves on the Panel for a 3-year period, with an option for reappointment. The Panel also may include liaison members from the National Perinatal HIV Hotline, the American Academy of Pediatrics Committee on Pediatric AIDS, the American College of Obstetricians and Gynecologists, the Society of Obstetricians and Gynaecologists of Canada, and the Canadian Pediatric and Perinatal Research Group. 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 to manage HIV infection. See Financial Disclosure for a list of the latest disclosures.
Users of the Guidelines	Providers of care to pregnant women 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 were 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.

Topic	Comment
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. 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 review, discussion, and further modification to reach a final version that is acceptable to all Panel members. The recommendations in these final versions represent the consensus of Panel members and are included in the guidelines as official Panel recommendations.
Other Guidelines	These guidelines focus on pregnant women with HIV and their infants. Other guidelines (all of which are available on the ClinicalInfo 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 potential is briefly discussed in this document. However, for a more detailed discussion of the issues surrounding the treatment of nonpregnant adults, please consult the Adult and Adolescent Antiretroviral Guidelines and the Adult and Adolescent Opportunistic Infection Guidelines.
Update Plan	The Panel meets monthly by teleconference to review data that may affect the content 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 recommendations on the HIVinfo website until the guidelines can be updated with appropriate changes.
Public Comments	A 2-week public comment period follows the release of the updated guidelines on the ClinicalInfo website. The Panel reviews comments to determine whether additional revisions to the guidelines are indicated. The public also may submit comments to the Panel at any time at contactus@HIVinfo.nih.gov.

Basis for Recommendations

The recommendations in these guidelines are based on scientific evidence and expert opinion. Each recommendation statement includes a letter (**A, B,** or **C**) that represents the strength of the recommendation and a Roman numeral (**I, II,** or **III**) that represents the quality of the evidence that supports the recommendation.

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

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Maternal HIV Testing and Identification of Perinatal HIV Exposure

(Last updated December 29, 2020; last reviewed December 29, 2020)

Panel's Recommendations
• HIV testing is recommended as a standard of care for all sexually active women and should be a routine component of preconception care **(AII)**. • All 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 from the Centers for Disease Control and Prevention [CDC]) **(AII)**. • Partners of all pregnant women should be referred for 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 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 (see Revised Recommendations for HIV Testing of Adults, Adolescents, and Pregnant Women in Health-Care Settings from CDC), or those who reside in states that require third-trimester testing **(AII)**. • Repeat HIV testing is recommended for pregnant women with a sexually transmitted infection (STI) or with signs and symptoms of acute HIV infection **(AIII)**. • Expedited HIV testing should be performed during labor or delivery for women with undocumented HIV status and for those who tested negative early in pregnancy but are at increased risk of HIV infection and were not retested in the third trimester **(AII)**. Testing should be available 24 hours a day, and results should be available within 1 hour. If results are positive, intrapartum antiretroviral (ARV) prophylaxis should be initiated immediately **(AI)**. • Women who were not 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)**. • When a woman has a positive HIV test result during labor and delivery or postpartum, or when a newborn's expedited antibody test is positive, an appropriate infant ARV drug regimen should be initiated immediately, and the mother should not breastfeed while awaiting the results of supplemental HIV testing **(AII)**. See Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV for guidance. • 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 is recommended for infants and children in foster care and adoptees for whom maternal HIV status is unknown, to identify perinatal HIV exposure and possible HIV infection **(AIII)**, see Diagnosis of HIV Infections in Infants and Children.
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

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. In the United States, approximately 20% to 34% of infants with perinatal HIV exposure are born to women whose diagnosis was not known prior to pregnancy.[1] Early diagnosis 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.[2–6] All HIV testing should be performed in a manner that is consistent with state and local regulations. CDC recommends the "opt-out" approach, which is allowed in many jurisdictions, and which involves notifying pregnant women that HIV testing will be performed as part of routine care unless they choose not to be tested.[3] 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, which has been adopted by several states, involves testing newborns with or without maternal consent. In some areas, this applies to all newborns; in others, it applies only to the infants of mothers who have declined prenatal or intrapartum testing.

Partners of pregnant women also should 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 diagnosed with HIV infection. Because women are more susceptible to HIV acquisition during pregnancy and the postpartum period,[9] clinicians also can initiate a discussion about preventive interventions, including pre-exposure prophylaxis, for a pregnant woman without HIV who is at risk for acquiring HIV, e.g., living with a partner who has or is at high risk for HIV (see Prophylaxis (PrEP) to Reduce the Risk of Acquiring HIV During Periconception, Antepartum, and Postpartum Periods).

Clinicians should assess a woman's risk of acute HIV infection, particularly late in pregnancy, because a pregnant woman may receive a negative result for expedited or rapid HIV testing when she is in the window period (the window period lasts up to 15 days post-infection when using the combined antigen/antibody immunoassay, and up to 28 days when using other assays). However, during this period she will be viremic,[10] with a high risk of perinatal transmission to her newborn. The HIV RNA assay can detect the presence of HIV as early as 10 days post-infection, so this test should be used when acute HIV infection is suspected. 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.[11–14] Maternal HIV testing should be performed as early as possible during pregnancy, wherever a woman seeks care (including emergency departments and prenatal clinics), to avoid missed opportunities to identify pregnant women with HIV. Repeat HIV testing should be performed in the third trimester for women who are at increased risk of acquiring HIV or who are living in areas of high HIV incidence, and at the time of a diagnosis of a sexually transmitted infection (STI), or when they show symptoms and signs of possible acute HIV infection. Women with unknown or undocumented HIV status who present to care in labor should be tested during delivery or as soon as possible after delivery.[11–14]

Determining antenatal maternal HIV status enables—

- Women with HIV to receive appropriate antiretroviral therapy (ART) and prophylaxis against opportunistic infections;
- Initiation of treatment in the identified women to maintain and improve their health, decrease risk of HIV transmission to their fetus/infant and their partners;[3,15,16]
- Referral of partners for testing, which allows them to initiate either treatment if the results are positive or preventive interventions if the results are negative;
- Provision of ART to the mother during pregnancy and labor, and provision of an appropriate antiretroviral (ARV) drug regimen to the newborn, to reduce the risk of perinatal transmission;

- Counseling of women with HIV about the indications for (and potential benefits of) scheduled elective cesarean delivery to reduce the risk of perinatal transmission of HIV;[17–19]
- Counseling of women with HIV about the risks of HIV transmission through breast milk (in the United States, breastfeeding is not recommended for women with HIV, see Counseling and Managing Women Living With HIV in the United States Who Desire to Breastfeed;[20] *and*
- Early diagnostic evaluation of infants exposed to HIV (see Diagnosis of HIV Infection in Infants and Children), as well as testing of other children, to permit prompt initiation of ART and any indicated prophylaxis measures.[2,21–23]

New technology has made it possible to detect HIV earlier and has reduced the performance time for laboratory-based assays, which now can be completed in <1 hour. Accordingly, the Panels now base their recommendations for HIV testing on CDC's 2014 Laboratory Testing for the Diagnosis of HIV Infection: Updated Recommendations.[24] 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 plasma HIV RNA assay to establish a diagnosis of acute HIV infection (see CDC's Recommended Laboratory HIV Testing Algorithm for Serum or Plasma Specimens).

Discordant HIV testing results can be seen, requiring careful evaluation and often repeat tests. Early in HIV infection, prior to HIV seroconversion, the antigen-antibody screen will be negative and the HIV RNA assay will be positive. This is seen in acute infection, because the HIV RNA assay is positive before the antigen/antibody screen. The test combination of a positive antigen-antibody screen, negative antibody differentiation assay, and positive HIV RNA assay also can be seen early in HIV infection, because the IgG-based antibody differentiation assay is positive later in infection than the antigen capture or the IgM result in the antigen-antibody screen.

Clinicians should be aware that as more individuals undergo repeat HIV testing, the number of false-positive screens will increase. The combination of a positive antigen-antibody screen with a negative antibody differentiation assay and a negative HIV RNA assay is seen in persons without HIV infection who have a false-positive antigen-antibody screen.

These examples should make it clear that for any positive HIV 1/2 antigen-antibody screen, an HIV RNA assay should be done, since it is the HIV RNA assay that is needed to resolve questions raised by discordant results on the antigen-antibody screen and the antibody differentiation assay.

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, 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 performed 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)[25] for pregnant women with negative results on their initial HIV antibody tests who[5]—

- Are 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 a suspected or diagnosed STI during pregnancy); *or*
- Are receiving health care in facilities where prenatal screening identifies 1 or more pregnant women 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).[3,26–28]

Women who decline testing earlier in pregnancy should be offered testing again during the third trimester. An antigen/antibody combination immunoassay should be used, because these tests have a higher sensitivity in the setting of acute HIV infection than older antibody tests.[24,29] 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 when indicated in areas where it is not routine. 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.[14] 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 cases, 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] In a more recent study from a high-prevalence area of Florida, 91.7% had first- or second-trimester screening, and although only 82.2% had a third-trimester test, 89.3% of those without third-trimester screening had rapid testing upon admission.[31]

Repeat HIV testing at other times during pregnancy also should be considered when clinically indicated. For example, repeat testing should be performed when a woman presents with symptoms that are suggestive of an STI, a confirmed STI diagnosis, or symptoms or signs that are consistent with acute HIV infection.

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 for fetal/infant prophylaxis (see Intrapartum Care for Women with HIV) and in developing an appropriate ARV regimen for infants who are at high risk of perinatal HIV transmission (see Table 11).[2–4,21,27,32,33]

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 for 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.[24] Immediate initiation of maternal intravenous intrapartum zidovudine is recommended to prevent perinatal transmission of HIV pending the supplemental result (see Intrapartum Care for Women with HIV).[2–4,6,21,27] Pending results of supplemental maternal testing, infants should receive an ARV regimen that is appropriate for infants who are at high risk of perinatal HIV transmission as soon as possible (see Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV or contact the National Perinatal HIV Hotline). No further testing is required for specimens that are nonreactive (negative) on the initial immunoassay, unless acute HIV infection is suspected (see Acute HIV Infection).[24]

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. 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 RNA test should be sent, as well. When mothers are unavailable for testing, their newborns should undergo expedited HIV testing.[2,21,27] 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 mothers or infants, it is strongly recommended that clinicians initiate an ARV regimen that is appropriate for infants who are at high risk of perinatal HIV transmission and counsel the mothers 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 exposure and possible infection in these infants or children.[2] The choice of test will vary based on the age of the child (see Diagnosis of HIV Infection in Infants and Children). Mechanisms should be developed to facilitate prompt HIV screening for infants who have been abandoned and who are in the custody of the state.

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 and postpartum women who previously tested negative for HIV, including women who are breastfeeding. 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 and Pre-exposure Prophylaxis (PrEP) to Reduce the Risk of Acquiring HIV During Periconception, Antepartum, and Postpartum Periods). Women who have acute HIV during pregnancy or lactation have an increased risk of perinatal transmission and secondary sexual transmission of HIV (see Acute HIV Infection).[25,34–37] The antigen/antibody combination immunoassay will detect acute HIV infection earlier than other immunoassays, within approximately 15 days of acquisition. 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 approximately 5 days 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.[20] Breast milk can be expressed while HIV diagnostic testing is completed. Breastfeeding can resume

if HIV infection is excluded and there is no ongoing risk. 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 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.

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Pre-exposure Prophylaxis (PrEP) to Reduce the Risk of Acquiring HIV During Periconception, Antepartum, and Postpartum Periods

(Last updated December 29, 2020; last reviewed December 29, 2020)

Panel's Recommendations
• Health care providers should offer and promote oral combination tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) pre-exposure prophylaxis (PrEP) to individuals who are at risk for HIV and are trying to conceive or are pregnant, postpartum, or breastfeeding **(AII)**. Indications for PrEP include any risk factors for acquiring HIV, such as condomless sex with a partner with HIV whose HIV-RNA level is detectable or unknown, recent sexually transmitted infection (STI), or injection drug use. Because risk factors may be underreported, those who report feeling at risk for HIV acquisition should be counseled on the benefits and risks of and be offered PrEP. • People who become pregnant while using TDF/FTC as PrEP can continue PrEP throughout their pregnancy. Risk for HIV acquisition should be reassessed and people should be counseled regarding benefits and risks of PrEP use in pregnancy **(AII)**. • Providers should counsel patients about the benefits of PrEP to reduce the risk of maternal HIV acquisition and perinatal HIV transmission **(AI)** and about potential risks of PrEP to mother and fetus or infant during periconception, pregnancy, postpartum, and breastfeeding periods **(AII)**. • In cases when the individual's risk factor is one identified partner with HIV and that partner is on antiretroviral therapy (ART) with sustained viral suppression, PrEP may be optional because condomless sexual intercourse is associated with effectively no risk of sexual HIV transmission when HIV viral load is suppressed **(AI)** (see Reproductive Options for Couples When One or Both Partners Have HIV). • Providers should counsel patients about the importance of daily adherence to oral PrEP in preventing HIV acquisition (AI). Women should be counseled to take a once-daily pill of coformulated TDF/FTC PrEP for 20 days prior to being protected from HIV and therefore should use back-up protection in the interim **(BII)**. No data support on-demand PrEP use for people exposed to HIV through vaginal exposure. • Providers should offer routine PrEP follow-up, including testing for HIV every 3 months and counseling on signs and symptoms of acute retroviral syndrome **(AI)** (see the Centers for Disease Prevention and Control Guidelines for HIV Pre-Exposure Prophylaxis and Maternal HIV Testing and Identification of Perinatal HIV Exposure). More frequent testing may be appropriate when clinically indicated (e.g., adherence challenges, nonstandard visit schedule). *Other novel PrEP agents including oral tenofovir alafenamide (TAF)/FTC and injectable agents are not yet recommended for people exposed to HIV through receptive vaginal sex.*
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

Rationale for Use of PrEP During Periconception, Antepartum and Postpartum Periods

HIV pre-exposure prophylaxis (PrEP) is the use of specific antiretroviral (ARV) drugs to prevent HIV acquisition among persons at risk for acquiring HIV. The use of combination tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) as daily oral PrEP to reduce HIV acquisition among individuals exposed to HIV was approved by the U.S. Food and Drug Administration (FDA) in 2012. When taken as prescribed, TDF/FTC can confer greater than 90 percent protection against acquiring HIV. PrEP is recommended for all people who have condomless sex with a partner with HIV who has not achieved HIV RNA suppression or whose viral suppression status is unknown, and for people with other risks, such as recent sexually transmitted infection (STI), injection drug use, or reporting that one feels at risk for HIV.[1,2] Women account for nearly 20 percent of new HIV diagnoses in the United States, most via heterosexual transmission.[3,4] Although data about the use of PrEP among periconception, pregnant, and postpartum women are less robust than for non-pregnant women,

PrEP is highly efficacious for women, and a large body of data from pregnant women using TDF/FTC as treatment for HIV and hepatitis B virus (HBV) suggests these agents are safe for pregnant and breastfeeding women and their infants.[5-8] Of note, other novel PrEP agents, including oral tenofovir alafenamide (TAF)/FTC and injectable cabotegravir, are not yet approved for people with vaginal exposure to HIV, and only limited safety data are available for their use during pregnancy.

Partners of people with HIV who do not have HIV themselves and are planning to have a child or who are pregnant or breastfeeding should be offered PrEP or referred for PrEP care services when indicated to reduce the risk of HIV acquisition and potential perinatal HIV transmission.[1]

The guidance in this section focuses on the use of PrEP during periconception, antepartum, and postpartum periods (through 6 months postpartum and throughout breastfeeding). Most research on PrEP cited here was conducted with cisgender women, but there are patients who are assigned female at birth, do not identify as female (i.e., transgender men, genderqueer, or non-binary individuals), and become pregnant and give birth. PrEP should be offered and promoted for all individuals with an indication for PrEP using a gender-affirming approach to care, see Transgender People with HIV in the Adult and Adolescent Antiretroviral Guidelines.

Susceptibility to HIV acquisition is greater during periconception, antepartum, and early postpartum periods through 6 months. Data suggest that women trying to conceive are at higher risk for HIV acquisition, likely due to increased condomless sex.[9,10] The increase in HIV acquisition risk continues in pregnancy and is likely due to a combination of behavioral factors—such as no longer needing to use condoms for contraception—and biological factors that include increased innate and suppressed adaptive immunity, increased genital tract inflammation, alterations in the vaginal microbiome, decreased integrity of the vaginal epithelium, and both gross and micro-trauma to the genital tract during delivery.[11-13] HIV incidence among women during pregnancy and postpartum is two to six times greater than outside of pregnancy.[13-17] Two large HIV prevention studies conducted in Africa demonstrated the probability of HIV acquisition per condomless sex act increases beginning in early pregnancy and peaks in the early postpartum period (in data analyzed from birth through 24 weeks postpartum in most studies). After adjustment for age, use of PrEP, and male partner HIV viral load, the probability of HIV acquisition was significantly higher throughout pregnancy and the postpartum period (adjusted relative risk 2.76; 95% CI, 1.58–4.81).[18] In addition, women who acquire HIV while pregnant or breastfeeding are more likely to transmit HIV to their infant. The risk of perinatal transmission is 9 to 15 times higher in women diagnosed with HIV during pregnancy compared to those diagnosed prior to pregnancy.[19-21]

Despite the risks of HIV acquisition and known efficacy of PrEP,[6-8] PrEP remains underutilized among women[22,23], especially during pregnancy and breastfeeding. The American College of Obstetricians and Gynecologists[2] and the World Health Organization (WHO)[24] agree that all viable HIV prevention options, including PrEP, should be encouraged for women at risk for HIV, especially during pregnancy and breastfeeding, given the increased risk of HIV acquisition during pregnancy and the potential for perinatal transmission with maternal seroconversion during pregnancy. Of note, although the bulk of the data on HIV acquisition risk comes from populations exposed to HIV in the context of sexual exposure, women who inject drugs during pregnancy and postpartum also face substantial risks and should be offered PrEP for prevention.[1,2,25]

Efficacy of TDF/FTC as PrEP During Periconception, Pregnancy and Postpartum Periods

Data from two randomized controlled trials that enrolled heterosexual-identifying men and women demonstrated the efficacy of TDF/FTC as PrEP to be 63 to 75 percent. In women with detectable drug levels (or taking PrEP), PrEP protected against 90 percent of incident transmissions.[26] In a meta-analysis of all available

clinical trial data, a mixed-effects model suggested that if women adhere to at least 75 percent of doses, PrEP decreases HIV acquisition risk by 61 percent (relative risk 0.39, 95% CI, 0.25– 0.60).[27] Although pregnant women were not enrolled in these clinical trials, subsequent data from demonstration projects suggest that PrEP uptake and adherence are high during periconception and pregnancy and can reduce HIV acquisition risks. In Kenya, 74 HIV-serodifferent couples—including 40 women without HIV—enrolled into a safer conception study. In the month preceding pregnancy confirmation, 81 percent of partners who were HIV negative were highly adherent to PrEP.[28] In South Africa, 526 individuals (334 women and 192 men) from 334 partnerships were enrolled into a study to promote safer conception care. PrEP was initiated as part of safer conception care by 51 percent (n=22) of women without HIV in this study. No sexual or perinatal HIV transmission events were observed.[29]

In terms of demand for PrEP, pregnant and postpartum women (n=9,736) in the PrEP Implementation in Young Women and Adolescents (PrIYA) program in Kenya were assessed for behavioral risk factors and willingness to initiate PrEP. Overall, 2,030 women (22%) initiated PrEP.[30] In South Africa, an ongoing observational study of PrEP use in pregnancy observed that 414 (91%) of 455 enrolled women opted to start PrEP at their first antenatal visit.[31]

Adherence and Timing Considerations for PrEP Use

Adherence is particularly important to achieve effective drug concentrations in vaginal and cervical tissues and may be even more important in the second and third trimesters of pregnancy, when drug levels drop because of expanding volume of distribution and increased renal clearance. Studies in non-pregnant women demonstrate that it may take up to 20 days to reach maximum intracellular concentrations of tenofovir and/or FTC in cervicovaginal tissue, compared to only 7 days in anal tissues.[32-34] Although pharmacokinetic data are limited in pregnant women, data suggest that pregnant women taking daily PrEP experience lower drug levels.[35,36] The available data are limited and the Centers for Disease Control and Prevention (CDC) guidelines suggest 20 days are needed to achieve protective levels in cervicovaginal tissues, whereas WHO guidelines suggest that 7 days of oral PrEP use are needed to achieve systemic protection from vaginal receptive exposure to HIV.[1,24] Given the increased volume of distribution and concomitant lower levels of TDF/FTC in plasma, the Panel recommends continued use of other prevention strategies (e.g., condoms) until PrEP has been taken for at least 20 days and protection against transmission can be assumed in pregnant or postpartum PrEP users. Six to seven doses a week (or daily dosing) are needed to maintain levels in cervicovaginal tissue in non-pregnant women. When women initiate PrEP and have not yet reached protective drug levels or struggle with daily adherence, other strategies should be used to prevent HIV in the presence of ongoing risk factors for acquiring HIV.

Safety of TDF/FTC as PrEP for Women, Including Those Who Are Pregnant or Breastfeeding

Efficacy trials of TDF/FTC as PrEP excluded women who reported plans to become pregnant and/or were pregnant, but abundant data are available from (a) PrEP use during early pregnancy among women who are HIV negative, due to inadvertent exposure in clinical trials (e.g., pregnancy occurred and the study drug was discontinued once pregnancy was detected), (b) PrEP use during periconception, pregnancy, and breastfeeding from demonstration projects, including pregnant women and those planning for pregnancy, (c) tenofovir use during late pregnancy for HBV treatment in women who are HIV negative, and (d) use of tenofovir and FTC as antiretroviral therapy (ART) by pregnant women with HIV. These data all indicate that TDF/FTC PrEP is safe for use during pregnancy.

A 2017 systematic review of 26 studies involving TDF and FTC exposure during pregnancy did not identify safety concerns that would limit the use of PrEP in pregnant or lactating women or require discontinuation of PrEP in women who become pregnant while still at continuing risk of HIV acquisition.[5] In 2020, an additional systematic review examined five completed studies that included 1,042 PrEP-exposed pregnancies.[37] Four of the five studies did not observe differences in pregnancy or perinatal outcomes associated with PrEP exposure.

One study did find that PrEP-exposed infants had a lower z-score for length at 1 month of age; however, no difference was observed at 1 year. These studies all come from sub-analyses of clinical trials. Because pregnant women were excluded from these trials, most of the data regarding PrEP exposure reflect early first-trimester exposures. The authors also noted that at least nine ongoing studies, to be completed by 2022, will provide data on more than 6,200 additional PrEP-exposed pregnancies and will assess perinatal, infant growth, and bone health outcomes. Currently available data suggest that the benefits of TDF/FTC as PrEP to prevent HIV outweigh any potential toxicities. PrEP should be promoted for women who are at risk of HIV acquisition during periconception, pregnancy, and postpartum periods.

TDF/FTC and Birth Outcomes

Data on birth outcomes, including congenital abnormalities, among women who used PrEP during pregnancy are commensurate with the general population.[38-41] In women with HIV who take TDF/FTC as treatment during pregnancy, similarly, no evidence exists of increased aneuploidy, congenital anomalies, or adverse maternal or neonatal pregnancy outcomes, such as low birth weight.[5,42-48] Conflicting data exist regarding a possible association between TDF-containing ART regimens and possible preterm birth, but the evidence is mixed, and benefits of HIV prevention outweigh this possible risk.[49]

Renal and Bone Effects of TDF/FTC as PrEP for Women

The main toxicities of concern for women taking TDF as PrEP or ART involve the renal and bone systems, based on animal data. Data from humans suggest minimal and reversible impacts to maternal renal systems.[50,51] Reversible bone density changes have been observed in adults taking TDF/FTC as PrEP.[52,53] These data are more limited for exposure during pregnancy or breastfeeding, when bone turnover is high. In a substudy of a randomized controlled trial of TDF to prevent perinatal transmission of HBV, no significant effects of maternal TDF use (from 28 weeks gestation to 2 months postpartum) on maternal bone density were observed at 1 year.[54]

Renal and Bone Effects of TDF/FTC as PrEP for Infants Exposed to PrEP in Utero or During Breastfeeding

No evidence suggests renal pathophysiology in infants exposed to TDF/FTC in utero. The only signal of bone impact on infants, to date, was in the Partners PrEP clinical trial, in which PrEP-exposed infants had a lower z-score for length at 1 month of age; however, no difference between PrEP-exposed infants and those not exposed was observed at 1 year.[38] In a substudy of a randomized controlled trial of TDF to prevent perinatal transmission of HBV, no significant effects of maternal TDF use (from 28 weeks gestation to 2 months postpartum) on infant or maternal bone density were observed at 1 year.[54]

Impacts of TDF/FTC on Breastfeeding Infants

TDF/FTC impacts on breastfeeding infants appear to be minimal given that (a) very little drug is contained in breastmilk and (b) the drug in breastmilk is tenofovir (not TDF), which has limited bioavailability.[55] In a short-term study of oral TDF/FTC as PrEP in women without HIV who were breastfeeding, the estimated infant doses from breast milk and plasma concentrations were 12,500-fold (tenofovir) and >200-fold (FTC) lower, respectively, than proposed therapeutic doses for infants. Tenofovir was not detected in 94 percent of plasma samples from infants, suggesting minimal infant exposure.[56] Additional studies confirm minimal systemic exposure to tenofovir and FTC via breastmilk.[55] For women who are at risk for acquiring HIV, the benefits of PrEP appear to outweigh the risks, and the Panel recommends that TDF/FTC as PrEP be offered to people exposed to HIV while breastfeeding.

See the Tenofovir Disoproxil Fumarate and Emtricitabine sections for additional data about TDF and FTC during pregnancy and breastfeeding.

Clinical Management of PrEP Use During Periconception, Antepartum, and Postpartum Periods

Initiating and Stopping PrEP

Clinicians who prescribe PrEP should counsel patients about potential risks and benefits and all available strategies for reducing HIV acquisition risks during periconception, antepartum, and postpartum periods. People who become pregnant while using PrEP can continue PrEP throughout their pregnancy and should be counseled regarding risks and benefits as outlined above. CDC has issued guidelines for the use of PrEP for people exposed to HIV through vaginal exposure.[1] It is recommended that an individual who does not have HIV and may be at risk for acquiring HIV through vaginal exposure start daily oral TDF plus FTC beginning 20 days before condomless sex exposure and continuing for 28 days after such exposures.[1] Adherence is easiest with one daily pill, and TDF/FTC is available as a fixed-dose combination tablet. Of note, for people using PrEP for periconception, antepartum, and postpartum periods, indications for PrEP use may change during the course of their reproductive journey; for example, indications for PrEP may resolve if a partner is found not to have HIV or to have HIV-RNA suppression. As the increased risks for HIV acquisition associated with pregnancy and postpartum status resolve, women may have ongoing risks of HIV acquisition, regardless of pregnancy status. In addition, women may have repeat pregnancies and, therefore, ongoing discussion regarding the possibility of pregnancy (planned or unplanned) and the need for PrEP should continue. Because PrEP does not protect against other STIs, condom use remains an important strategy for reducing risks of STI acquisition.

Episodic or on-demand PrEP has not been shown to be effective for vaginal exposure and is not expected to be effective given that six to seven doses per week are required to achieve protective levels in cervicovaginal compartments.

Patients should be counseled that, once their HIV risk is reduced (i.e., a partner with HIV has initiated ART and maintained reliable HIV viral suppression), PrEP should be continued for an additional month to minimize risks of seroconversion. Condomless sex with a partner who has sustained viral suppression is associated with effectively no risk of HIV sexual transmission.[57-60] For additional information, see Reproductive Options for Couples When One or Both Partners Have HIV.

Adherence Support

Before initiating PrEP, providers should assess barriers to PrEP adherence and address concerns regarding PrEP use during the periconception, antepartum, and postpartum periods. The decision to initiate PrEP should be reached using a shared decision-making process, and barriers to PrEP adherence should be addressed at each visit. Data suggest that some adherence challenges stem from adherence fatigue, low personal perceptions of risk, stigma, cost, misinformation about PrEP, peer perspectives, mental health challenges, and intimate partner violence.[61-63] Based on barriers, providers can discuss strategies tailored to each woman's needs to promote adherence and maximize benefits. Approaches include providing accurate information about the risks and benefits of PrEP, developing reminder strategies, and identifying supportive individuals as part of the health care team or the woman's social network who can provide social support toward PrEP adherence. Just like HIV care, PrEP should ideally be delivered in a comprehensive manner and address social determinants of health, including how clients will make sure that PrEP and related services are affordable, and address housing instability, access to health insurance and transportation, since these factors have been shown to interfere with adherence. CDC provides PrEP resources for providers and consumers and a compendium of evidence-based PrEP support interventions.

Laboratory Testing

Recommended laboratory testing for individuals receiving PrEP should include HIV diagnostic testing with an antigen/antibody combination immunoassay at baseline and then every 3 months, or more frequently if indicated based on clinical symptoms. HIV testing for pregnant women taking PrEP should include HIV testing

at entry into antenatal care, with re-testing in the second and third trimester. More frequent testing may be appropriate for women when clinically indicated (e.g., adherence challenges, non-standard visit schedule). See Maternal HIV Testing and Identification of Perinatal HIV Exposure.

Renal function testing is recommended at baseline and then every 6 months, and pregnancy testing should be done at baseline and then every 3 months for those who can become pregnant. Testing for HBV infection should be performed before initiating PrEP. Individuals with no prior HBV infection who lack HBV immunity should be vaccinated if they have not received HBV vaccination or consider reimmunization if they have been vaccinated but still lack immunity. Individuals with chronic HBV should be monitored for possible hepatitis flares when PrEP is stopped.[64] Testing for STIs (gonorrhea, chlamydia, syphilis) is recommended at baseline and then every 3 months. Additional information and details about recommended laboratory testing is available in the CDC HIV Pre-Exposure Prophylaxis Guidelines. Clinicians are strongly encouraged to register women who become pregnant while receiving PrEP with the Antiretroviral Pregnancy Registry.

Individuals who are taking PrEP should be educated about the symptoms that are associated with acute HIV infection and advised to contact their providers immediately for HIV testing and further evaluation if symptoms occur (see Acute HIV Infection). Patients experiencing symptoms of acute retroviral syndrome should be instructed to use a condom during sex, stop attempts at conception, and stop breastfeeding. If HIV is documented, they should be immediately referred to an HIV specialist, started on ART, and receive appropriate care to prevent perinatal transmission if pregnancy has occurred.

Contraception

Contraception is an important component of reproductive health care for women receiving PrEP who do not want to become pregnant.[57] No known significant drug-drug interactions exist between TDF and different modes of hormonal contraception used during periconception and the postpartum period, although interactions with FTC have not been studied.[65,66] However, TDF/FTC PrEP does not seem to alter significantly the effectiveness of contraception for pregnancy prevention.[67] For additional information, refer to CDC's U.S. Medical Eligibility Criteria for Contraceptive Use, 2016, a subsequent update addressing hormonal contraception among women at high risk of HIV infection, and the most recent update regarding use of contraception by women at high risk of HIV infection.

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Preconception Counseling and Care for Women of Childbearing Age with HIV

(Last updated December 29, 2020; last reviewed December 29, 2020)

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. With the increasing prevalence of the opioid epidemic, 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., access to a syringe services program) **(AII)**. • Women with HIV should attain maximum viral suppression before attempting conception for their own health to prevent sexual HIV transmission to partners without HIV **(AI)** and to minimize the risk of *in utero* HIV transmission to the infant **(AI)**. • When selecting or evaluating an antiretroviral (ARV) regimen for women of childbearing age with HIV, consider a regimen's effectiveness, a woman's hepatitis B status, the teratogenic potential of the drugs in the ARV regimen, and the possible adverse outcomes for the mother and fetus **(AII)**. See Teratogenicity and 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 shared decision making regarding all ARV regimens for people with HIV **(AIII)**. • HIV infection does not preclude the use of any contraceptive method; however, drug-drug interactions between hormonal contraceptives, antiretrovirals, and other medications should be considered (see Table 3). **(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, tailoring education and counseling 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 requires integrating ongoing care and interventions into primary care to address the needs of women during the different stages of reproductive life. Integrating comprehensive family planning and preconception care into routine health care visits is important because almost half of all pregnancies in the United States are unplanned.[2–5] Providers should initiate and document a nonjudgmental conversation with all women of reproductive age about their reproductive desires because women may be reluctant to bring up the subject themselves.[6–10] Health care providers who routinely care for women of reproductive age with HIV play an important role in promoting preconception health and informed reproductive decisions. However, even among providers who offer primary care to women with HIV, the delivery of comprehensive reproductive counseling often falls short of the current guidelines.[11–13]

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 with HIV have specific needs that should be addressed.[14–17] 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 the experts of HIV and women's health, including experts in reproductive endocrinology and infertility when necessary.[6,18]
- Recognize that the primary treatment goal for women who are on antiretroviral therapy (ART) and are planning a pregnancy should include sustained suppression of plasma viral load below the limit of detection before conception, which is important for the health of the woman because the risk of perinatal HIV transmission is minimized and sexual HIV transmission to a partner without HIV is prevented (see Reproductive Options for Couples When One or Both Partners Have HIV).
- Explain to women that people with HIV who take ART as prescribed and who achieve and maintain an undetectable viral load have effectively no risk of transmitting HIV through sex, commonly known as Undetectable = Untransmittable or U=U. For more information, see Let's Stop HIV Together from CDC.
- 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. The use of opioids should be treated (e.g., with methadone or buprenorphine) and managed appropriately (e.g., provide access to syringe services program) when elimination is not feasible.
- Counsel women on maintaining a healthy diet and healthy weight before and during pregnancy.
- Counsel women who are contemplating pregnancy to take a daily multivitamin that contains 400 mcg of folic acid to help prevent neural tube defects (NTDs). Women with a history of having a child with NTDs, a family history of NTDs, or on certain anti-epileptic medications are candidates for receiving a higher dose (1–4 mg) of folic acid.
- Educate and counsel women about the risk factors for perinatal HIV transmission, the strategies to reduce those risks, and the potential effects of HIV or taking antiretroviral drugs (ARVs) during pregnancy on pregnancy course and outcomes. Education and counseling also should be directed at helping women to understand the recommendation that women 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 alternatives to infant feeding.
- Support women's shared decision making about ART and educating and counseling them about the factors that affect the selection of ARVs for women who are trying to conceive, pregnant women, or postpartum women. This support includes discussing the small but statistically significant increase in the risk of infant NTDs when dolutegravir (DTG) is taken around the time of conception with women who currently are receiving DTG as part of their ART regimen or with women who wish to be started on DTG. For more information, see Teratogenicity, updated guidance about the use of dolutegravir in pregnancy in Recommendations for Use of Antiretroviral Drugs During Pregnancy, Dolutegravir, and Appendix C: Antiretroviral Counseling Guide for Health Care Providers: Pregnant Women and Women who are Trying to Conceive.
- Consider the following factors when prescribing ART to women of childbearing age: the regimen's effectiveness, an individual's hepatitis B virus (HBV) status, the potential for teratogenicity, the likelihood of developing drug resistance, and the possible adverse outcomes for mother and fetus.[19–21]
- Use the preconception period to modify the ARV regimen for women who are contemplating pregnancy to optimize virologic suppression and minimize potential adverse effects (see Recommendations for Use of Antiretroviral Drugs During Pregnancy and Table 5).
- Recognize that women with perinatally acquired HIV may have special needs[22] (see Prenatal Care, Antiretroviral Therapy, and HIV Management in Women with Perinatal HIV Infection).
- Evaluate and manage therapy-associated adverse effects (e.g., hyperglycemia, anemia, hepatotoxicity) that may affect 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), which includes vaccination for influenza, pneumococcus, HBV, and tetanus. All women, including those with HIV, should receive Tdap (tetanus, diphtheria, and pertussis) vaccination during pregnancy.
- Offer all women who currently do not desire pregnancy the effective and appropriate contraceptive methods to reduce the likelihood of an unintended pregnancy. Women with HIV can use all available contraceptive methods, including hormonal contraception (e.g., pill, patch, ring, injection, implant) and intrauterine devices (IUDs).[23] Providers should be aware of potential interactions between ARV drugs, hormonal contraceptives, and other medications that could lower contraceptive efficacy or increase the risk of such adverse effects as blood clots (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). Emergency contraceptive pills that contain estrogen and progestin and those that only contain levonorgestrel (LNG) may have interactions with ARV drugs that are similar to the ones observed with combined oral contraceptives.[24] No data are available on potential interactions between ARV drugs and ulipristal acetate, a progesterone receptor modulator; however, ulipristal acetate is metabolized predominantly by cytochrome P450 (CYP) 3A4, so interactions may occur (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 ARVs and hormonal contraceptives primarily come from drug labels and several studies on the pharmacokinetics (PKs) and pharmacodynamics among the different forms of contraception and ARVs.[24–45] The contraceptive effectiveness of the levonorgestrel IUD is largely through local (i.e., intrauterine) release of levonorgestrel, not through systemic absorption. CDC's U.S. Medical Eligibility Criteria for Contraceptive Use lists the levonorgestrel IUD 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 the use of an IUD.

Hormonal contraceptives can be used with ARVs in women without other contraindications. Additional or alternative methods of contraception may be recommended when drug interactions are known. For women who are using ritonavir (RTV)-boosted protease inhibitors (PIs) and who are also on combination hormonal contraceptives (e.g., pills, patches, rings) or progestin-only pills, the use of an alternative or additional method of contraception may be considered because the area under the curve (AUC) of hormones may be decreased with the use of some RTV-boosted PIs (i.e., darunavir/ritonavir [DRV/r], fosamprenavir/ritonavir, and lopinavir/ritonavir [LPV/r]) but not 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 ARVs.[26,28,38,46] Doses of hormonal contraceptives do not need to be adjusted in patients who are receiving nucleoside reverse transcriptase inhibitors.

Although contraceptive implants (e.g., etonogestrel [ENG]/LNG) generally can be used in women who are receiving ARVs, both PK and clinical data suggest that these implants have decreased efficacy when used with efavirenz (EFV)-based regimens.[36,47–49] Scarsi et al. reported on three groups of Ugandan women with HIV: those who were not on ART (17 women), those taking nevirapine (NVP)-based ART (20 women), and those taking EFV-based ART (20 women) who had LNG implants placed and had LNG PK levels assessed at 1, 4, 12,

24, 36, and 48 weeks post-insertion. The geometric mean ratios of LNG concentrations (patients taking EFV-based ART vs. ART-naive patients) were 0.53 at 24 weeks and 0.43 at 48 weeks. Three pregnancies occurred in the EFV group (15%) between weeks 36 and 48, whereas no pregnancies occurred in the ART-naive or NVP groups.[40]

In a study of 570 women with HIV in Swaziland who had LNG implants (i.e., Jadelle), none of the women on NVP- or LPV/r-based regimens (n = 208 and n = 13, respectively) became pregnant, whereas 15 women on EFV (n = 121; 12.4%) became pregnant.[36] Because of their overall efficacy, implants remain as effective as or more effective than oral and injectable contraceptives among women with HIV who are using EFV, and all hormonal contraceptives remain more effective than no contraception among these women.[48,50] 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 percent of the women used implants (mostly LNG), 40 percent used injectables, and 14 percent used oral contraceptives; 31 percent of these women took ART during the follow-up period, mostly NVP-containing (75%) or EFV-containing (15%) regimens. Among women who were 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% confidence interval [CI], 0.01–0.45) and women who were not on ART (aHR 0.05; 95% CI, 0.02–0.11). Injectables and oral contraceptives also reduced pregnancy risk but to lesser degrees. ART use did not significantly diminish contraceptive effectiveness, although all methods showed nonstatistically significant reduced contraceptive effectiveness when a woman used EFV concurrently.[50]

In a retrospective study among 1,152 women with HIV and using either EFV or NVP and ENG or LNG implants, there were 115 pregnancies, yielding a pregnancy incidence rate of 6.32 (5.27–7.59), with a rate of 9.26 among ENG and 4.74 among LNG implant users, respectively. Pregnancy incidence rates did not differ between EFV- and NVP-based regimens (incidence rate ratio [IRR] = 1.00; 95%CI, 0.71–1.43). No pregnancies were recorded among women on PI-based regimens. Pregnancy rates of EFV- and NVP-containing regimens were similar at 6.41 (4.70–8.73) and 6.44 (5.13–8.07), respectively. Pregnancy rates differed by implant type with LNG implant users half as likely to become pregnant as ENG implant users (IRR = 0.51; 95% CI, 0.33–0.73, $P > 0.01$).[51]

Genetic contributions also may influence observed drug-drug interactions between contraceptives and ARVs. In a study of 19 women not on ART (control group), 19 women on EFV, and 19 women on NVP with ENG implants, the women in the EFV group with cytochrome P450 2B6 (CYP2B6) 516 G>T were associated with 43% lower ENG C_{min} and 34 percent lower $AUC_{0–24}$ at 24weeks. For patients on NVP, NR1I2 63396 C>T had lower ENG C_{min} and 37 percent lower $AUC_{0–24}$ at 24weeks.[44]

Other medications, such as those for tuberculosis (TB) treatment and ARVs, also may have drug-drug interactions with contraceptives. A pharmacokinetic study of DMPA among women with HIV/TB coinfection who received EFV-based treatment and rifampicin-based TB treatment showed that among 42 evaluable women, five women (11.9%; 95% CI, 4.0–25.6%) had medroxyprogesterone acetate (MPA) <0.1 ng/ml at week 12, the level above which ovulation is prevented; of these women, one had MPA <0.1 ng/ml at week 10. The median clearance of MPA was higher in women on EFV compared with women with HIV who were not on ART, thus leading to subtherapeutic concentrations of MPA in 12 percent of women at week 12.[52] The authors suggest redosing DMPA more frequently, such as every 8–10 weeks.

Because data are limited on pregnancy rates among women on different hormonal contraceptives and ARVs, some of 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 ARVs and combined hormonal methods, DMPA, and LNG and ENG implants. The smallest decrease in PK for which an alternative

method was recommended was a 14 percent decrease in norethindrone (with DRV/r). For women who are using atazanavir without RTV 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 the use of oral contraceptives that contain ≤30 µg ethinyl estradiol. The Panel does not recommend any change in ethinyl estradiol dose in women who are receiving etravirine (ethinyl estradiol increased 22%), rilpivirine (ethinyl estradiol increased 14%), or indinavir (ethinyl estradiol increased 25%, norethindrone increased 26%).

A contraceptive vaginal ring containing segesterone/ethinyl estradiol (Annovera) has been approved by the U.S. Food and Drug Administration. No available drug-drug interaction studies with this new contraceptive vaginal ring and ARV and CYP inducers/inhibitors are known. The contraceptive possibly could be metabolized in the same way as ENG and ethinyl estradiol in the NuvaRing. Our recommendation is extrapolated from what is known with the NuvaRing.

Table 3. Drug Interactions Between Antiretroviral Agents and Hormonal Contraceptives

Note: All recommendations in this table are based on consensus expert opinion. More details can be found in 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 for POPs	Dosing Recommendation/ Clinical Comment for DMPAa	Dosing Recommendation/ Clinical Comment for Etonogestrel Implants	Justification/ Evidence for Recommendation
NNRTIs							
EFV	**COC:** • No effect on EE concentrations • ↓ active metabolites of norgestimate; LNG AUC ↓ 83% and norelgestromin AUC ↓ 64%[29] • Etonogestrel (in COC) C_{24h} ↓ 61%[35] **DMPA:** • No effect on DMPA levels[26,28] **Etonogestrel Implant:** • ↓ 49% in Etonorgestrel concentration [45] • Etonogestrel AUC ↓ 63% to 82%[49,53] • ↑ pregnancy incidence rate among women using LNG or ENG implants, more among ENG users.[51]	**COC:** • No difference in pregnancy rates[50] • Pregnancy rate was 13% higher in women using COCs and EFV than in women using COCs alone[48,57] • Progesterone >3 ng/mL (a surrogate for ovulation) in three of 16 women[58] • No ovulations[29] **DMPA:** • No increase in pregnancy rates [26,48,50,55]	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.

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 for POPs	Dosing Recommendation/ Clinical Comment for DMPAa	Dosing Recommendation/ Clinical Comment for Etonogestrel Implants	Justification/ Evidence for Recommendation
NNRTIs, continued							
	LNG Implant: • ↓61% LNG concentration [45] • LNG AUC ↓ 47%[40] • LNG (emergency contraception) AUC ↓ 58%[24] • ↑ pregnancy incidence rate among women using LNG or ENG implants, more among ENG users.[51] **Changes in ARV Levels and/or Effects on HIV** *COC*: • No effect on EFV concentrations[29] • EFV C_{12h} ↓ 22%; was under therapeutic threshold in three of 16 subjects[35] *DMPA:* • No effect on HIV disease progression[26,54,55] • No effect on EFV concentrations[26]	• Low progesterone[26,28,55] **Etonogestrel Implant:** • Pregnancy rate higher with EFV compared with no ART, but still lower with implants than with other hormonal methods of contraception[48] • Presumptive ovulation in 5%[53] **LN Implant:** • 12% pregnancy rate[36] • 15% pregnancy rate[40] • Pregnancy rate higher with EFV compared with no ART, but still lower with implants than with other hormonal-					For implants, some studies suggest higher pregnancy rate and decreased hormone levels. For vaginally administered etonogestrel/EE, PK evaluation showed that etonogestrel levels were 79% lower and EE levels were 59% lower in participants on EFV than in controls after 21 days.[56]

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 for POPs	Dosing Recommendation/ Clinical Comment for DMPAa	Dosing Recommendation/ Clinical Comment for Etonogestrel Implants	Justification/ Evidence for Recommendation
NNRTIs, continued							
	LNG Implant: • No effect on HIV disease progression[40] **Vaginally Administered Etonogestrel/EE:** • Etonogestrel ↓ 79% EE ↓ 59%[56]	methods of contraception[48] • No increase in pregnancy rate[50]					For implants, some studies suggest higher pregnancy rate and decreased hormone levels. For vaginally administered etonogestrel/EE, PK evaluation showed that etonogestrel levels were 79% lower and EE levels were 59% lower in participants on EFV than in controls after 21 days.[56]
ETR	EE AUC ↑ 22%[59] No significant effect on NE[59]	**COC:** No ovulations[59]	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, one study found no ovulations and no significant change in progestin levels. No data on POPs.

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 for POPs	Dosing Recommendation/ Clinical Comment for DMPAa	Dosing Recommendation/ Clinical Comment for Etonogestrel Implants	Justification/ Evidence for Recommendation
NNRTIs, continued							
NVP	EE AUC ↓ 29%;[60] no change in EE AUC[61] NE AUC ↓ 18%[60] Etonogestrel (in COC) C_{24h} ↓ 22%[35] **DMPA:** • No significant change[26] **LNG Implant:** • LNG AUC ↑ 35%[40] • ↑ pregnancy incidence rate among women using LNG or ENG implants, more among ENG users.[51] **Changes in ARV Levels and/or Effects on HIV** *COC:* • No significant effect on NVP levels[58,60,62] *DMPA:* • No effect on HIV disease progression[26,54,55,63] *LNG Implant:* • No effect on HIV disease progression[40,64]	**COC:** • No increase in pregnancy[48,50,57,65,66] • No ovulations[58,61,66] **DMPA:** • No increase in pregnancy rate[48,50,55,65] • No ovulations[26] **Etonogestrel Implant:** • No increase in pregnancy rate[48] **LNG Implant:** No increase in pregnancy[36,40,48,50,64]	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. No effect on NVP levels. For DMPA, evidence does not show effects on pregnancy rate, ovulation, or DMPA levels. No effect on HIV disease progression. For implants, evidence does not show effects on pregnancy rate or HIV disease progression.

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 for POPs	Dosing Recommendation/ Clinical Comment for DMPAa	Dosing Recommendation/ Clinical Comment for Etonogestrel Implants	Justification/ Evidence for Recommendation
NNRTIs, continued							
RPV	EE AUC ↑ 14%[34] No significant change on NE[34] **Changes in ARV Levels and/or Effects on HIV** C*OC:* No change in RPV levels compared to historical controls[34]	**COC:** No change in progesterone[34]	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. No change in RPV levels. No data on POPs.
DOR	No clinically significant interaction with EE and LNG[67]	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.
RTV-Boosted PIs							
ATV/r	EE AUC ↓ 19%[68] Norgestimate AUC ↑ 85%[68] **POP:** • NE AUC ↑ 50%[69] **Vaginally Administered Etonogestrel/EE:** • Etonogestrel ↑ 71% • EE ↓ 38%[56]	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 one study. For POPs, increase in progestin levels seen in only one study. RTV inhibits CYP3A4, which may increase contraceptive hormone levels.

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 for POPs	Dosing Recommendation/ Clinical Comment for DMPAa	Dosing Recommendation/ Clinical Comment for Etonogestrel Implants	Justification/ Evidence for Recommendation
RTV-Boosted PIs, continued							
DRV/r	EE AUC ↓ 44%[70] NE AUC ↓ 14%[70]	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 data on POPS.
LPV/r	EE AUC ↓ 55%[25] NE AUC ↓ 17% **Patch:** • EE AUC ↓ 45%[25] • Norelgestromin AUC ↑ 83%[25] **DMPA:** • DMPA AUC ↑ 46%[38] **Etonogestrel Implant:** • Etonogestrel AUC ↑ 52%[53]	**COC:** • Increased pregnancy rate, but CIs overlap[48] **Patch:** • No ovulations[25] **DMPA:** • No pregnancies and no ovulations[38] • Increased pregnancy rate, but CIs overlap[48]	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. Progestin levels increased.

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 for POPs	Dosing Recommendation/ Clinical Comment for DMPAa	Dosing Recommendation/ Clinical Comment for Etonogestrel Implants	Justification/ Evidence for Recommendation
RTV-Boosted PIs, continued							
	Changes in ARV Levels and/or Effects on HIV *Patch:* • LPV/r ↓ 19%[25] *DMPA:* • No effect on HIV disease progression[38] • No change in LPV/r levels[38]	**Etonogestrel Implant:** • No increase in pregnancy rate[48] **LN Implant:** No increase in pregnancy rate[36,48]					For implants, evidence shows no effect on pregnancy rate. Progestin levels increased.
COBI-Boosted PIs							
ATV/c	Drospirenone AUC ↑ 2.3-fold No change in LNG concentration 25% decrease in EE C_{24}[42]	N/A	**Contraindicated** with drospirenone-containing hormonal contraceptives due to potential for hyperkalemia. Consider alternative or additional contraceptive method.	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	No data on POPs.
DRV/c	Drospirenone AUC ↑ 1.6-fold EE AUC ↓ 30%[43]	N/A	Clinical monitoring is recommended when DRV/c is used in combination with	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	No data on POPs

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 for POPs	Dosing Recommendation/ Clinical Comment for DMPAa	Dosing Recommendation/ Clinical Comment for Etonogestrel Implants	Justification/ Evidence for Recommendation
COBI-Boosted PIs, continued							
			drospirenone-containing COCs as a result of the potential for hyperkalemia. Consider alternative or additional contraceptive method.				
PIs without RTV							
ATV	**COC:** • EE AUC ↑ 48%[71] • NE AUC ↑ 110%[71]	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 the only data available are from the product label. No data on POPs
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 data on POPs

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 for POPs	Dosing Recommendation/ Clinical Comment for DMPAa	Dosing Recommendation/ Clinical Comment for Etonogestrel Implants	Justification/ Evidence for Recommendation
INSTIs							
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 • No change in DTG AUC[39]	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 data on POPs.
EVG/c	**COC:** • Norgestimate AUC ↑ 126% • EE AUC ↓ 25%[73,74]	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 four-drug regimen EVG/c/FTC/ TDF, increases in progestin and a small decrease in EE were observed. No clinical data. No data on POPs.
RAL	**COC:** • No change in EE • Norgestimate AUC ↑ 14%[75]	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 a small increase in progestin. No clinical data.

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 for POPs	Dosing Recommendation/ Clinical Comment for DMPAa	Dosing Recommendation/ Clinical Comment for Etonogestrel Implants	Justification/ Evidence for Recommendation
INSTIs, continued							
							No data on POPs.

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

Key to Symbols:
↑ = increase
↓ = decrease

Key: APV = amprenavir; ART = antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; AUC = area under the curve; BIC = bictegravir; C_{12h} = concentration at 12 hours post-dose; C_{24h} = concentration at 24 hours post-dose; CD4 = CD4 T lymphocyte; CDC = Centers for Disease Control and Prevention; CHC = combination hormonal contraceptives; CI = confidence interval; Cmin = minimum plasma concentration; COBI = cobicistat; COC/P/R = combined oral contraceptives/patch/ring; CYP = cytochrome P450; DMPA = depot medroxyprogesterone acetate; DOR= doravirine; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EE = ethinyl estradiol; EFV = efavirenz; ENG = etonogestrel; ETR = etravirine; EVG/c = elvitegravir/cobicistat; FPV = fosamprenavir; FPV/r = fosamprenavir/ritonavir; FTC = emtricitabine; IDV = indinavir; INSTI = integrase strand transfer inhibitor; LNG = 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 = protease inhibitor/ritonavir; 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 = tipranavir; 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 21a, 21b, and 21d.

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Reproductive Options for Couples When One or Both Partners Have HIV

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Panel's Recommendations

For Couples Who Want to Conceive When One or Both Partners Have HIV:
• Expert consultation is recommended to tailor guidance to couples' specific needs **(AIII)**.
• Both partners should be screened and treated for genital tract infections before attempting to conceive **(AII)**.
• Partners with HIV should achieve sustained viral suppression (e.g., two recorded measurements of plasma viral loads that are below the limits of detection at least 3 months apart) before attempting conception to maximize their health, prevent HIV sexual transmission **(AI)** and, for pregnant persons with HIV, to minimize the risk of HIV transmission to the infant **(AI)**.
• When partners have different HIV statuses, sexual intercourse without a condom allows conception with effectively no risk of sexual HIV transmission to the partner without HIV if the partner with HIV is on antiretroviral therapy (ART) and has achieved sustained viral suppression **(BII)**.
• Additional guidance might be required in the following scenarios:
  • The partner with HIV has not achieved sustained viral suppression or the partner's HIV viral suppression status is unknown,
  • There are concerns that the partner with HIV might be inconsistently adherent to ART during the periconception period, *or*
  • The provider wishes to share additional information with the patient regarding options to prevent sexual HIV transmission during the periconception period.
• In these circumstances, providers can choose to counsel their patient about the following options:
  • Administration of antiretroviral pre-exposure prophylaxis (PrEP) to the partner without HIV reduces the risk of sexual acquisition of HIV **(AI)** see Pre-exposure Prophylaxis (PrEP) to Reduce the Risk of Acquiring HIV During Periconception, Antepartum, and Postpartum Periods.
  • Timing condomless sex to coincide with ovulation (peak fertility) is an approach that can optimize the probability of conception **(AIII)**.
  • When partners with different HIV statuses attempt conception, the partner without HIV can choose to take PrEP even if the partner with HIV has achieved viral suppression **(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 safer 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 have HIV, expert consultation is recommended so that approaches can be tailored to their specific needs.

The Centers for Disease Control and Prevention (CDC) states that people with HIV who take antiretroviral therapy (ART) as prescribed and who maintain an undetectable viral load have effectively no risk of transmitting HIV through sex.[1] Couples in which one or both partners have HIV should be counseled that once the partner(s) with HIV have initiated ART and have maintained HIV viral suppression, condomless sex to achieve conception is associated with effectively no risk of HIV sexual transmission.[2–5] HIV viral suppression can be demonstrated with two recorded measurements of plasma viral loads that are below the limits of detection and that were taken at least 3 months apart.

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 increased genital tract shedding of HIV.[6,7]

If conception does not occur within 6 months, providers should pursue a workup for infertility, including a semen analysis. HIV, and possibly the use of antiretroviral (ARV) drugs, can be associated with a greater prevalence of semen abnormalities such as low sperm count, low motility, a higher rate of abnormal forms, and low semen volume. Early evaluation is indicated because of concerns about higher rates of infertility among people with HIV.[8–10] Coordination of care across multiple disciplines, including HIV primary care, OB/GYN (specifically reproductive endocrinology and infertility), case management, and peer support, is advised. Integration of reproductive health counseling, including counseling about pregnancy desires and/or prevention, is recommended.[11]

Couples with Differing HIV Status

Before attempting conception, the partner with HIV should be on ART and should have achieved sustained viral suppression. The implications of initiating therapy before conception, the selection of ART for women trying to conceive and the need for adherence to achieve durable plasma viral loads below the limits of detection should be discussed with the couple. Consultation with an expert in HIV care **is strongly recommended.**

In two large studies that included heterosexual couples with differing HIV statuses (HPTN 052 [HIV Prevention Trials Network trial 052] and PARTNER [Partners of People on ART-A New Evaluation of the Risks] study), no genetically linked HIV transmissions occurred while the partner with HIV was virally suppressed. HPTN 052 was a randomized clinical trial designed to evaluate whether immediately initiating ART in people with CD4 T lymphocyte (CD4) cell counts of 350 to 550 cells/mm³ 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 initiating ART earlier led to a 93% reduction in the rate of sexual transmission of HIV to the partner. During the study, 877 participants with HIV delayed initiation of ART until their CD4 cell counts fell below 250 cells/mm³, and 886 participants with HIV began ART immediately. Forty-six cases of HIV infection were genetically linked to the partner with HIV during the study; 43 of these cases occurred in couples where one partner delayed initiation of ART, and three cases occurred in couples where one partner began immediate ART. No linked infections occurred between partners when the partner with HIV had a viral load that was stably suppressed by ART. Thus, this randomized trial clearly demonstrated that providing treatment to persons with HIV can reduce the risk of HIV transmission to their sexual partners.[12] In addition, the PARTNER study—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—reported no cases of transmission after a median follow up of 1.3 years and approximately 58,000 condomless sex acts.[13]

A prospective cohort study evaluated couples with differing HIV statuses who were planning to conceive. Among 161 couples (133 couples included a male partner with HIV) where the partner with HIV received suppressive ART for at least the previous 6 months 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.[14]

For couples with differing HIV statuses where the partner with HIV is on ART and has achieved sustained viral suppression, sexual intercourse without a condom allows conception with effectively no risk of sexual transmission to the partner without HIV. It is not known how frequently viral load testing should be conducted when a patient is relying on treatment and viral suppression as a prevention strategy.[1] Not enough evidence currently exists to determine the optimal schedule for viral load testing in people with HIV who rely on this

prevention strategy. Consider monitoring the viral load more frequently in these individuals than the current treatment guidelines recommend.

Timing condomless sex to coincide with ovulation (peak fertility) can optimize the probability of conception. The use of an ovulation kit is the optimal method for identifying the most fertile time of the cycle.[15]

Pre-Exposure Prophylaxis and Other Options for Couples with Differing HIV Statuses and Inconsistent and Unknown Viral Suppression

For couples with differing HIV statuses who attempt conception via sexual intercourse without a condom when the partner with HIV has not been able to achieve viral suppression or when viral suppression status is not known, administering PrEP to the partner without HIV is recommended to reduce the risk of sexual transmission of HIV (see Prophylaxis (PrEP) to Reduce the Risk of Acquiring HIV During Periconception, Antepartum, and Postpartum Periods). PrEP is the use of ARV medications by an individual without HIV 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 (FTC) is currently approved by the Food and Drug Administration for use as PrEP. Tenofovir alafenamide (TAF) and FTC has also been approved for PrEP in men but not in women. **Adherence is critical**.

When a woman with HIV is in a relationship with a partner who does not have HIV, assisted insemination during the periovulatory period at home or in a provider's office with semen from her partner is an option for conception that eliminates the risk of HIV transmission to her partner.

When a man with HIV is in a relationship with a partner without 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. When a man with HIV is in a relationship with someone who does not have HIV, the use of sperm preparation techniques (e.g., "sperm washing" followed by testing the sample for HIV RNA), 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 PrEP in decreasing the risk of HIV transmission to sexual partners without HIV. Assisted reproductive technologies might be useful in cases of male infertility or for couples who are using donor sperm or a surrogate parent.

In addition to reducing the risk of HIV transmission between partners, starting ART before conception in women with HIV can also further reduce the risk of perinatal transmission.[16] Evidence suggests that early and sustained control of HIV can decrease the risk of perinatal transmission,[17,18] but it does not eliminate the risk completely.[18] 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 might be more frequent among women who are on ART at conception.[19–23]

Monitoring of Pregnant Women Without HIV Who Have Partners with HIV

Women without HIV who present during pregnancy and indicate that their partners have 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 (this is the opt-out strategy; see Maternal HIV Testing and Identification of Perinatal HIV Exposure). Women who test HIV seronegative and have partners with HIV should continue to be counseled regularly regarding consistent condom use to decrease their risk of sexual transmission of HIV if the partner with HIV has not achieved sustained virologic suppression. 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. Women should also 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 with acute HIV infection during pregnancy or lactation are at high risk of transmitting HIV to their infants and should receive HIV testing with an HIV RNA polymerase chain reaction assay if acute HIV infection is suspected (see Maternal HIV Testing and Identification of Perinatal HIV Exposure and Acute HIV Infection).[24,25] Repeat HIV testing in the third trimester is recommended for pregnant women who initially test HIV negative but who are at increased risk of acquiring HIV. Women who are at increased risk include those living in a city or state or ZIP code that is considered a high-risk jurisdiction by CDC. More frequent testing is indicated when a woman's partner has HIV; these women should be tested every trimester.

Monitoring of Men Without HIV Who Have Partners with HIV

Men without HIV who are attempting pregnancy with partners who have HIV should continue to be counseled regularly on methods to prevent acquisition of HIV, including suppressive ART for his partner and PrEP. CDC recommends HIV testing every 3 months for the partner who does not have HIV while the couple is attempting to conceive without condoms. The National Perinatal HIV Hotline (888-448-8765) is a resource for a list of institutions that offer reproductive services for couples where one or both partners have HIV.

Couples Where Both Partners Have HIV

Both partners with HIV should be on ART with sustained viral suppression before attempting conception. 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.[26]

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General Principles Regarding Use of Antiretroviral Drugs During Pregnancy

Panel's Recommendations
• Initial evaluation of pregnant women 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 (1-888-448-8765) provides free clinical consultation on all aspects of perinatal HIV care. • All pregnant women with HIV should initiate ART as early in pregnancy as possible, regardless of their HIV RNA level or CD4 T lymphocyte count, to maximize their health and prevent perinatal HIV transmission and secondary sexual transmission **(AI)**. Women with HIV should maintain an HIV viral load that is below the limit of detection during pregnancy, postpartum, and throughout their lives **(AII)**. • To minimize the risk of perinatal transmission, women with HIV should receive ART throughout pregnancy (including the intrapartum period), and neonates should receive appropriate antiretroviral (ARV) drugs **(AI)**. See Recommendations for Use of Antiretroviral Drugs During Pregnancy and Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection. • Women with HIV should be counseled on the known benefits and potential risks of all medications, including ARV drugs used during pregnancy and postpartum, as well as the importance of ART adherence. **(AIII)**. • ARV drug-resistance genotype evaluations or assays 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 copies/mL 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.** When 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 substance use disorder treatment services, intimate partner violence support services, and public assistance programs is essential to help ensure that women 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, lifelong HIV therapy, family planning and contraceptive options, infant feeding, infant ARV prophylaxis, and timing of infant diagnostic testing **(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 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 count;
- Current plasma HIV RNA level;
- Assessment of the need for prophylaxis against opportunistic infections, such as *Pneumocystis jirovecii* pneumonia (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), see Hepatitis B Virus/HIV Coinfection and Hepatitis C Virus/HIV Coinfection;
- Screening for and treatment of sexually transmitted infections (STIs), such as syphilis, *Chlamydia*

trachomatis, Trichomonas vaginalis, 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 the use of abacavir is anticipated (see Table 10);
- History of prior and current antiretroviral (ARV) drug use, including prior ARV drug use for the prevention of perinatal transmission or treatment of HIV;
- Assessment of the patient's self-affirmed gender identify, preferred pronouns, use of gender-affirming hormonal therapy, and potential interactions with ARV (see Transgender People with HIV);
- 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 (see Screening for Perinatal Depression);[6]
- Assessment of the need for supportive care (e.g., social services, mental health services, substance use disorder treatment services, smoking cessation services), as well as support to help ensure lifelong adherence to antiretroviral therapy (ART);
- Screening for intimate partner violence and assessment of the need for interventions or referrals for supportive care;
- Assessing the HIV status of sexual partner(s) and referral of partner(s) for HIV testing and ARV treatment or prophylaxis as needed (see Pre-Exposure Prophylaxis [PrEP] to Reduce the Risk of Acquiring HIV During Periconception, Antepartum, and Postpartum Periods); *and*
- Referral of children for HIV testing.

The National Perinatal HIV Hotline

The National Perinatal HIV Hotline (1-888-448-8765) is a federally funded service that provides free clinical consultation to providers who are caring for women with HIV and their infants.

How Antiretroviral Drugs Prevent Perinatal Transmission and Improve Maternal Health

All pregnant women with HIV should receive ART early in pregnancy, regardless of their viral load or CD4 count, to maximize their health and to prevent perinatal HIV transmission and secondary sexual transmission. ARV drugs are important for maintaining maternal health, because they decrease the rate of HIV disease progression, reduce the risk of opportunistic disease, and reduce the risk of maternal death.

ARV drugs reduce the risk of perinatal transmission of HIV in all pregnant women, regardless of their CD4 counts and HIV RNA levels. ARV drugs can reduce the risk of 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 and sustained 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] Studies have reported low-level cervicovaginal HIV RNA and DNA shedding in women who were on ART and who had 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, because maternal viremia is not the only risk factor for perinatal 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 ARV 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 the risk of perinatal transmission is demonstrated by the reduced efficacy of interventions that

involve administration of ARV drugs only during labor and/or to the newborns.[21-28] Therefore, using a combination of 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 or presumptive HIV therapy is recommended to prevent perinatal transmission of HIV.

General Principles of Drug Selection

In general, the recommendations 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 Antiretroviral 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 4 and Recommendations for Use of Antiretroviral Drugs During Pregnancy).

Clinicians and patients should discuss the substantial benefits of ARV drugs for maternal health and for reducing the risk of transmission of HIV to infants; this helps put the potential risks of using these drugs into perspective (see Table 10 and Appendix B: Supplement: Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy). Counseling of pregnant women about ARV drug 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 ARV regimens should include information about the following:

- Maternal risk of disease progression and the benefits and risks of therapy for maternal health;[29]
- The benefits of ART for preventing perinatal transmission of HIV;[11]
- The benefits of using ART to achieve and maintain viral suppression, which reduces the risk of sexual transmission to partners who do not have HIV;[30]
- The need for strict adherence to the prescribed drug regimen to avoid resistance, optimize health outcomes, and minimize the risk of perinatal HIV transmission;
- The potential adverse effects of ARV drugs for women, fetuses, and infants, including potential interactions with other medications the women may already be receiving (see Recommendations for Use of Antiretroviral Drugs During Pregnancy);[31-34] *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 standard genotypic resistance testing (i.e., >500 copies/mL to 1,000 copies/mL), ARV drug-resistance testing should be sent for analysis before starting ART; however, ART should be initiated before results of drug-resistance testing are available, because earlier viral suppression is associated with a lower risk of perinatal transmission.[35,36] The ARV regimen can be modified, if necessary, based on resistance assay results[37] (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 loads at delivery.[38]

Transplacental passage of ARV drugs is thought to be an important mechanism of infant pre-exposure prophylaxis. Thus, when selecting a regimen for a pregnant woman, ARVs with high placental transfer should be included as a component of the ARV regimen (see Table 10).[39-43]

Patient Counseling and Coordination of Care

Coordination of services among prenatal care providers, primary care and HIV specialty care providers, mental health and substance use disorder treatment services, social services, and public assistance programs is essential to ensure that women with HIV are well supported during all stages of their pregnancies and during the postpartum period. Medical care of pregnant women with HIV requires coordination and communication between HIV specialists and obstetric providers. General counseling should include current knowledge about risk factors for perinatal HIV transmission. Risk of perinatal transmission of HIV has been associated with potentially modifiable factors, including cigarette smoking, substance use disorders, 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 screened for mental health conditions, assessed for the risk of intimate partner violence, and counseled about disclosure of their HIV status when needed.[44] It is important to be aware that COVID-19 may increase the risk of depression, substance use, and intimate partner violence at a time when the frequency of in-person health care services has decreased (see Interim Guidance for COVID-19 and Persons with HIV). Fears of stigma and violence that could result from disclosure require comprehensive culturally informed services to assist pregnant and postpartum women planning to disclose their status,[45,46] and women who have not disclosed their status require support to maintain privacy during telemedicine visits. Transgender and non-binary individuals may have specific concerns, particularly regarding interactions of ARV drugs with gender affirming-hormones, that should be assessed and addressed.

In addition, providers should counsel women with HIV about what to expect during labor, delivery, and the postnatal period. This includes discussing 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 (see Counseling and Managing Women with HIV in the United States Who Desire to Breastfeed).

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Teratogenicity

(Last updated December 29, 2020; last reviewed December 29, 2020)

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 very small potentially 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 and evolving. • Currently, in the United States there are not enough data to determine the risk of NTDs with preconception use of many of the *Preferred* and *Alternative* regimens, including DTG. • DTG exposure around the time of conception has been associated with a small but significant increase in the prevalence of infant NTDs in Botswana, where food is not routinely fortified with folate. Although this prevalence of NTDs with periconception DTG (0.19%) was higher than the prevalence for NTDs in infants born to women who were receiving efavirenz (0.07%) and women without HIV (0.07%), the risk was not significantly increased compared to women with HIV receiving any non-DTG ARV regimen at conception (0.11%, risk difference [0.09% difference; 95% CI 0.03%, 0.30%]). • 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 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 C: Antiretroviral Counseling Guide for Health Care Providers: Pregnant Women and Women who are Trying to Conceive. • Clinicians should discuss future reproductive plans and timing, as well as the risks and benefits of conceiving on specific ARV medications and the 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)**. For additional information, see Recommendations for Use of Antiretroviral Drugs During Pregnancy, Preconception Counseling and Care for Women of Childbearing Age with HIV, Pregnant Women with HIV Who Are Currently Receiving Antiretroviral Therapy.
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 (APR) 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 APR 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 also must 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 administered during pregnancy, in addition to data on the long-term safety in infants who were exposed to these drugs *in utero*. However, the data remain 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 are 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]

It is important to consider potential confounding factors in studies of ARV drugs and birth defects. Several factors that are associated with HIV also may increase the risk of birth defects, such as exposure to folate antagonists (e.g., trimethoprim-sulfamethoxazole),[3] nutritional and folate status,[4] and tobacco and alcohol use.[5] Clinicians also should 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 various ARV regimens during observational studies found no difference in rates of total birth defects between first-trimester drug exposures and later exposures.[6–10] The APR 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] Although 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. Furthermore, risk may be underestimated when defects are ascertained only after live births, because 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.

When considering whether a woman should continue an effective antiretroviral regimen when she presents in early pregnancy, the potential risk of viral rebound with switching regimens must be considered, as well as the specific or unknown risks for birth defects of the current drug regimen and stage of gestation.[11] For additional information, see Pregnant Women with HIV Who Are Currently Receiving Antiretroviral Therapy.

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 cases of NTDs among infants born to 426 women (0.94%) who became pregnant while receiving a DTG-based regimen.[12] These data were updated in a planned analysis in March 2019 and again in April 2020. In the most recent analysis of the Tsepamo study in Botswana, seven NTDs were identified (0.19%) among 3,591 deliveries to women who were taking DTG around the time of conception; the defects included three instances of myelomeningocele, one of anencephaly, two of encephalocele, and one of iniencephaly. In comparison, 21 NTDs were found among 19,361 deliveries (0.11%) in which the mother was taking any ART that did not include DTG at conception, eight NTDs were found among 10,958 deliveries (0.07%) in which the mother was taking efavirenz (EFV) at conception, two NTDs were found among 4,581 deliveries (0.04%) in which the mother started treatment with DTG during pregnancy, and 87 NTDs were found among 119,630 deliveries (0.07%) to mothers without HIV.[13] The risk of NTDs in infants who were exposed to DTG around the time of conception (0.19%) remains significantly higher than among infants exposed to EFV (0.07%) and infants born to women without HIV (0.07%) but is no longer significantly elevated compared to infants exposed to any non-DTG ARV (0.11%, risk difference 0.09%, 95% CI -0.03%, 0.30%) around conception. Although some increased risk of NTDs with DTG exposure in early pregnancy in the setting without folate food supplementation continues to be noted, the risk is lower than originally observed.

Although there are limited data on the association between NTDs and DTG exposure, two 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 APR, 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 382 live births (0.26%) of infants with periconception DTG exposure and no NTDs among 298 live births of infants with periconception elvitegravir (EVG) exposure and 327 live births of infants with periconception raltegravir (RAL) exposure.[1] An additional retrospective study that did not include evaluation of defects in stillbirths or terminations evaluated infants born to 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, 0.0–0.0099) or among 1,109 pregnancies in which infants were exposed to EFV or RAL (95% CI, 0.0–0.003).[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 on integrase inhibitors periconceptionally 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, although 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 tenofovir disoproxil fumarate (TDF) plus emtricitabine (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 are unclear.[17,18] Additional studies are needed to clarify the role of folate and to explore other potential mechanisms.

The risk of NTDs decreases after early pregnancy, although 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.[19] 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 (DRV/r) was switched to atazanavir (ATV) plus EVG/cobicistat/FTC/TDF at 9 weeks because of 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.[20] In the APR, defects were reported in 11 of 323 infants (3.4%; 95% CI, 1.7% to 6.0%) 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 APR, reported 155 prospective periconception exposures to EVG with no NTDs.[21] Review of a surveillance database in Canada found no NTDs among 28 infants with first-trimester exposures.[10]

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.[20] 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 APR, birth defects were reported in 13 of 422 infants (3.1%; 95% CI, 1.7% 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 APR data, and data from the United Kingdom, Ireland, and French pregnancy cohorts reported

456 periconception exposures to RAL with no NTDs.[22]

The Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission continues to review and update its recommendations regarding the use of ARV drugs during pregnancy and at the time of conception (see Recommendations for Use of Antiretroviral Drugs During Pregnancy, Preconception Counseling and Care for Women of Childbearing Age with HIV, and the Adult and Adolescent Antiretroviral Guidelines). The benefits and risks of ARV drugs, including the potential risk of NTDs, the benefits and risks of changing antiretroviral therapy should be discussed with women who need to initiate ART during the first trimester or who are planning to become pregnant or are currently taking ART (see Appendix C: Antiretroviral Counseling Guide for Health Care Providers: Pregnant Women and Women who are Trying to Conceive). 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 similar to human therapeutic exposures.[23] 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 APR to rule out at least a 1.5-fold increase in the risk of overall birth defects and a twofold increase in risk of birth defects in the cardiovascular and genitourinary systems. Twenty-seven of 1,142 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).[24] The number of reported first-trimester EFV exposures in this meta-analysis is sufficient to rule out a twofold increase in low-incidence birth defects, such as NTDs. Incidence of NTDs in the general U.S. population is 0.02% to 0.2%.[2,24] A recent report from a South African pregnancy exposure registry of births at a single hospital found no increase in risk of congenital malformations with EFV exposure at conception (1/297, 0.3%) compared with infants born to women without HIV (29/7,532, 0.4%).[25]

The Tsepamo study discussed above found eight NTDs among 10,958 live births and stillbirths (0.07%) to women who were on EFV at conception, which was identical to the prevalence of NTDs among infants born to women without HIV.[26] 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 with women without HIV (0.68% vs. 0.59%).[26] 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.[27] 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.

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* EFV exposure. The relative risk of microcephaly in infants with *in utero*

EFV exposure was 2.56 (95% 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.[28] 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 TDF and 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.

The EFV package insert advises women to avoid becoming pregnant while taking EFV and advises health care providers to avoid administering EFV during the first trimester of pregnancy, because fetal harm may occur. However, with the data from Botswana on nearly 11,000 periconception exposures, we can now rule out a threefold 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.[29] 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 APR showed that 91 of 3,851 (2.4%) infants born to women with first-trimester TDF exposure had birth defects, which is 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).[30]

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.[31] 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.[32] 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 with infants who had 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).[33] 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.[5]

Atazanavir

In an analysis from the PHACS that included 2,580 live births, first-trimester ARV drug exposure overall was

not associated with an increased risk of birth defects.[34] However in an adjusted analyses, ATV was the only individual ARV drug for which first-trimester exposure, occurring in 222 infants, was associated with birth defects (primarily skin and musculoskeletal defects). In the APR, no increase was evident in the risk of birth defects with first-trimester ATV exposure among 1,328 births.[1]

Rilpivirine

A report from the French Perinatal Cohort evaluated pregnancy outcomes among women receiving rilpivirine (RPV). Among 247 women receiving RPV at conception, livebirths occurred in 241 cases, with birth defects noted in 3.8% (95% CI, 1.6% to 7.7%), including three infants with heart defects, three with lower-limb malformations, and one with renal hypoplasia.[11] Of note, viral rebound occurred in 20% of women who were changed to other regimens because of concerns regarding limited safety data and concerns about PK changes compared to none of the women maintained on RPV. In the APR, seven defects were reported among 495 first-trimester RPV exposures; 1.4% (95% CI, 0.6% to 2.9%) compared with a 2.7% total prevalence of birth defects in the U.S. population based on Centers for Disease Control and Prevention surveillance.[1]

Other Antiretroviral Drugs

In the APR, sufficient numbers of first-trimester exposures have been monitored to detect at least a twofold increase in the risk of overall birth defects for cobicistat, darunavir, didanosine (ddI), EVG, indinavir, ralteravir, rilpivirine, stavudine, and telbivudine; however, no such increases have been detected to date. For abacavir, ATV, EFV, FTC, 3TC, lopinavir, nelfinavir (NFV), nevirapine, RTV, 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 twofold 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 APR 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 with the Texas Birth Defect Registry rate of 4.17%, an additional comparator now included in the APR. 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 APR 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.

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Antiretroviral Drug Regimens and Maternal and Neonatal Outcomes

(Last updated December 29, 2020; last reviewed December 29, 2020)

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 (ART). However, given the clear benefits of ART for both a woman's health and the prevention of perinatal transmission, HIV treatment should not be withheld due to concern for adverse 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

In this section, the Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission (the Panel) provides a summary of data on antiretroviral therapy (ART) and adverse maternal and neonatal outcomes published since 2015.Women with HIV, regardless of antiretroviral (ARV) drug use, may be at increased risk for adverse neonatal outcomes. These outcomes may include preterm delivery (PTD) (delivery before 37 weeks gestation), very preterm delivery (vPTD) (delivery before 32 weeks gestation), low birth weight (LBW) infants (those weighing <2,500 g), small-for-gestational-age (SGA) infants (those with a birth weight <10th percentile expected for gestational age), and stillbirth (delivery of a nonviable infant after 20 weeks). The gestational age cut-off used to define stillbirth in the studies described varies by gestational age from ≥20 weeks to ≥28 weeks. Limited data suggest a potential association between HIV infection and maternal complications of pregnancy, such as hypertensive disorders of pregnancy (HDP) (pregestational hypertension, gestational or pregnancy-induced hypertension, pre-eclampsia, and eclampsia). Some of the data described in this section include historical HIV treatment strategies, such as single-drug and two-drug ARV regimens, and older ARV drugs that are no longer commonly prescribed. For additional historical data related to this topic, please refer to the archived versions of this section. For information related to ARV use and teratogenicity (birth defects), please refer to Teratogenicity and the individual drug sections in Appendix B and Table 10.

Key Points

Maternal ARV use for the prevention of perinatal HIV transmission, especially pre-conception or in the first trimester, may be associated with an increase in PTD. The Panel does not recommend that women with HIV stop ART before conception or in early pregnancy for the purpose of preventing PTD.

ART that contains boosted lopinavir (LPV/r) may increase the risk of PTD compared with other boosted protease inhibitor (PI)-based regimens. For pregnant women who require PI-based regimens during pregnancy, the Panel recommends the use of darunavir/r (DRV/r) or atazanavir (ATV/r).

Infants exposed to ART before birth may be at increased risk of being LBW or SGA. Maternal ARV use during pregnancy may be an indication for enhanced antenatal surveillance, such as ultrasound, to evaluate for poor fetal growth.

Stillbirth is a rare outcome in resource-rich settings, and data related to stillbirth and ARV use are limited. The Panel cannot make a specific recommendation regarding the prevention of stillbirth among women with HIV.

Limited data suggest an association between HDP and maternal HIV, but no known interventions effectively

reduce this risk. Providers should not withhold or adjust ART for the purpose of preventing HDP.

Interpretation of Adverse Pregnancy Outcomes Data

The association between ARV use and preterm birth, fetal growth restriction, and stillbirth has been an area of research for many years, with multiple studies that include conflicting results. These outcomes are common and often occur without an identifiable cause, so it can be difficult to establish a causal link with a medication in an individual case. However, because these outcomes are relatively common, even a small increase in risk can have a substantial public health impact.

Much of the conflicting data in earlier studies about ARV drugs and adverse pregnancy outcomes can be ascribed to the use of inappropriate comparison groups and failure to stratify the data by timing of ARV initiation (before or after conception). Potential associations between ART and adverse pregnancy outcomes are difficult to establish because of the challenge of finding appropriate comparator groups. Women with HIV who do not receive ART in pregnancy are not an appropriate comparator, because they have an increased risk of adverse outcomes due to their immunocompromised status. Comparing pregnant women on ART to women without HIV is confounded by HIV status. Growing evidence suggests that the risk of adverse outcomes varies by ARV drug, even within ARV drug classes. Risks of adverse outcomes may also depend on the timing of ART initiation. A suggested approach to evaluate ART and pregnancy outcomes is to use a comparative safety approach in which ARV regimens or ARV drug classes are compared with each other. Unfortunately, many available studies continue to use comparison groups of women without HIV and women with HIV who are not on ARVs or who are on a single-drug or two-drug ARV regimen, which are no longer recommended for treatment in pregnancy. More studies are needed to fully evaluate the association between the risk of adverse pregnancy outcomes and the use of specific ARV drugs, classes of ARVs, and ART.

Preterm Delivery

Several meta-analyses and systematic reviews are available to evaluate the potential association of ARV use and PTD. Three large meta-analyses did not demonstrate a significant association between ARV use and PTD. The sample sizes pooled for these meta-analyses ranged from 14 to 90 studies and included 11,224 to 37,877 women and/or infants. Most of the studies that were included in these meta-analyses were observational studies, and most were older studies that do not include some of the ART or ARV drug classes currently used.[1–3] The meta-analysis by Kourtis et al. showed a modest, but statistically significant, increase in the risk for PTD in women who initiated ART before pregnancy or during the first trimester, compared with women who initiated ART during the second trimester or later (odds ratio [OR] 1.71, 95% confidence interval [CI], 1.09–2.67).[1] The meta-analysis by Nachega et al. compared pregnancy outcomes between women who received tenofovir disoproxil fumarate (TDF)-based regimens and women who received regimens that did not contain TDF. This study found no difference in the risk of PTD between these two groups. A recent network meta-analysis of seven randomized controlled trials evaluated seven different ART regimens and their associations with PTD (including spontaneous PTD in three trials), LBW (six trials), and SGA (two trials).[4] An overall increase in PTD was associated with ART regimen ZDV/3TC/LPV/r compared with ZDV single-drug regimen (n = 5,789, relative risk [RR] 1.43, 95% CI, 1.08–1.91), and, compared with ZDV/3TC/ABC, ZDV/3TC/LPV/r was associated with an increased risk of spontaneous PTD (sPTD) (n = 991, RR 1.81, 95% CI, 1.21–2.71). There were no differences in vPTD between the regimens evaluated (4 trials, n = 1,819).[4]

Among the observational studies that reported an association between the use of ARVs and PTD, the RRs/ORs for PTD ranged from 1.2 to 3.4.[1,5–27] Some studies have reported increased rates of PTD when ART is initiated before pregnancy or during early pregnancy compared to later in pregnancy. Variability in the available data may be a factor in conflicting results. Maternal factors, such as HIV disease severity, may have affected the timing of ART initiation during pregnancy and may be associated with PTD independent of ARV use.[28–31] In general, none of the studies reviewed in this section have comprehensively controlled for all factors that may

be associated with PTD. A recent observational study that evaluated ARV use among women with HIV in British Columbia reduced confounding variables by excluding multigestation pregnancies and antiquated ARV regimens (single- and two-drug therapy, and triple nucleoside reverse transcriptase inhibitor [NRTI] regimens). They determined that women with HIV were twice as likely to experience PTD as the general population. Compared with women who were not on ART during pregnancy, women who were on any ART were less likely to have sPTD (hazard ratio [HR] 0.54, 95% CI, 0.29–1.04), and the protective effect for each week of ART was cumulative (HR 0.98, 95% CI, 0.96–0.99). Neither preconception/first-trimester ARV use nor PI-based ART was associated with PTD.[32]

Preterm Delivery and Antiretroviral Therapy Exposure Before Pregnancy

Some studies report an association between initiating ART before pregnancy and PTD, reporting RRs and ORs that range from 1.20 to 2.05.[5,21–23,26,31,33–36] These studies were conducted in Asia, Europe, Latin America, Africa, and North America and included various ART (including no ART and single-drug, two-drug, and multidrug regimens). The association between PTD and ARV use prior to conception is attenuated in some multivariate analyses.[17,21,36–38] An observational study of >2,000 women on multidrug ART did not show an association between ART initiation before pregnancy and PTD.[34] Certain ART, such as regimens that contain LPV/r, may be more closely associated with PTD than others.

Antiretroviral Therapy Regimens That Are Associated with Preterm Delivery

Protease Inhibitor-Based Regimens

The association between the use of protease inhibitor (PI)-based ART and PTD has been investigated in multiple studies. These studies include populations in Europe, North America, and Africa. The RRs/ORs of PTD reported in these studies range from 1.14 to 3.4.[1,4,5,7–9,11,16,18,20,21,23,35,36,39–42] However, a small meta-analysis of 10 studies (eight prospective cohort studies, one randomized controlled trial, and one surveillance study) demonstrated that the use of PI-based ART is associated with an increased risk of PTD, 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 not significant.[43]

Not all the studies reviewed for this section have identified an association between PI use and an increased risk of PTD. Seven studies did not demonstrate a significant association between PI based ART and PTD.[18,32,39–41,44,45] For example, a retrospective Canadian study of women who were on regimens that included unboosted PIs did not report increased rates of PTD among these women.[18]

Regimens that include PIs boosted with ritonavir may be associated with an increased risk of PTD compared with unboosted PI regimens. The Promoting Maternal and Infant Survival Everywhere (PROMISE) trial study compared outcomes in women who received zidovudine (ZDV) alone with outcomes in women who received LPV/r-based ART with a two-drug NRTI backbone of either ZDV plus lamivudine (3TC) or emtricitabine (FTC) plus TDF initiated during pregnancy. Compared to women who received ZDV alone, women who received ZDV/3TC/LPV/r had higher rates of PTD (13% vs. 20.5%; $P < 0.001$). PTD rates among women who received TDF-based ART and those who received ZDV-based ART were not statistically different (19% vs. 18%; $P = 0.77$).[46] Sebikari et al. published a follow-up study of the PROMISE trial. After controlling for other risk factors, receipt of either ZDV/3TC/ LPV/r or FTC/TDF/ LPV/r remained associated with PTD. The aOR of PTD for women who received ZDV/3TC/LPV/r compared to ZDV alone was 1.8 (95% CI, 1.5–2.3), and the aOR for women who received FTC/TDF/LPV/r compared to ZDV alone was also 1.8 (95% CI, 1.3–4.0). Comparing these two LPV/r-based regimens with each other found no significant difference in the risk of PTD (aOR 0.97; 95% CI, 0.72–1.31).[42]

An observational study of >6,000 women in the United Kingdom and Ireland demonstrated increased rates of PTD among women with HIV who were on PI-based ART before pregnancy, especially regimens that contained LPV/r. This effect was increased when the women had CD4 T lymphocyte (CD4) cell counts <350 cells/mm³ (aOR 1.99; 95% CI, 1.02–3.85).[23] An observational study combined data from the Surveillance Monitoring for ART Toxicities (SMARTT) study and the International Maternal and Pediatric Adolescent AIDS Clinical Trials (IMPAACT) for a total of 4,646 live-birth outcomes. Risk of PTD was similar or slightly higher in women who received FTC/TDF/LPV/r compared with women who received FTC/TDF/ATV/r. Among women who initiated ART before conception, the risk of PTD was higher for the LPV/r regimen.[21] In a follow-up study, these authors evaluated the impact of ART among women who had enrolled in SMARTT and experienced subsequent pregnancies. Notable limitations of this study were inclusion of iatrogenic PTDs, counting more than one subsequent delivery for some participants, and the potential for short interval pregnancy effect. In subsequent pregnancies, women starting PI-based ART in the first trimester experienced an increased risk of PTD (OR 1.97, 95% CI, 9.27–3.07). This effect was not seen with preconception PI-based ART or second-and third-trimester ART initiation.[36] Although more prospective data are needed, ART that contains LPV/r may increase the risk of PTD compared to regimens that contain other ritonavir-boosted PIs. Despite this potential association between the use of PI-based ART and PTD, some pregnant women may require PI-based regimens. In these cases, the Panel recommends the use of DRV/r or ATV/r over LPV/r.

Nucleoside Reverse Transcriptase Inhibitor–Based Regimens and Non-Nucleoside Reverse Transcriptase Inhibitor–Based Regimens

Fewer studies have evaluated the risk of PTD among women on non-PI-based regimens. A meta-analysis of 17 studies of women with HIV who were on ART (n = 37,877) compared those on TDF regimens with women who were on regimens that did not include TDF. TDF-based ART was associated with a modest reduction in the rate of PTD (RR 0.9; 95% CI, 0.81–0.99; I^2 = 59%); however, there was no significant difference in the risk of very PTD between these two groups.[2] Some observational studies have shown an association between the use of non-PI based regimens and PTD. When compared with women without HIV, South African women with HIV who were taking NPV/FTC/TDF had higher rates of PTD (aOR 1.2; 95% CI, 1.0–1.5).[22] When compared with women without HIV, women who were taking EFV/FTC/TDF were at increased risk of PTD.[25] As stated in the introduction, using women without HIV as a control group may be an inappropriate study design choice. Another study of South African women who received EFV/FTC/TDF did not show an increased risk of PTD, SGA infants, or LBW infants when these women were compared with women who were on NVP-based ART or other multidrug regimens.[34]

Integrase Strand Transfer Inhibitor-Based Regimens

Integrase strand transfer inhibitors (INSTIs) are preferred ARVs for HIV treatment. As INSTI use increases among persons with HIV, INSTI exposure during pregnancy is observed more often.[32,36,47,48] Limited data from observational studies are available to assess the relationship between INSTI-based regimens and PTD. In the Tsepamo study, women who initiated EFV/FTC/TDF or DTG/FTC/TDF during pregnancy were at increased risk of PTD (aOR 1.2; 95% CI, 1.1–1.3) compared with women without HIV. However, when these regimens were compared with one another, no significant differences existed in the risk of PTD.[24] This study was included in a systematic review of six sources (two cohort studies, three databases, and one report) that was designed to evaluate adverse pregnancy outcomes related to DTG exposure. A total of 845 women who received DTG/FTC/TDF were compared with 4,593 historical controls who received EFV/FTC/TDF, and no clear difference existed in the risk of PTD between these groups.[49] Pooled data from the Antiretroviral Registry (APR) (n = 265) and the European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC) (n = 101) determined that rates of PTD among women on ART containing DTG were similar to or slightly higher than the general population (10.9% APR and 13.8% EPPICC).[50] Women in the Pediatric HIV/AIDS Cohort (PHACS) SMARTT study who initiated INSTIs during the first trimester had an increased risk of PTD in subsequent pregnancies (OR 2.39, 95% CI, 1.04–5.46). Limitations to this study are detailed in the previous section.[36] In an observational study of women with HIV in British Columbia, INSTI use was not associated with an increased

risk of PTD.[32] Additional studies are needed to determine potential impact of INSTI use in pregnancy outcomes.

Birth Weight

For the purpose of this section, abnormalities of birth weight related to ARV use are commonly reported as LBW infants (those weighing <2,500 g) or SGA infants (those with a birth weight <10th percentile expected for gestational age). LBW may be a reflection of preterm birth or growth restriction; SGA may be a reflection of growth restriction or constitutionally small infants. Given that LBW and SGA may be caused by different mechanisms, this section discusses studies that have reported LBW and SGA separately.

Low Birth Weight

Multiple studies have demonstrated an association between any ARV use and LBW infants.[19,22,45,46,51–55] Reported rates of LBW among infants who were exposed to ART range from 7.4 percent to 36 percent.[3,11,17,19,21,22,24,30,35,37,39,41,42,46,52,53,56,57] In a systematic review of 13 studies (nine observational studies and four randomized controlled trials) that compared ZDV single-drug therapy with NNRTI- and PI-based regimens, the NNRTI- and PI-based regimens were associated with LBW infants.[27] In a network meta-analysis of six RCTs (n = 5,471), when compared to ZDV alone, ZDV/3TC/LPV/r was associated with the highest risk of LBW (RR 1.87, 95% CI, 1.58–2.2).[4] In a Chinese cohort of 748 infants exposed to either NVP, EFV, or LPV/r with a two-drug NRTI backbone, any preconception ARV use was associated with an increased risk of LBW infants (aOR 1.92; 95% CI, 1.1–3.4).[26] An observational study that included 4,646 births reported an increased risk of LBW infants among women who received preconception FTC/TDF/LPV/r compared with those who received FTC/TDF/ATV/r (unadjusted risk ratio 1.97; 95% CI, 1.2–3.4).[21] Women enrolled in the PROMISE trial who were randomized to ART following their first delivery or after breast feeding had increased risk of having LBW infants in subsequent pregnancies (OR 2.65, 95% CI, 1.2–5.81 and 2.94, 95% CI, 1.24–6.98, respectively).[57]

Small for Gestational Age

Among infants born to women with HIV, the reported rates of SGA infants range from 7.3 percent to 31 percent.[14,17,19,22–25,30,34,37,44,45,58,59] A South African prospective observational study reported that women with HIV were more likely to have SGA infants than women without HIV (14% vs. 8%).[25] Three studies in Botswana reported a positive association between ARV use (for both PI-based and PI-sparing regimens) and SGA.[14,35,60] In a study that compared the effects of initiating single-drug therapy during pregnancy with the effects of initiating ART before pregnancy and continuing ART during pregnancy, SGA occurred more frequently in women who continued ART that was initiated before conception, but this finding was not statistically significant (RR 1.34; 95% CI, 0.98–1.84).[19] When compared with FTC/TDF/EFV, both NVP-based and LPV/r-based ART were associated with an increased incidence of SGA.[35] When compared with women on non-nucleoside reverse transcriptase inhibitor–based ART, women in the Netherlands on PI-based ART before pregnancy had a higher risk of SGA (OR 1.35; 95% CI, 1.03–1.77).[45] Brazilian women on LPV/r-based ART had an increased risk of delivering SGA infants compared with women taking NFV-based ART.[37] In contrast, an observational study of women with HIV who were on FTC/TDF/EFV, NPV-based ART, or other multidrug regimens before pregnancy did not show an association between these regimens and SGA.[34]

In summary, the data are mixed regarding the effect of ARV use on birth weight. Given the potential for LBW or SGA infants, maternal use of ARV during pregnancy may be an indication for enhanced antenatal surveillance of fetal growth, especially in cases where ART was initiated preconception.

Stillbirth

Reported rates of stillbirth among women with HIV range from 0.5 percent to 11.4 percent.[10,14,15,17,24,30,31,33,35,41,49,52,53,61] In a meta-analysis of 17 studies that included 37,877 women with HIV who were on ART, three studies included stillbirth outcomes. Women with HIV who were on TDF-based ART had a lower risk of stillbirth than those who were on other regimens (pooled RR 0.6; 95% CI, 0.43–0.84; $I^2 = 72\%$).[2]

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 PI-based regimens and PI-sparing regimens. In one study, a greater risk of stillbirth was observed among women who continued preconception ART during pregnancy than women who initiated ART during pregnancy (aOR 1.5; 95% CI, 1.2–1.8).[14] Zash et al. reported that preconception use of ZDV/3TC/NVP was associated with a significantly increased rate of stillbirth compared with the use of FTC/TDF/EFV (adjusted relative risk 2.3, 95% CI, 1.6–3.3).[35] Among women with HIV who delivered in the United Kingdom and Ireland between 2007 and 2015 (n = 10,434), preconception ARV use was not associated with an increased risk of stillbirth.[61] Women with HIV who delivered in Malawi from 2012 to 2015, 71 percent of whom were on ART preconception or in the first trimester, did not experience higher rates of stillbirth compared with the general population (2.5%, n = 8,380).[62]

When evaluating the association between the use of ARV and adverse pregnancy outcomes, more studies have examined PTD, LBW infants, and SGA infants than stillbirth. Given that stillbirth is a relatively rare outcome in resource-rich settings, data related to stillbirth and ARV use are limited.

Maternal Outcomes

Hypertensive Disorders of Pregnancy

Limited data suggest that women with HIV may have an increased risk of HDP. No studies have evaluated the effect of specific ARV drugs on HDP. A meta-analysis did not reveal a clear association between maternal HIV and HDP.[63] An observational Italian study comparing women with HIV with women without HIV demonstrated an increased risk for both early-onset and late-onset pre-eclampsia (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).[64] A secondary analysis of observational data from South Africa revealed that women with low CD4 counts (<200 cells/mm^3) on ART had an increased risk of maternal death from HDP compared with women not on ART during pregnancy (RR 1.15; 95% CI, 1.02–1.29).[65] Among these women, those on ART before pregnancy and those who were not on ART before pregnancy had similar rates of HPD (15.7% and 14.9%, respectively). These authors also described that women with HIV were less likely to have HDP than women without HIV (OR 0.67; 95% CI, 0.48–0.93).[33] A small U.S. observational study demonstrated that women with HIV (n = 85) were not more likely to experience HPD than women without HIV (n = 3,556). They observed higher rates of HDP among women on INSTIs (25%, n = 23) and NNRTIs (24%, n = 7) compared with women on PI-based ART (10%, n = 55). Preconception ARV use was associated with an increased risk of HDP.[48]

Although these limited data may suggest an association between HDP and maternal HIV, no known interventions reduce this risk, and providers should not withhold ART in the setting of HDP.

Summary

Clinicians should be aware of a possible increased risk of adverse maternal and neonatal outcomes with the use of ARV 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 using their provider-recommended regimens. Clinicians should monitor pregnant women with HIV for potential pregnancy complications, including PTD, LBW infants, and SGA infants. Monitoring may require additional prenatal visits and fetal ultrasounds; see Monitoring of the Woman and Fetus During Pregnancy for more information.

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

Panel's Recommendations

- When choosing an antiretroviral (ARV) drug regimen for a pregnant woman, providers and patients should consider multiple factors, including adverse effects, drug interactions, pharmacokinetics (PKs), convenience of the individual drugs and drug combinations in the regimen, available pregnancy safety and outcome data, and the patient's resistance test results and comorbidities **(AIII)**.
- The same regimens that are recommended for the treatment of nonpregnant adults should be used in pregnant women when sufficient data suggest that appropriate drug exposure is achieved during pregnancy; clinicians should weigh the risks of adverse effects for women, fetuses, or infants against the benefits of these regimens and recognize that there are often incomplete data on the safety of ARV drugs in pregnancy **(AII)**. For more information, see Tables 4 and 5.
- In most cases, women who present for obstetric care on fully suppressive ARV regimens should continue their current regimens **(AIII)**.
- PK changes in pregnancy may lead to lower plasma levels of some ARV drugs and necessitate increased doses, more frequent dosing, boosting, more frequent viral load monitoring, or a change in ARV regimen; see Pregnant Women with HIV Who Are Currently Receiving Antiretroviral Therapy **(AII)**.
- The Panel emphasizes the importance of counseling and informed decision-making regarding all ARV regimens for people with HIV **(AIII)**. For additional information, see Preconception Counseling and Care for Women of Childbearing Age with HIV, Teratogenicity, Appendix C: Antiretroviral Counseling Guide for Health Care Providers, and Tables 4 and 5.
- After delivery, clinicians should discuss reproductive desires, the risks and benefits of conceiving on the current ARV regimen, and contraceptive options **(AIII).** See Preconception Counseling and Postpartum Care for more information.
- Folic acid is known to prevent neural tube defects in the general population. All pregnant women and women who might conceive should take at least 400 mcg of folic acid daily **(AI)**.

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

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

This section provides an overview of the key clinical and pharmacokinetic (PK) issues that are relevant to the selection of specific antiretroviral (ARV) drugs for use in pregnancy. Additional recommendations for women with HIV who have never received antiretroviral therapy (antiretroviral therapy [ART]-naive women), women who are currently receiving ART, and women who were previously on ART or who have used ARV drugs for prophylaxis can be found in the other sections that follow this overview. Table 4 provides specific information about recommended ARV drugs when **initiating** ART in treatment-naive pregnant women. The table also includes considerations for ARV regimen selection and modification in pregnant women who are treatment-experienced and women who are attempting to become pregnant. For recommendations about the use of ARV drugs in people of childbearing potential who are not actively trying to conceive, see Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV.

Table 5 consolidates situation-specific recommendations for the use of ARV drugs in women with HIV during conception and pregnancy into a single table for ease of reference. Table 5 includes recommendations for the use of ARV drugs in the following situations:

- Initiating ART in pregnant women who have never received ARV drugs;
- Continuing ART in women who become pregnant while on a fully suppressive regimen that has been well

tolerated;
- Restarting ART in pregnant women who received ART or ARV drugs for prophylaxis in the past;
- Changing to a new ARV regimen in pregnant women whose current ART is not well tolerated and/or is not resulting in virologic suppression; *and*
- Initiating or modifying ART in women who are trying to conceive.

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

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

The Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission (the Panel) reviews clinical trial data published in peer-reviewed journals and data prepared by manufacturers for U.S. Food and Drug Administration review that are related to the treatment of adult women with HIV, both those who are pregnant and those who are not. The durability, tolerability, and simplicity of a medication regimen are particularly important for ensuring adherence and preserving future treatment options. Regimen selection should be based on several factors that apply to all pregnant women, as well as factors that will vary for individual patients.

Pregnancy-related factors include—
- Potential teratogenic effects and other short-term and long-term adverse effects on fetuses or newborns, including, but not limited to, preterm birth, mutagenicity, and carcinogenicity;
- Available safety and outcome data on the use of the drug in pregnancy;
- PK changes in pregnancy; *and*
- Potential adverse effects for the woman, especially those that may be exacerbated during pregnancy.

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

The Panel uses information from several sources to develop recommendations on specific drugs or regimens for pregnant women. These sources include—
- Data from randomized clinical trials and prospective cohort studies that demonstrate durable viral suppression in pregnancy, as well as immunologic and clinical improvement;
- Incidence rates and descriptions of short-term and long-term drug toxicity of ARV regimens;
- Evidence from clinical studies on the risk of maternal toxicity, teratogenicity, adverse pregnancy outcomes, and adverse infant outcomes;
- Specific knowledge about drug tolerability and simplified dosing regimens;
- Known efficacy of ARV drug regimens in reducing perinatal transmission of HIV;
- PK (drug exposure) data during pregnancy;

- Data from animal teratogenicity studies; *and*
- Antiretroviral Pregnancy Registry data and other post-marketing surveillance data.[4]

Categories of ARV drugs and drug combinations for use in pregnancy include—

- **Preferred:** Drugs or drug combinations are designated as *Preferred* for therapy in pregnant women when clinical trial data in adults have demonstrated efficacy and durability with acceptable toxicity and ease of use, and when pregnancy-specific PK data are available to guide dosing. In addition, the available data must suggest a favorable risk-benefit balance for the drug or drug combination compared to other ARV drug options; the assessment of risks and benefits should incorporate outcomes for women, fetuses, and infants. Some *Preferred* drugs or regimens may have minimal toxicity or teratogenicity risks that are offset by other advantages for women with HIV who are pregnant or trying to conceive.
- **Alternative:** Drugs or drug combinations are designated as *Alternative* options for therapy in pregnant women when clinical trial data in adults show efficacy and the data in pregnant individuals are generally favorable but limited. Most *Alternative* drugs or regimens are associated with more PK, dosing, tolerability, formulation, administration, or interaction concerns than those in the *Preferred* category, but they are acceptable for use in pregnancy. Some *Alternative* drugs or regimens may have known toxicity or teratogenicity risks that are offset by other advantages for women with HIV who are pregnant or trying to conceive.
- **Insufficient Data to Recommend:** The drugs and drug combinations in this category are approved for use in adults, but pregnancy-specific PK or safety data are too limited to make a recommendation for use in pregnant women. In some cases, it may be appropriate to continue using these drugs or drug combinations in women who become pregnant on ART that has been well tolerated.
- **Not Recommended Except in Special Circumstances:** Although some drugs are not recommended for initial ART in ART-naive women due to specific safety concerns or very limited safety and efficacy data in pregnancy, there may be circumstances in which ART-experienced women need to initiate or continue using specific drugs to reach or maintain viral suppression.
- **Not Recommended:** Drugs and drug combinations listed in this category are not recommended for use in pregnancy due to inferior virologic efficacy or potentially serious maternal or fetal safety concerns. They may also be categorized as not recommended for initial therapy in ARV-naive populations, regardless of pregnancy status. This category includes drugs or drug combinations for which PK data demonstrate low drug levels and risk of viral rebound during pregnancy. Levels of these drugs are often low in late pregnancy (during the second and third trimesters) when risk for perinatal transmission is high if maternal viremia occurs. In some situations, it may be appropriate to continue using these drugs or drug combinations in women who become pregnant on fully suppressive ART that has been well tolerated, though viral load monitoring should be performed more frequently in these instances. See Pregnant Women with HIV Who Are Currently Receiving Antiretroviral Therapy and Monitoring of the Woman and Fetus During Pregnancy.

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

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

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

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

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

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

Pharmacokinetic Considerations for Antiretroviral Drugs

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

in the liver and intestine. Placental transport of drugs, compartmentalization of drugs in the embryo/fetus and placenta, biotransformation of drugs by the fetus and placenta, and elimination of drugs by the fetus can also affect drug PKs in the pregnant woman. In general, the PKs of NRTIs and non-nucleoside reverse transcriptase inhibitors (NNRTIs) are similar in pregnant and nonpregnant women (although PK data for etravirine [ETR] are limited). PI and INSTI PKs are more variable, particularly during the second and third trimesters. Currently available data on the PKs and dosing of ARV drugs in pregnancy are listed for each drug below and summarized in Table 10.

Nucleoside Reverse Transcriptase Inhibitors

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

Abacavir plus lamivudine is the NRTI component in some *Preferred* regimens for nonpregnant adults. It offers the advantage of once-daily dosing and is well tolerated in pregnancy.[15] Testing for the HLA-B*5701 allele should be performed and documented as negative before starting ABC, and women should be educated about symptoms of hypersensitivity reactions. Clinicians should determine whether a patient has hepatitis B virus (HBV)/HIV coinfection; for women with HBV/HIV coinfection, two NRTIs that are active against HBV should be chosen (e.g., TDF with FTC or 3TC) in place of ABC plus 3TC (see HBV/HIV Coinfection).

TDF plus emtricitabine or lamivudine is the NRTI component in some *Preferred* regimens for nonpregnant adults. This combination has several advantages, including extensive experience with use in pregnancy, once-daily dosing, enhanced activity against HBV, and less toxicity than zidovudine (ZDV) plus 3TC. Although there have been concerns about bone and growth abnormalities in infants who were exposed to TDF *in utero*, the duration and clinical significance of study findings require further evaluation (see Tenofovir Disoproxil Fumarate).[16] The authors of one meta-analysis have suggested that ZDV plus 3TC should be used in place of TDF plus FTC;[17] however, this suggestion was based on data from a single study, the Promoting Maternal and Infant Survival Everywhere (PROMISE) trial.[18] The generalizability of the PROMISE findings is limited by study design and statistical considerations (for details, see Tenofovir Disoproxil Fumarate and Lopinavir/Ritonavir). After considering all available evidence, the Panel concluded that the assessment of expected benefits and risks favored the use of TDF plus FTC over ZDV plus 3TC. The Panel maintains the *Preferred* classification for TDF plus FTC and the *Alternative* classification for ZDV plus 3TC.

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

Zidovudine plus lamivudine is an *Alternative* NRTI combination for ARV-naive pregnant women. Despite proven efficacy in preventing perinatal HIV transmission and extensive experience with use in pregnancy, this NRTI combination is classified as *Alternative* rather than *Preferred* because it requires twice-daily dosing and is associated with higher rates of mild-to-moderate adverse effects, including nausea, headache, and reversible maternal and neonatal anemia and neutropenia (see Zidovudine).

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

medications.

Integrase Strand Transfer Inhibitors

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

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

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

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

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

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

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

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

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

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

Protease Inhibitors

Atazanavir/ritonavir and **darunavir/ritonavir** are *Preferred* PIs for use in ARV-naive pregnant women, based on efficacy studies in adults and experience with use in pregnancy. Factors that impact the decision of which medication to use may include limitations in administering concomitant antacid, H2 blocker, or proton pump inhibitors (for ATV/r), and the requirement for twice-daily dosing (for DRV/r). Although the use of once-daily dosing for DRV/r is approved for nonpregnant adults, PK data are insufficient to support its use in pregnancy.[49]

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

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

Current data suggest that with standard adult dosing, plasma concentrations of LPV, ATV, and DRV are reduced during the second and/or third trimesters. Dose adjustment is recommended for LPV/r and may be considered for ATV/r, but dose adjustment is not recommended for DRV/r (see Table 10).[56] Specific dosing recommendations depend on the PI, an individual patient's treatment experience, and use (if any) of concomitant medications with potential for drug interactions.[56-64] Clinicians may consider therapeutic drug monitoring in specific situations.

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

Non-Nucleoside Reverse Transcriptase Inhibitors

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

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

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

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

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

Rilpivirine may be used as part of an *Alternative* regimen for nonpregnant adults with pretreatment HIV RNA <100,000 copies/mL and CD4 T lymphocyte (CD4) cell counts >200 cells/mm^3. Sufficient data from use in pregnancy exist to recommend RPV as an *Alternative* agent for ARV-naive pregnant women who meet these same CD4 count and viral load criteria.[5,43,76] Although PK data indicate that RPV plasma concentration is reduced during the second and third trimesters, the reduction is less than the reductions seen with EVG/c or DRV/c, and most women will have adequate exposure;[5] however, viral breakthroughs may be possible. Higher-than-standard doses of RPV have not been studied, so data are insufficient to recommend a dosing change in pregnancy. RPV must be taken with a meal, which may make it difficult to tolerate in pregnancy. With standard dosing of RPV, viral loads should be monitored frequently (e.g., every 1–2 months; see Monitoring of the Woman and Fetus During Pregnancy).

Nevirapine **is not recommended** for initial ART in ARV-naive pregnant women or for nonpregnant adults because of a greater potential for adverse effects, complex lead-in dosing, and a low barrier to resistance. **Etravirine** **is not recommended** for ARV-naive pregnant patients, because it is not recommended for ARV-naive nonpregnant patients, and because of insufficient safety and PK data on the use of ETR during pregnancy. Available PK data in women who received ETR as part of clinical care suggest that a standard adult dose is appropriate during pregnancy; unlike other ARV drugs, ETR exposure is increased during pregnancy.[27,77] However, it may be appropriate to initiate either of these ARV drugs in special circumstances, or it may be appropriate to continue using them in ART-experienced women who become pregnant on well-tolerated, fully suppressive regimens that include these drugs.

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

Entry, Attachment, and Fusion Inhibitors

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

Ibalizumab is a humanized monoclonal antibody to the CD4 receptor. **Fostemsavir** is an attachment inhibitor. Both drugs are indicated for patients with multi-drug resistant HIV for whom no therapeutic alternatives may be available. However, no data exist on the use of these drugs in pregnancy.

Pharmacologic Boosters

Low-dose **ritonavir** as a pharmacologic booster for other PIs, as described above, is currently the preferred pharmacologic booster for use in pregnancy. **Cobicistat**-boosted ARV drugs (ATV, DRV, or EVG) **are not**

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

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Pregnant People with HIV Who Have Never Received Antiretroviral Drugs (Antiretroviral Naive)

(Last updated February 10, 2021; last reviewed February 10, 2021)

Panel's Recommendations
• Antiretroviral therapy (ART) is recommended for all pregnant people with HIV to reduce the risk of perinatal HIV transmission and to optimize the health of the pregnant person **(AI)**. Initiating ART as soon as possible in pregnant people 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 ARV regimens in people 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 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 people 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 4 and Recommendations for 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 with HIV **(AIII)**. See Appendix C: Antiretroviral 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 people 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 people and offer antiretroviral (ARV) regimens that contain at least three drugs. These regimens reduce the risk of perinatal HIV transmission and optimize the person'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 people 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 people 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 people with viral loads <50 copies/mL (0.09%) than in people 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 people on ART at the time of conception and reductions in the proportion of people who either initiated ART late in pregnancy or who never received ART prior to delivery.

Initiating ART early increases the likelihood that a person 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 people who had achieved viral loads <50 copies/mL at the time of delivery, transmission risk was 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, perinatal transmission rate was higher for people with viral loads of 50 copies/mL to 400 copies/mL near delivery than for those with <50 copies/mL, and it was higher for people with viral loads >400 copies/mL at delivery (4.4% for people 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 people 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 people, 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 the time of delivery; thus, prompt initiation of ART is particularly important in pregnant people who have high baseline viral loads.[5–8]

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 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 people who received ARV regimens during pregnancy have been reassuring. No differences have been found 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] (see Teratogenicity for a more detailed discussion of the adverse events that are associated with the use of specific ARV drugs). 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 person's health status, the risks and benefits to the individual's health, and the potential risks and benefits to the fetus.

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

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

With pre-exposure prophylaxis, 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 intensive viral exposure occurs.

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 postexposure prophylaxis, 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.

The decision about which ARV drugs to use during pregnancy should be made by a person after discussing the known and potential benefits and risks to the individual and the fetus (infant).

Table 4 and Table 5 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 people with HIV who have never received ARV drugs, people who are continuing or restarting ART in pregnancy, or people who are trying to conceive (see Pregnant Women with HIV Who Have Previously Received Antiretroviral Treatment and Preconception Counseling and Care for Women of Childbearing Age with HIV. Drugs or drug combinations are designated as *Preferred* for therapy in pregnant people when clinical trial data in adults have demonstrated efficacy and durability with acceptable toxicity and ease of use, and when 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 people, fetuses, and infants. Some *Preferred* drugs or regimens may have minimal toxicity or teratogenicity risks that are offset by other advantages for people with HIV who are pregnant or who are trying to conceive. Therefore, it is important for health care providers to read all the information on each drug in the Perinatal Guidelines before administering any of these medications to patients (see Appendix B: Supplement: Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy), and provide appropriate patient counseling to support informed decision-making (see Appendix C: Antiretroviral Counseling Guide for Health Care Providers). *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 pregnant people, irrespective of trimester. It is a recommended option for an initial ARV regimen in nonpregnant adults. Sufficient data exist about the efficacy and safety of DTG in pregnancy.[25–28] Maternal use of DTG at the time of conception or in early pregnancy has been associated with an increased risk of neural tube defects (NTDs) in infants. However, given the benefits of DTG in terms of rapid viral suppression and low incidence of side effects, as well as updated evidence that indicates a very low potential risk of NTDs with preconception use, DTG is a *Preferred* ARV during pregnancy, irrespective of trimester, and it is now also a *Preferred* ARV for people trying to conceive (see Recommendations for Use of Antiretroviral Drugs During Pregnancy).

RAL is also a *Preferred* INSTI for ARV-naive people, and the amount of efficacy and safety data for RAL in pregnant people is increasing. The selection of drugs for an ARV regimen should be based on individual patient characteristics and needs (see Table 4 and Table 5).

RAL or DTG have been suggested for use when ART is initiated late in pregnancy, particularly for people who have high viral loads, because of the ability of RAL and DTG 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 the Dolutegravir in Pregnant HIV Women and Their Neonates (DolPHIN 2) study, 268 ART-naive women in Uganda and South Africa were randomized to receive DTG plus two NRTIs or EFV plus two NRTIs at a median gestational age of 31 weeks. At delivery, women in the DTG arm were significantly more likely to achieve viral loads of

<50 copies/mL (74.1% vs. 42.7%; adjusted risk ratio 1.64 [1.31–2.06], $P < 0.0001$) than women in the EFV arm.[28] Similarly, the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) 1081 trial randomized 408 ART-naive women in South America, Africa, Thailand, and the United States who presented late in pregnancy (20 to <37 weeks gestation) to receive RAL plus two NRTIs or EFV plus two NRTIs. Among 307 women in the primary efficacy analysis, 84% in the EFV group and 94% in the RAL group achieved a viral load of <200 copies/mL at or near delivery (absolute difference 10% [95% CI, 3% to 18%], $P = 0.0015$); the difference primarily occurred among women enrolling later in pregnancy (interaction $P = 0.040$). 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 in the women who received RAL than in those who received EFV at 2, 4, and 6 weeks after initiation.[34]

DTG is *Preferred* for treatment of acute HIV 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 an *Alternative* ARV for the treatment of acute HIV infection during pregnancy (see Acute HIV Infection). For a discussion regarding the addition of DTG or RAL to current ARV regimens, see Women Who Have Not Achieved Viral Suppression on Antiretroviral Therapy.

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 people who are at risk for INSTI resistance (e.g., people with partners who were treated with INSTIs, people 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 people 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 people 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 people.

All pregnant people 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 person 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. People 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 which specific ARV agents to use postpartum should be made by people 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 person'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).

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Table 4. What to Start: Initial Combination Regimens for Antiretroviral-Naive Pregnant Women (Last updated, February 10, 2021; last reviewed, February 10, 2021)

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 show no evidence of significant resistance to regimen components (also see Pregnant Women with HIV Who Have Never Received Antiretroviral Drugs and Table 5).

In general, the Panel recommends that **women who are already on fully suppressive ARV regimens when pregnancy occurs should continue to use those regimens**, unless they are receiving an ARV drug or ARV regimen that is not recommended for use in adults, or there are concerns about safety and inferior efficacy during pregnancy (see Table 5 and Pregnant Women 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 with HIV Who Have Previously Received Antiretroviral Treatment or Prophylaxis but Are Not Currently Receiving Any Antiretroviral Medications and Table 5).

Regimens are listed alphabetically within each drug class and recommendation category, so 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)*. The table also indicates antiretroviral drugs or regimens that are available in fixed-dose combination (FDC) tablets.

Note: For more information about the use of specific drugs and dosing in pregnancy, see Table 5, 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 with 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 particularly 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

Preferred INSTI Regimens	
	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 Recommendations for Use of Antiretroviral Drugs During Pregnancy, Table 5, Teratogenicity, and Appendix C: Antiretroviral Counseling Guide for Health Care Providers.
RAL plus a Preferred Dual-NRTI Backbone	PK data are available for RAL in pregnancy when using the twice-daily formulation (400 mg twice daily), but data are not available for the once-daily 1,200 mg (2 x 600 mg) extended-release formulation "raltegravir HD". Twice-daily dosing is required in pregnancy. 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 particularly useful when drug interactions or the potential for preterm delivery with PI-based regimens are a concern. 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	
TAF/FTC	Available as an FDC. Data about the use of TAF at conception and during pregnancy are limited. For both boosted and non-boosted regimens, plasma TAF exposures in pregnant adults are similar to those seen in nonpregnant adults; a change in dosing is not required.
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, which increases the potential for hematologic toxicities and other toxicities.

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, no evidence has been found of an increased risk of birth defects in human studies and extensive experience in pregnancy; cautionary text remains in the package insert (see Teratogenicity, Efavirenz, 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/TAF/FTC (FDC)** **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)	Limited data on the use of BIC in pregnancy.
DOR	No data on the use of DOR in pregnancy.
IBA	No data on the use of IBA 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 limited data about use in pregnancy and/or concerns about maternal or fetal safety or PK changes or inferior efficacy, including viral breakthroughs in the second and third trimester (see Table 5 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 ARV regimen (see Pregnant Women with HIV Who Are Currently Receiving Antiretroviral Therapy and Table 5).	
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 the 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.
EVG/c/FTC/TAF (FDC)	Limited data on the use of EVG with COBI (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 the 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 and LPV/r, 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 circumstances may exist in which pregnant women who are ART-experienced may need to initiate or continue these drugs to reach or maintain viral suppression (see Table 5).	
ETR	Not recommended for use in ART-naive populations. Data about the use of ETR in pregnancy are limited.
LPV/r plus a Preferred Dual-NRTI Backbone	Abundant experience and established PKs in pregnancy. Has been associated with an increased risk of preterm delivery; see Antiretroviral Drug Regimens and Maternal and Neonatal Outcomes. More nausea than with *Preferred* or *Alternative* 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.
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.

Note: The following drugs and drug combinations (not listed above) should not be used during pregnancy; women who become pregnant while taking these medications 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 ARV regimens, 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.

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 = darunavir; 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 5. Situation-Specific Recommendations for Use of Antiretroviral Drugs in Pregnant People and Nonpregnant People Who Are Trying to Conceive

(Last updated December 15, 2020; last reviewed December 15, 2020)

People should be given information about the benefits and risks of initiating an antiretroviral (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 People Who Have Never Received ARV Drugs and Who Are Initiating ART for the First Time	Continuing ART for People Who Become Pregnant on a Fully Suppressive, Well-Tolerated Regimen	ART for Pregnant People Who Have Received ARV Drugs in the Past and Who Are Restarting ART[a]	New ART Regimen for Pregnant People Whose Current Regimen Is Not Well Tolerated and/or Is Not Fully Suppressive[a]	ART for Nonpregnant People Who Are Trying to Conceive[a,b]
Integrase Strand Transfer Inhibitor (INSTI) Drugs Used in combination with a dual-nucleoside reverse transcriptase inhibitor (NRTI) backbone[c]					
DTG	Preferred	Continue	Preferred	Preferred	Preferred
RAL	Preferred	Continue	Preferred	Preferred	Preferred
BIC	Insufficient data	Insufficient data	Insufficient data	Insufficient data	Insufficient data
EVG/c[d]	Not recommended	Continue with frequent viral load monitoring or consider switching	Not recommended	Not recommended	Not recommended
Protease Inhibitor (PI) Drugs 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	Not recommended, except in special circumstances	Continue	Not recommended, except in special circumstances	Not recommended, except in special circumstances	Not recommended, except in special circumstances
ATV/c[d]	Not recommended	Continue with frequent viral load monitoring or consider switching	Not recommended	Not recommended	Not recommended
DRV/c[d]	Not recommended	Continue with frequent viral load monitoring or consider switching	Not recommended	Not recommended	Not recommended

Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI) Drugs Used in combination with a dual-NRTI backbone[c]					
EFV	Alternative	Continue	Alternative	Alternative	Alternative
RPV[e]	Alternative	Continue	Alternative	Alternative	Alternative
DOR	Insufficient data	Insufficient data	Insufficient data	Insufficient data	Insufficient data
ETR[f]	Not recommended	Continue	Not recommended, except in special circumstances	Not recommended, except in special circumstances	Not recommended, except in special circumstances
NVP[f]	Not recommended	Continue	Not recommended, except in special circumstances	Not recommended, except in special circumstances	Not recommended, except in special circumstances
NRTI Drugs[c,g]					
ABC[h]	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[i]	Alternative	Continue	Alternative	Alternative	Alternative
Entry, Attachment, and Fusion Inhibitor Drugs					
IBA	Insufficient data	Insufficient data	Insufficient data	Insufficient data	Insufficient data
MVC[f]	Not recommended	Continue	Not recommended, except in special circumstances	Not recommended, except in special circumstances	Not recommended, except in special circumstances
T-20[f]	Not recommended	Continue	Not recommended, except in special circumstances	Not recommended, except in special circumstances	Not recommended, except in special circumstances
FTR	Insufficient data	Insufficient data	Insufficient data	Insufficient data	Insufficient data
Fixed-Dose Combination (FDC) Regimens[d,g] The individual drug component that is most responsible for the overall recommendation is indicated in parentheses.					
ABC/DTG/3TC[h]	Preferred	Continue	Preferred	Preferred	Preferred
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[e]	Alternative (RPV)	Continue (RPV)	Alternative (RPV)	Alternative (RPV)	Alternative (RPV)
BIC/FTC/TAF	Insufficient data (BIC)	Insufficient data (BIC)	Insufficient data (BIC)	Insufficient data (BIC)	Insufficient data (BIC)

DOR/3TC/TDF	Insufficient data (DOR)	Insufficient data (DOR)	Insufficient data (DOR)	Insufficient data (DOR)	Insufficient data (DOR)
FTC/RPV/TAF	Alternative	Continue	Alternative	Alternative	Alternative
EVG/c/FTC/TDF[d]	Not recommended (EVG/c)	Continue with frequent viral load monitoring or consider switching (EVG/c)	Not recommended (EVG/c)	Not recommended (EVG/c)	Not recommended (EVG/c)
EVG/c/FTC/TAF[d]	Not recommended (EVG/c)	Continue with frequent viral load monitoring or consider switching (EVG/c)	Not recommended (EVG/c)	Not recommended (EVG/c)	Not recommended (EVG/c)
DRV/c/FTC/TAF[d]	Not recommended (DRV/c)	Continue with frequent viral load monitoring or consider switching (DRV/c)	Not recommended (DRV/c)	Not recommended (DRV/c)	Not recommended (DRV/c)
DTG/3TC As a complete regimen[j]	Not recommended	Not recommended; switch, or add additional agents	Not recommended	Not recommended	Not recommended
DTG/RPV As a complete regimen[j]	Not recommended	Not recommended; switch, or add additional agents[e]	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 people who are pregnant or trying to conceive. These recommendations are not intended for all people 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 and TAF plus FTC are *Alternative* dual-NRTI backbones for ARV regimens.

[d] DRV/c, EVG/c, and ATV/c **are not recommended** for use in pregnancy because of 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 people present to care on regimens that include these drugs, these drug combinations can be continued with frequent viral load monitoring or can be switched to a recommended or alternative agent. If there are concerns about switching, see Pregnant People with HIV Who Are Currently Receiving Antiretroviral Therapy. If the cobicistat pharmacologic booster is replaced with ritonavir for ATV and DRV, attention to dosing in pregnancy is critical, with higher doses of ATV required if coadministered with TDF or antacids, and twice-daily dosing required for DRV, in the second and third trimesters.

[e] 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 use of EVG/c or DRV/c. Higher-than-standard doses of RPV have not been studied, so data are insufficient to recommend a dose change in pregnancy. With standard dosing, viral load should be monitored more frequently.

[f] Although these drugs are not recommended for initial treatment in ART-naive pregnant people, there may be special circumstances in which ART-experienced people may need to continue or initiate ETR, NVP, MVC, and T-20 in order to maintain or achieve viral suppression. Safety and efficacy data are limited about the use of ETR, MVC, and T 20 in pregnancy. NVP **is not recommended** for ART-naive people, 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 person presents to care on a well-tolerated, NVP-containing regimen, it is likely that NVP will be safe and effective during pregnancy. See Table 4 and Nevirapine for more information.

[g] When using FDC tablets, refer to Table 8 and the drug sections in Appendix B for information about the dosing and safety of individual components of the FDC tablet during pregnancy.

[h] 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.

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

[j] 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 person 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 4 for ARV regimens that are recommended for use in pregnancy.

Key: 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; BIC = bictegravir; d4T = stavudine; ddI = didanosine; DOR = doravirine; DRV = darunavir; 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; FTR = fostemsavir; IBA = ibalizumab; IDV = indinavir; IDV/r = indinavir/ritonavir; INSTI = integrase strand transfer inhibitor; LPV = lopinavir; 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 with HIV Who Are Currently Receiving Antiretroviral Therapy

(Last updated February 10, 2021; last reviewed February 10, 2021)

Panel's Recommendations
• Women 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)**. • When considering changes in ART during pregnancy, the Panel recommends patient counseling to support informed decision making. See Appendix C: Antiretroviral Counseling Guide for Health Care Providers. • 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 during pregnancy **(AIII)**. See Table 5 for more information. • No data exist on the use of two-drug regimens during pregnancy (e.g., dolutegravir [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. • The use of atazanavir/cobicistat, darunavir/cobicistat, or elvitegravir/cobicistat regimens during pregnancy is associated with lower plasma drug exposures due to physiologic changes associated with pregnancy. These lower drug exposures pose an increased risk of virologic failure during the second and third trimesters of pregnancy (see Table 4 and Table 5). When a pregnant woman presents to care on one of these regimens, providers should decide whether to continue the regimen or to switch 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 by taking the drugs with food, 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 4 and Table 5) **(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 still should be considered **(BII)**. See Women Who Have Not Achieved Viral Suppression on Antiretroviral Therapy for more information. • Clinicians should discuss future reproductive plans and timing, 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. The Panel emphasizes the importance of patient counseling and informed decision making when changing ARV regimens during pregnancy. For additional information, see Appendix C: Antiretroviral Counseling Guide for Health Care Providers.

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 4 and Table 5).

No data exist 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.

The use of regimens containing atazanavir/cobicistat, darunavir/cobicistat, or elvitegravir/cobicistat (EVG/c), is associated with lower plasma drug exposures during the second and third trimesters of pregnancy due to the physiologic changes associated with pregnancy. These low drug exposures pose an increased risk of virologic failure in the second and third trimesters and potential perinatal HIV transmission. When a pregnant woman presents to care on one of these regimens, providers should consider continuing the regimen with more frequent viral load monitoring or switching to a more effective regimen that is recommended for use in pregnant women (see Table 4 and Table 5).[2–4] 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.[5] 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 (e.g., every 1–2 months) in patients taking cobicistat-boosted regimens (see Monitoring of the Woman and Fetus During Pregnancy).[3] 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 pharmacokinetic (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 significant experience in pregnancy and limited PK and safety data are lacking. 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 during 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 neural tube defects 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 with women who received regimens that did not include EFV (RR 0.78; 95% confidence interval, 0.56–1.08).[6] 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. No difference was found in the prevalence of birth

defects among infants in these three groups.[7] 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, 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 with HIV).

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Pregnant Women with HIV Who Have Previously Received Antiretroviral Medications but Are Not Currently Receiving Any Antiretroviral Medications

(Last updated December 29, 2020; last reviewed December 29, 2020)

Panel's Recommendations
• Obtain an accurate history of all prior antiretroviral (ARV) medications used for HIV treatment or prevention of HIV transmission, including virologic efficacy, patient's tolerance of the medications, results of prior resistance testing, and problems with adherence **(AIII)**. • Choose and initiate an antiretroviral therapy (ART) regimen based on results of prior resistance testing, prior ARV drug use, concurrent medical conditions, and current recommendations for ART in pregnancy (see Table 5) **(AII)**. • If HIV RNA is above the threshold for standard genotypic drug resistance testing (i.e., >500 to 1,000 copies/mL), ARV drug-resistance testing should be performed prior to starting an ARV drug regimen (see Antiretroviral Drug Resistance and Resistance Testing in Pregnancy) **(AIII)**. • ART should be initiated prior to receiving results of current ARV resistance assays. 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 when choosing an ART regimen for women who previously received ARV drugs or modifying ART for 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 with HIV who are currently not receiving antiretroviral therapy (ART) may have received antiretroviral (ARV) drugs in the past for their own health and/or prevention of HIV transmission to their infant or their sexual partners (e.g., treatment as prevention).[1] A small number of clinical trials and observational studies have generated information about the effectiveness of ART in individuals who previously received ART to prevent perinatal transmission of HIV.[2–5]

There has been concern that prior, time-limited use of ART during pregnancy to prevent perinatal transmission may lead to resistance and, thus, reduced efficacy if these ARV drugs are used as a part of subsequent ART regimens. Standard genotyping has shown that the rates of resistance after time-limited use of ART appear to be low. Resistance seems to be a concern primarily in patients who received time-limited non-nucleoside reverse transcriptase inhibitor (NNRTI)-based therapy.[6–8] In a comparison between 5,372 ARV-naive pregnant women and 605 women who previously had received ART in the pre-integrase strand transfer inhibitor (INSTI) era (but who were not being treated immediately before the current pregnancy), ARV-experienced women had a small, but statistically significant, increase in the risk of detectable viral load at delivery (adjusted odds ratio 1.27; 95% confidence interval, 1.01–1.60). However, this increased risk only was seen in women who previously received NNRTI-based therapy but not in those who previously received protease inhibitor (PI)-based therapies.[6]

Both standard and sensitive genotyping techniques appear to show a low rate of resistance to PIs after pregnancy-limited use of PI-based ART, but these results reflect assessments in a small number of women.[9,10] Increased risk of treatment failure has not been demonstrated with re-initiation of ART after time-limited use of ART for the prevention of perinatal transmission, especially when using ART regimens with a PI-based regimen or an INSTI.[11] In AIDS Clinical Trials Group (ACTG) 5227, 52 women who previously had 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.[2] The data from the French Perinatal Cohort were used to assess the rates of virologic suppression among women who received PI-based ART; ARV-naive women and women who had received ART during previous pregnancies to prevent perinatal transmission had similar rates of viral load suppression at delivery.[11]

ART is now recommended worldwide for everyone with HIV, including all women with HIV during pregnancy and throughout their lives.[12] The data have been reported regarding the benefits of ART for women with higher CD4 T lymphocyte (CD4) cell counts (>350 cells/mm³) and the potential harm of stopping ART after pregnancy in such women. The data from the Promoting Maternal and Infant Safety Everywhere (PROMISE) study (HAART Standard version) showed that women with CD4 counts ≥400 cells/mm³ who were randomized to continue ART postpartum had half the rate of World Health Organization stage 2 and 3 events as those who were randomized to discontinue ART.[13] Furthermore, poor adherence was a common problem for women during the postpartum period in this study. Among women who were randomized to continue ART, 189 of 827 women (23%) had virologic failure. Of the 156 women with virologic failure who had resistance testing, 33% had at least one mutation and 12% had resistance to their current ART regimen. Mutations and resistance occurred more often in women who experienced virologic failure on NNRTI-based regimens. However, most women did not have resistance to their current ART, which suggests nonadherence.[13] When counseling women about the benefits of taking ART during pregnancy and continuing therapy for life, health care providers should emphasize the health benefits of ART and the importance of adherence during the postpartum period (see Postpartum Follow-Up of Women with HIV Infection).

Women may choose to discontinue ART for a variety of reasons, and the length of time off of treatment before pregnancy may vary. A woman's HIV treatment history and all prior drug resistance test results should be considered when choosing ART regimens for pregnant women who previously have received treatment, 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 resistance testing is most accurate when performed while an individual is still taking ART or within 4 weeks of discontinuing treatment (see Antiretroviral Drug Resistance and Resistance Testing in Pregnancy). In the absence of selective drug pressure, resistant virus may revert to wild type; thus, a negative finding does not rule out the presence of archived resistant virus that could re-emerge once ART is restarted (see Antiretroviral Drug Resistance and Resistance Testing in Pregnancy). Therefore, when selecting a new ART regimen, all information, including regimens received, viral response, laboratory testing (including HLA-B*5701 screening results), any tolerance or adherence problems, food requirements, concomitant medications, prior medical conditions, and results of all prior resistance testing should be considered. In general, ART should be initiated before receiving the results of ARV drug-resistance testing, especially because longer durations of ART during pregnancy have been associated with reduced perinatal transmission rates, compared with shorter treatment periods.[14,15] ART should be modified, when necessary, based on subsequent resistance assay results. Careful monitoring of virologic response is essential (see Monitoring Woman and Fetus During Pregnancy).

A woman may restart a previous ART regimen that successfully suppressed her viral load as long as the regimen was tolerated well and no evidence of resistance to that regimen is indicated. Ideally, the regimen also should be recommended currently as a first-line or alternative regimen for initial ART in pregnancy (see Table 4: What to Start and Table 5). Drugs that are not recommended 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 also should be avoided, if possible (see Table 5). 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 $\log^{10}$ drop over 2–4 weeks),[16] repeat resistance testing, including testing for resistance to integrase strand transfer inhibitors if indicated (see Antiretroviral Drug Resistance and Resistance Testing in Pregnancy), and assess medication adherence, food requirements, and potential drug interactions (including relevant pharmacokinetic studies when available) to inform potential regimen changes. Consultation with an HIV treatment specialist is recommended (see Women Who Have Not Achieved Viral Suppression on ART).

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Monitoring of the Woman and Fetus During Pregnancy

(Last updated December 29, 2020; last reviewed December 29, 2020)

Panel's Recommendations
• The 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 therapy (ART) **(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 Intrapartum Care for Women with HIV and to inform decisions about optimal management for the newborn (see Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection) **(AIII)**.
• CD4 T lymphocyte (CD4) cell count should be measured at the initial antenatal visit **(AI)**. Patients who have been on ART for ≥2 years and who have had consistent viral suppression and CD4 counts that are consistently >300 cells/mm3 do not need to have their CD4 counts monitored after the initial antenatal visit during this pregnancy, per the Adult and Adolescent Antiretroviral Guidelines **(CIII)**. Women who have been on ART for <2 years, women with CD4 counts <300 cells/mm^3, and women with inconsistent adherence and/or detectable viral loads should have CD4 counts monitored every 3 months during pregnancy **(CIII)**.

• HIV drug-resistance testing (genotypic testing and, if indicated, phenotypic testing) should be performed in women whose HIV RNA levels are above the threshold for standard resistance testing (i.e., >500 copies/mL to 1,000 copies/mL) before—
  • Initiating ART in antiretroviral (ARV)-naive pregnant women who have not been previously tested for ARV drug resistance (AII);
  • Initiating ART in ARV-experienced pregnant women **(AIII)**; *or*
  • Modifying ARV regimens for women who become pregnant while receiving ARV drugs or women who have suboptimal virologic response to ARV drugs that were started during pregnancy **(AII)**.

• ART should be initiated in pregnant women prior to receiving the results of ARV-resistance tests. ART should be modified, if necessary, based on the results of resistance testing **(BIII)**.
• Laboratory testing to monitor 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 who are taking ART during pregnancy should undergo standard glucose screening **(AIII)**. Some experts suggest performing glucose screening early in pregnancy for women who are receiving protease inhibitor (PI)-based regimens that were 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.
• Amniocentesis, if clinically indicated, should be performed on women with HIV only after initiation of an effective ARV regimen and, ideally, when HIV RNA levels are undetectable **(BIII)**. If a woman with detectable HIV RNA levels requires amniocentesis, consultation with an expert in the management of HIV during 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, see Table 6 below. Individuals who are adherent to their antiretroviral therapy (ART) and who do not harbor resistance mutations to the prescribed drugs should achieve viral suppression within 8 to 12 weeks. Individuals with higher viral loads and lower CD4 T lymphocyte (CD4) cell counts are more likely to require more time

to achieve viral suppression[1,2] than those with lower viral loads and higher CD4 counts. In addition, those using integrase strand transfer inhibitors (INSTIs) are more likely to achieve suppression in much shorter time frames.[3–5] Most patients with adequate viral response at 24 weeks of treatment have had at least a 1 $\log_{10}$ viral load decrease within 1 to 4 weeks after starting therapy.[6,7] Viral load should be monitored in pregnant women with HIV at the initial clinic visit, 2 to 4 weeks after initiating or changing ART, 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 increased risk of perinatal HIV transmission associated with detectable HIV viremia during pregnancy.[8–10] Similarly, pregnancy may reduce the drug exposure levels or the efficacy of some drugs; women who are taking these drugs may require a change in therapy or more frequent viral load monitoring (see Table 4 and Table 5). More frequent viral load monitoring is recommended for women who are receiving regimens containing rilpivirine or cobicistat-boosted elvitegravir, atazanavir, or darunavir. Although increasing the frequency of viral load monitoring may help detect viral rebound, this may be difficult to implement if visit attendance or access to viral load monitoring is limited. In addition, viremia detected in late pregnancy may be challenging to manage, requiring medication changes shortly before delivery (see Pregnant Women Living with HIV Who Are Currently Receiving Antiretroviral Therapy).

Viral load also should be assessed at approximately 34 to 36 weeks gestation to inform decisions about the mode of infant delivery and optimal treatment for newborns (see Intrapartum Care for Women with HIV).

In pregnant women with HIV, CD4 count should be measured at the initial clinic visit (see Table 6 below). For patients who have been on ART for ≥2 years, have had consistent viral suppression and CD4 counts that are consistently >300 cells/mm^3, and are tolerating ART during pregnancy, CD4 count should be monitored only at the initial antenatal visit; CD4 counts do not need to be repeated for these patients during this pregnancy, per the Adult and Adolescent Antiretroviral Guidelines.[6, 11, 12] Women who have been on ART for <2 years, women with CD4 counts of <300 cells/mm^3, and women with inconsistent adherence and/or detectable viral loads should have CD4 counts monitored every 3 months during pregnancy. The safety of this approach is supported by research that demonstrates that patients who are stable on ART (defined as patients who have viral load levels <50 copies/mL and CD4 counts >500 cells/mm^3 for 1 year) are highly unlikely to experience a CD4 count <350 cells/mm^3 in the span of a year.[13]

HIV drug-resistance testing should be performed in women with HIV before starting or modifying ART if HIV RNA levels are above the threshold for standard resistance testing (i.e., >500 copies/mL to 1,000 copies/mL) (see Table 6 below). Genotypic testing should be performed. In cases of treatment-experienced individuals with multidrug resistance on failing regimens, phenotypic testing should be additionally performed. See Drug-Resistance Testing in the Adult and Adolescent Antiretroviral Guidelines and 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. Antiretroviral (ARV) drug-resistance testing should also be performed on women who are taking ART 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 ART (see Women Who Have Not Achieved Viral Suppression on ART 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 discontinuing 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, although it may not detect all resistance mutations that were selected by previous ARV regimens.

The laboratory tests that are used to monitor complications of ARV drugs during pregnancy should be chosen

based on what is known about the adverse effects of the drugs a woman is receiving (see Table 6 below). For example, routine hematologic monitoring is recommended for women who are receiving zidovudine-containing regimens, and routine renal monitoring is recommended for women who are receiving tenofovir disoproxil fumarate. Liver function should be monitored in all women who are receiving ART, ideally within 2 to 4 weeks after initiating or changing ARV drugs and approximately every 3 months thereafter or as needed for other clinical care. Hepatic dysfunction has been observed in pregnant women on PIs, and the use of any PI during pregnancy has been associated with higher rates of liver function test abnormalities than the rates observed with non-nucleoside reverse transcriptase inhibitor-based ART. Hepatic steatosis and lactic acidosis in pregnancy have been related to the use of older nucleoside reverse transcriptase inhibitors, such as stavudine, didanosine, and zidovudine. Pregnant women in general are more likely to have elevated levels of liver enzymes than their nonpregnant counterparts.[14–16]

Pregnancy itself increases the risk of glucose intolerance. In a recent meta-analysis, the pooled prevalence of gestational diabetes among women with HIV was 4.42% (95% confidence interval, 3.48% to 5.35%), with women in Asia demonstrating the highest prevalence (7.10%) and those in Africa demonstrating the lowest prevalence (3.19%). These rates do not appear to be higher than those in non-HIV populations.[17,18] The majority of studies in pregnant women have not demonstrated an association between HIV infection and gestational diabetes,[19–23] although some studies with stringent definitions of gestational diabetes did show an increased risk of gestational diabetes in women who were taking PI-based regimens during pregnancy.[24] Two studies reported higher odds of gestational diabetes in women who were receiving PI based regimens,[25,26] but another prospective study reported that pregnant women with HIV who received PI-containing regimens did not have a greater risk for glucose intolerance or insulin resistance than women who received regimens that did not contain a PI.[27] Women with HIV who are on ART during pregnancy should receive the standard glucose screening that is recommended for all pregnant women. However, some experts would perform glucose screening earlier in pregnancy for women who are receiving PI-based ART that was initiated before pregnancy, in accordance with recommendations for women with risk factors for glucose intolerance, such as obesity (see Table 6 below).[28]

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).[29] Therefore, it is recommended that health care providers follow the current obstetric guidelines for gestational age dating by ultrasound.[30]

Noninvasive methods of aneuploidy screening should be offered, using tests with high sensitivity and low false-positive rates as recommended by the American College of Obstetricians and Gynecologists. Screening can be accomplished using any of the following:

- Serum analyte screening alone or combined with nuchal translucency;
- Cell-free DNA screening; *or*
- Ultrasonographic screening alone.[31]

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 perinatal HIV transmission along with other risks of the procedure so that they can make an informed decision about testing. Although the data on women who are receiving ART are still somewhat limited, the risk of perinatal 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.[32,33] 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 twofold to fourfold increase in the risk of perinatal transmission of HIV.[34–37] 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.[38–41] 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 ideally should 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. If a woman with detectable HIV RNA levels requires amniocentesis, consultation with an expert in the management of HIV during pregnancy should be considered (see Intrapartum Care for Women with HIV).

Table 6. HIV-Related Laboratory Monitoring Schedule for Pregnant Women with HIV

	Timepoint or Frequency of Testing						
Laboratory Test	**Entry Into Antenatal Care**	**ART Initiation or Modification**	**2 to 4 Weeks After ART Initiation or Modification**	**Monthly**	**Every 3 Months During Pregnancy**	**At 24 to 28 Weeks Gestation**	**At 34 to 36 Weeks Gestation to Inform Mode of Delivery and Infant ARV Regimen**
HIV RNA Levels[b]	✓	✓ If a result is not available within 2 weeks of ART initiation or modification	✓	✓ Until HIV RNA levels are undetectable	✓ At least every 3 months[c]		✓
CD4 Count[d]	✓				✓ For women who have been on ART for <2 years, women with CD4 counts <300 cells/mm^3, and women with inconsistent adherence and/or detectable viral loads		
Resistance Testing[e]		✓					
Standard Glucose Screening[f]						✓ For women on ART[f]	

LFTs for Women on ART		✓			✓ Or as needed		
Monitoring for ARV-Specific Toxicities[g]	Refer to the recommendations in the package inserts for the individual ARV drugs.						

[a]For additional information see Laboratory Monitoring in the Adult and Adolescent Antiretroviral Guidelines

[b] The 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 therapy (ART) **(BI)**, monthly until RNA levels are undetectable **(BIII)**, and then at least every 3 months during pregnancy **(BIII)**. Obtain an HIV RNA level at the time of ART initiation or modification if a recent result within 2 weeks prior is not available.

[c] More frequent viral load monitoring (every 1-2 months) may be indicated for women who are taking ARVs that have been shown to have reduced drug levels in the 2nd and 3rd trimesters and are at risk for loss of viral suppression, e.g., cobicistat, elvitegravir or rilpivirine (see Table 4 and Table 5 and Pregnant Women Living with HIV Who Are Currently Receiving Antiretroviral Therapy).

[d] CD4 T lymphocyte (CD4) cell count should be measured at the initial antenatal visit **(AI)**. Patients who have been on ART for ≥2 years and who have had consistent viral suppression and CD4 counts that are consistently >300 cells/mm^3 do not need to have their CD4 counts monitored after the initial antenatal visit during this pregnancy, per **the** Adult and Adolescent Antiretroviral Guidelines **(CIII)**. Women who have been on ART for <2 years, women with CD4 counts <300 cells/mm^3, and women with inconsistent adherence and/or detectable viral loads should have CD4 counts monitored every 3 months during pregnancy **(CIII)**.

[e] ARV drug-resistance testing (genotypic testing and, if indicated, phenotypic testing) should be performed in women whose HIV RNA levels are above the threshold for standard 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 drug resistance **(AII)**;
- Initiating ART in ARV-experienced pregnant women **(AIII)**; *or*
- Modifying ARV regimens for women who become pregnant while receiving ARV drugs or women who have suboptimal virologic response to ARV drugs that were started during pregnancy **(AII)**.

ART should be initiated in pregnant women prior to receiving the results of ARV-resistance tests. ART should be modified, if necessary, based on the results of resistance testing **(BIII)**.

[f] Women who are taking ART during pregnancy should undergo standard glucose screening **(AIII)**. Some experts suggest performing glucose screening early in pregnancy for women who are receiving protease inhibitor (PI)-based regimens that were 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.

[g] Laboratory testing to monitor 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)**.

Key: ART = antiretroviral therapy; ARV = antiretroviral; CD4 = CD4 T lymphocyte; LFT = liver function test; PI = protease inhibitor

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Antiretroviral Drug Resistance and Resistance Testing in Pregnancy

(Last updated December 29, 2020; last reviewed December 29, 2020)

Panel's Recommendations
• HIV drug-resistance testing (genotypic and, if indicated, phenotypic) 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 (including those who have received pre-exposure prophylaxis) **(AIII)**, *or* • Modifying ARV regimens for women who are newly pregnant and receiving ARV drugs or who have suboptimal virologic response to the ARV drugs started during pregnancy **(AII).** • Phenotypic resistance testing is indicated for treatment-experienced persons on failing regimens who are thought to have multidrug resistance **(BIII)**. • ART should be initiated in pregnant women prior to receiving results of ARV-resistance testing; ART should be modified, if necessary, based on the results of resistance assays **(BIII)**. • If the use of an integrase strand transfer inhibitor (INSTI) is being considered 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 if: • A patient received prior treatment that included an INSTI, *or* • A patient has a history with a sexual partner on INSTI therapy. • Documented zidovudine (ZDV) resistance does not affect the indications for use of intrapartum intravenous ZDV (see Intrapartum Care for Women with HIV)**(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 HIV Infection) **(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 risk of developing 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 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 obtaining a comprehensive history of ARV drug use) is recommended for women 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 (including those who have received pre-exposure prophylaxis), *or*
- Modifying ARV regimens for women who are newly pregnant and receiving ARV drugs or who have suboptimal virologic response to ARV drugs that were initiated during pregnancy.

In most settings, the results of resistance testing guide the selection of the initial ARV regimen. However, ART

should be initiated in ARV-naive pregnant women or ARV-experienced women who are not presently on ART without waiting for the results of resistance testing, as earlier viral suppression is associated with lower risk of perinatal transmission. The regimen can be modified, if required, when test results return.

It is increasingly common for integrase strand transfer inhibitors (INSTIs) to be included in ARV regimens for pregnant women.[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] and in 2.9% of ART-naive participants from an HIV clinic in Santa Clara County, California.[4] The prevalence of INSTI resistance increased slightly from 0.0% in 2004 to 1.4% in 2013 in Washington, DC.[5] A polymorphism or a substitution associated with INSTI resistance was found in 1.4% of INSTI-naive persons in 16 clinical trials.[6]

The development of INSTI resistance is infrequent among people who receive INSTI-based ART (only 1.48% to 3.80% of people develop resistance). A modeling study found that testing for INSTI resistance at ART initiation was not cost-effective and did not improve clinical outcomes.[7] Routine INSTI-resistance testing is generally not indicated in pregnant women. However, such testing can be considered when a patient received prior treatment that included an INSTI or when a patient has a history with a sexual partner on INSTI therapy.

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 and is recommended for treatment-experienced persons on failing regimens with suspected multidrug resistance (see Drug-Resistance Testing in the Adult and Adolescent Antiretroviral Guidelines). At some institutions, testing for INSTI resistance may have to be ordered separately.

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 with HIV. In addition, pre-existing resistance to a drug in an ARV regimen may diminish the regimen's efficacy in preventing perinatal transmission. Maternal drug resistance can be transmitted to the fetus, which can limit treatment options for the infant. Resistance to ARV drugs appears to be more common in women who acquired HIV perinatally than in other women with HIV.[8] The complexities of managing pregnant women with perinatally acquired HIV warrant consultation with an expert in HIV.[9] (see Prenatal Care, Antiretroviral Therapy, and HIV Management in Women with Perinatal HIV Infection for more information).

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, increasing the risk of developing resistance in women receiving ARV drugs. Pharmacokinetic changes during pregnancy (e.g., increased plasma volume and renal clearance) may lead to subtherapeutic drug levels, increasing the risk that resistance will develop.

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

Perinatal Transmission

There is little evidence that the presence of resistance mutations increases the risk of perinatal transmission when pregnant women with HIV are on suppressive ART. Some studies have suggested that drug-resistance mutations may diminish viral fitness,[10] possibly leading to a decrease in transmissibility. A nested case-control study that was conducted as part of the NICHD/HPTN 040 (P1043) study found that pre-existing drug-resistance mutations in pregnant women who did not receive antepartum ARV drugs were not associated with an increased risk of perinatal HIV transmission.[11] Another nested case-control study, which was part of a larger study in Cape Town, South Africa, examined elevated viral loads in pregnant and postpartum women. The study found that at a matched postpartum time point, <10% of the elevated viral loads could be attributed to ARV resistance.[12]

In a study of 84 children with perinatal HIV infection in France that collected data between 2006 and 2017, transmitted drug resistance was found in 8.3% of participants. No participants had triple-class resistance; 5% had INSTI-related mutations (an E157Q mutation that primarily affects susceptibility to raltegravir and elvitegravir but not dolutegravir).[13]

Maternal Response to Subsequent Treatment Regimens

A study that used data collected from pregnant women enrolled in the French Perinatal Cohort between 2005 and 2009 evaluated the association between exposure to ARV drugs to prevent perinatal transmission during a previous pregnancy and the presence of a detectable viral load after exposure to ARV drugs during the current pregnancy.[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. Forty-eight percent of these women had previously used a PI-based regimen for ARV prophylaxis, 4% had used a regimen that did not include a PI, 19% had used a dual-NRTI regimen, and 29% had used zidovudine (ZDV) alone. A PI-based ARV 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 who had previously taken ARV drugs to prevent perinatal transmission. These women had stopped taking ARV drugs at least 24 weeks before study entry and had initiated a regimen of efavirenz, tenofovir disoproxil fumarate, and emtricitabine for treatment during the study.[15] Previous drug-resistance tests had not documented resistance in any of the women, and standard bulk genotyping did not detect resistance in any of the women at screening. Viral suppression was observed in 81% of women after 24 weeks of follow-up. Neither the number of prior ARV drug exposures to prevent perinatal transmission nor the drug class of prior exposure was associated with a failure to achieve viral suppression. Recent clinical series have confirmed this observation.[16,17]

Management of Antiretroviral Drug Resistance During Pregnancy

Women who have documented ZDV resistance and who did not receive ZDV as part of their antepartum regimen should still receive intravenous (IV) ZDV during labor when indicated (IV ZDV is indicated for women with HIV RNA >1,000 copies/mL near delivery; see Intrapartum Care for Women with HIV). A patient's normal ARV regimen should be continued orally during labor to the extent possible. The rationale for including ZDV intrapartum when a woman is known to harbor virus with ZDV 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 ZDV resistance.[18] Other studies have suggested that drug-resistance mutations may diminish viral fitness and possibly decrease transmissibility.[10] The efficacy of ZDV prophylaxis appears to be based not only on a reduction in maternal HIV viral load but also on the use of pre-exposure and post-exposure prophylaxis in the infant.[19-21] ZDV crosses the placenta readily and has a high cord-to-maternal-blood ratio. In addition, ZDV is metabolized to the active triphosphate within the placenta,[22] which may provide additional protection against transmission. ZDV penetrates the central nervous system (CNS) better than other recommended nucleoside analogues; this may help eliminate a potential reservoir for transmitted HIV in the infant.[23] ZDV's unique characteristics and its proven record in reducing perinatal transmission support the recommendation to administer intrapartum IV ZDV when indicated, even in the presence of known ZDV resistance.

The optimal prophylactic regimen for newborns of women with 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 HIV Infection). There is no evidence that neonatal prophylaxis regimens that have been customized to address maternal drug resistance are more effective than standard

neonatal prophylaxis regimens.

Prevention of Antiretroviral Drug Resistance

The most effective way for a patient to prevent the development of ARV drug resistance in pregnancy is to adhere to an effective ARV regimen that achieves maximal viral suppression. However, several studies have demonstrated that women's adherence to ART may worsen during the postpartum period.[24-29]

Previous versions of the Perinatal Guidelines have provided guidance for clinicians in cases where women stop their ARV regimen postpartum. However, the Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission 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 Antiretroviral Guidelines).

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Women Who Have Not Achieved Viral Suppression on Antiretroviral Therapy

(Last updated December 29, 2020; last reviewed December 29, 2020)

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)**.
• For pregnant women who have not achieved viral suppression (after an adequate period of treatment):
  • Assess medication adherence, tolerability, dosing, potential problems with absorption, adherence to food requirements, and possible drug interactions.
  • If HIV RNA is >500 copies/mL, perform tests for resistance **(AII)**.
  • Consult an HIV treatment expert and consider possible antiretroviral regimen modification **(AIII)**.
• Please see Intrapartum Care for Women with HIV with HIV for guidance about use of intrapartum intravenous zidovudine prophylaxis and scheduled cesarean delivery for women who have not achieved viral suppression on ART **(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 viral suppression in both pregnant and nonpregnant individuals, and no difference in time to viral response has been observed between pregnant and nonpregnant women.[1,2] In women with HIV who participated in three prospective studies from seven African countries and who became pregnant after initiating antiretroviral therapy (ART), 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 the regimen's effectiveness.[4] Most patients with an adequate viral response at 24 weeks of treatment have had at least a 1 $\log_{10}$ decrease in HIV RNA within 1 week to 4 weeks after starting therapy.[4] In the United Kingdom, a multicenter, retrospective observational study of women initiating ART during pregnancy found that higher baseline viral load was the only independent factor associated with faster first-phase HIV RNA half-life decay, and that lower viral load on day 14 after starting ART was associated with an increased likelihood of achieving an undetectable plasma viral load by 36 weeks gestation.[5]

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, as well as maternal HIV progression. 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 through miscarriage or stillbirth.[6] However, a recent report from the HIV Outpatient Study noted that among 119 pregnancies that were analyzed between 2005 and 2015, 33 women (27.7%) were not virally suppressed (HIV RNA >500 copies/mL) at the end of pregnancy. Failure to achieve virologic suppression remains a common problem for pregnant women in the United States.[7]

Causes of Detectable Viremia

Poor adherence is frequently associated with lack of virologic suppression, and this issue should be addressed when the viral load does not decline as expected. A systematic review and meta-analysis of ART adherence during and after pregnancy in low-, middle-, and high-income countries (27% of studies were from the

United States) found that only 73.5 percent of pregnant women achieved adequate (>80%) ART adherence.[8] Factors that can contribute to suboptimal adherence include unplanned pregnancy, depression, a lack of HIV seropositive status disclosure, a history of intimate partner violence, a lack of prior experience with taking ART, and a lack of knowledge about the role of ART in preventing perinatal transmission.[9–12] Evaluation of and support for adherence during pregnancy are 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 percent of women achieved HIV RNA <50 copies/mL by delivery; success in achieving viral suppression varied by baseline HIV RNA level. In women with baseline HIV RNA levels <10,000 copies/mL, the gestational age of their infants at ART initiation did not affect the likelihood of achieving viral suppression up to 26.3 weeks gestation. In women with baseline HIV RNA levels >10,000 copies/mL, however, delaying ART initiation past 20.4 weeks in women with baseline HIV RNA levels >10,000 copies/mL significantly reduced the probability of achieving maximal suppression at delivery.[1] Among 1,070 ART-naive pregnant women with HIV who participated in the prospective cohort study IMPAACT P1025, initiating ART at >32 weeks gestation was also associated with a significantly higher risk of having a viral load >400 copies/mL at delivery.[13] A report from the French Perinatal Cohort found no perinatal transmission among 2,651 infants born to women who received ART before conception, continued ART throughout pregnancy, and delivered with a plasma HIV RNA <50 copies/mL, with an upper limit for the 95 percent confidence interval [CI] of 0.1 percent. In the entire cohort of 8,075 mother-infant pairs that were followed from 2000 through 2011, HIV RNA level and timing of ART initiation were independently associated with perinatal transmission in a logistic regression analysis.[14] A recent cross-sectional analysis of 10,052 pregnant women with HIV and receiving antenatal care (ANC) in public facilities in South Africa reported that failure to achieve viral suppression (HIV RNA <50 copies/mL) was primarily associated with late registration for antenatal care and late initiation of ART.[15]

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 HIV after adjusting for baseline CD4 count, but the rate of viral decline following ART initiation was significantly slower among women with acute HIV.[16] Strategies to accelerate viral decline may be considered in women with acute HIV, 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, perinatally acquired HIV in the mother was a risk factor for detectable viral load near delivery; this finding reflects complex clinical, psychosocial, adherence, and resistance issues.[17] Among 2,123 births that occurred between 2007 and 2015 and were reported in the Surveillance Monitoring of ART Toxicities Study as part of the Pediatric HIV/AIDS Cohort Study, women with perinatally acquired HIV had a higher perinatal transmission rate (1.1%; 95% CI, 0.3% to 4.3% vs. 0.4%; 95% CI, 0.2% to 1.0%) and higher likelihood of having HIV RNA >1,000 copies/mL close to delivery than women with non-perinatally acquired HIV.[18] If needed, ART regimens should be optimized in consultation with HIV treatment experts, and other possible contributing factors should be considered (see Prenatal Care, Antiretroviral Therapy, and HIV Management in Women with Perinatal HIV Infection).

Managing Suboptimal Viral Suppression

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

- Assessing adherence, tolerability, correct dosing, or potential problems with absorption (e.g., nausea/vomiting, use of gastroesophageal reflux disease medications, lack of attention to food requirements);

- Ordering ARV drug resistance tests if plasma HIV RNA is above the threshold for resistance testing (generally >500 copies/mL); *and*
- Considering modifying the ART regimen (see Pregnant Women with HIV Who Are Currently Receiving Antiretroviral Therapy and Table 5).

The role of therapeutic drug monitoring (TDM) in reducing the risk of virologic failure is still undefined. In a cohort of pregnant women with HIV, 66 (39%) received TDM.[19] Multivariate analysis found that receiving TDM was associated with medication alterations during pregnancy. However, the incidences of viral breakthrough during pregnancy or detectable viral load at birth were similar between women who received TDM and those who did not, and no instances of perinatal transmission were reported in either group. However, this analysis was limited by the retrospective observational nature of this study, the presence of significant baseline differences in adherence between those who received TDM and those who did not, and insufficient statistical power to establish some associations.

Before modifying an ARV regimen, consult an expert in clinical care for ARV-experienced adults. This is particularly important in cases where a drug regimen must be modified due to resistance or adverse effects. Regimen simplification may be considered to promote better adherence. Other possible interventions include adherence education, treating problems that may interfere with drug absorption (e.g., vomiting), ensuring that a patient is taking ART in accordance with food requirements, and directly observing drug administration in the home or hospital setting (see Table 10).[20]

Among 662 pregnancies that were followed in Italy between 2001 and 2008, treatment modification during pregnancy was independently associated with an HIV RNA level >400 copies/mL in late pregnancy (adjusted odds ratio 1.66; 95% CI, 1.07–2.57; $P = 0.024$). This highlights the importance of using potent and well-tolerated regimens during pregnancy to maximize effectiveness and minimize the need to modify treatment.[21] These findings also highlight the importance of avoiding changing effective ARV regimens whenever possible in women who become pregnant while taking ART (see Pregnant Women with HIV Who Are Currently Receiving Antiretroviral Therapy).

The Role of Integrase Strand Transfer Inhibitors in Women with Detectable HIV RNA Levels During Pregnancy

The integrase strand transfer inhibitor (INSTI) class of drugs has been associated with rapid viral load reduction. The use of raltegravir (RAL) or dolutegravir as a fourth ARV drug can be considered in ART-naive women with high viral loads; however, limited evidence exists of a benefit in this situation. (see Pregnant Women with HIV Who Have Never Received Antiretroviral Drugs, Table 4, and Table 5). Adding RAL or another INSTI to a three-drug ARV regimen has also been suggested in the setting of incomplete viral suppression due to known or suspected drug-resistant mutations or nonadherence.[22] However, the efficacy and safety of this approach during pregnancy have not been evaluated in clinical trials. The available data come from case series and two retrospective cohorts, and most of these data focus on the use of RAL.[23–25] A recent prospective cohort study from Thailand enrolled 154 pregnant women with HIV. These women had either started ART at ≥32 weeks gestation (73% of women) or were receiving ART and had plasma HIV RNA levels >1,000 copies/mL at 32 to 38 weeks gestation (27% of women). These women received a standard, three-drug ART regimen plus RAL intensification until delivery. The median gestational age at entry was 34 weeks (interquartile range [IQR] 33–36 weeks) and median duration of treatment was 21 days (IQR 8–34 days). The proportion of women with HIV RNA levels of <50 copies/mL and <1,000 copies/mL at delivery overall was 45 percent and 76 percent, respectively; 83 percent of those who were ART-naive had HIV RNA <1,000 copies/mL at delivery compared with 60 percent of those who were already on ART but who had not achieved virologic suppression. The overall perinatal transmission rate in this high-risk group of women was 3.9 percent (95% CI, 1.4% to 8.2%). Six instances of perinatal transmission occurred in this group; three of those instances occurred *in utero*.[26]

In cases where treatment failure is attributed to nonadherence and/or resistance, concerns exist that the addition of a single agent may further increase the risk of resistance and lead to the potential loss of future effectiveness of this agent. In addition, when poor adherence is the reason that the patient has not achieved or maintained virologic suppression, it is unclear that adding a new drug to the existing regimen will improve adherence. Currently, data are insufficient to recommend adding an INSTI to a failing ART regimen for women in late pregnancy. However, after reviewing a woman's full treatment history and drug resistance results, a clinician may consider using an INSTI as part of a new regimen for pregnant women who are experiencing virologic failure on a non-INSTI ART regimen.

Viral Rebound in Late Pregnancy

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 testing positive for hepatitis C virus RNA.[27] 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.

Intrapartum Management of Women with a Lack of Viral Suppression

Please see Intrapartum Care for Women with HIV for guidance about the use of intrapartum intravenous zidovudine prophylaxis and scheduled cesarean delivery for women who have not achieved viral suppression on ART.

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Stopping Antiretroviral Drugs During Pregnancy

(Last updated December 29, 2020; last reviewed December 29, 2020)

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 a complete, effective ARV regimen 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

Temporary discontinuation of antiretroviral (ARV) drug regimens during pregnancy may be indicated in some situations, including cases of serious drug-related toxicity, pregnancy-induced hyperemesis that is unresponsive to antiemetics, or acute illnesses or planned surgeries that prevent a patient from taking oral medications. Other reasons for discontinuing ARV drug regimens during pregnancy include a lack of available medication or patient request. For some women, possible toxicity or intolerance to a single ARV agent should prompt discussion about options for modifying, rather than stopping, their ARV regimen. The Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission strongly recommends against discontinuing antiretroviral therapy (ART). If a woman wants to discontinue ART during pregnancy or after delivery, it is strongly recommended that her clinician consult an HIV specialist for guidance (see Discontinuation or Interruption of Antiretroviral Therapy in the Adult and Adolescent Antiretroviral Guidelines). If an ARV drug regimen must be stopped for any reason, all ARV drugs should be stopped simultaneously. ART should be reinitiated as soon as possible, whether the patient restarts the same regimen or initiates 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 an 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 gestational age 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 gestational age 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% confidence interval [CI], 1.9% to 13.2%; adjusted odds ratio [aOR] 10.33; $P = 0.005$) with first-trimester interruption and 18.2% of mother-child pairs (95% CI, 4.5% to 72.7%; aOR 46.96; $P = 0.002$) with third-trimester interruption.[1]

Continuing all drugs during the intrapartum period 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.

Some ARV drugs, particularly non-nucleoside reverse transcriptase inhibitors, have longer serum half-lives than other ARV agents; if an ARV regimen that contains these ARV drugs is stopped, the woman may have subtherapeutic blood levels of these agents. This exposes the patient to what is essentially monotherapy, which may lead to drug resistance. For example, efavirenz can be detected in blood for longer than 3 weeks after discontinuation.[2,3] If an ARV drug that is known to have a long serum half-life must be stopped for more than a

few days, clinicians should consider assessing the patient for rebound viremia and potential drug resistance and consider restarting an approved ARV regimen when possible.[4] If an ARV drug regimen must be stopped for any reason, all ARV drugs should be stopped simultaneously to minimize the disruption of viral suppression.

In rare cases, a woman may not be able to meet the food requirements for certain ARV agents. In these instances, 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.

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Special Populations: Hepatitis B Virus/HIV Coinfection

(Last updated December 29, 2020; last reviewed December 29, 2020)

Panel's Recommendations

• All pregnant women with HIV should be screened during the current pregnancy for:
  • Hepatitis B virus (HBV) infection, unless they are already known to have HBV/HIV coinfection or have serologic documentation of HBV immunity, *and*
  • 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 with HIV who screen negative for HBV infection and lack HBV immunity (i.e., HBV surface antigen negative, HBV core antibody negative, and HBV surface antibody negative) should promptly 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 antibodies (either IgG or total antibody [IgG and IgM]), they should receive the HAV vaccine series **(AIII)**.
• All pregnant and postpartum women with HBV/HIV coinfection should receive antiretroviral therapy (ART) that includes tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF) plus lamivudine or emtricitabine **(AII)**.
• Pregnant women with HBV/HIV coinfection who are receiving ART should be counseled about signs and symptoms of liver toxicity, and liver transaminases should be assessed 1 month after initiating ART and at least every 3 months thereafter during pregnancy **(BIII)**.
• During and after pregnancy, women with chronic HBV should be counseled on the importance of continuing anti-HBV medications indefinitely. If ART that includes medications with anti-HBV activity is 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 is not an indication for cesarean delivery (see Intrapartum Care for Women with HIV **(AIII)**.
• Within 12 hours of birth, infants born to women with HBV 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:** = 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 management of HBV/HIV coinfection in pregnancy is complex, and consultation with an expert in HIV and HBV infection is strongly recommended. For additional information on hepatitis B virus (HBV) and HIV, see Hepatitis B Virus/HIV Coinfection in the Adult and Adolescent Antiretroviral Guidelines and Hepatitis B Virus Infection in the Adult and Adolescent Opportunistic Infection Guidelines.

Screening and Vaccination

All women with HIV should be screened for HBV and hepatitis C virus (HCV) at entry into general HIV care. All pregnant women with HIV should be screened for HBV during each pregnancy, unless they are known to have HBV/HIV coinfection, or they have serologic documentation of HBV immunity. They also should be screened for HCV during each pregnancy, 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 transmission of HIV and HBV from women with HBV/HIV coinfection to their sex partners, their sexual contacts should be counseled and tested for HIV and HBV. All HBV-susceptible contacts should then receive the HBV vaccine series; all sex partners who do not have HIV infection should be counseled about the benefits of condom use, pre-exposure prophylaxis, and having a partner with undetectable HIV (U=U) in preventing HIV transmission, see Reproductive Options for Couples When One or Both Partners Have HIV and Let's Stop HIV Together resources from the Centers for Disease Control and Prevention.[1–4] For more information specifically about preventing HBV transmission, see the CDC guidelines on pre-exposure prophylaxis and the Hepatitis B Virus Infection section of the Adult and Adolescent Opportunistic Infection Guidelines.

Pregnant women with HIV who screen negative for HBV (i.e., HBsAg negative, anti-HBc negative, and anti-HBs negative) or who lack HBV immunity (i.e., anti-HBs negative) should promptly receive the HBV vaccine series. Women with HIV who have remote HBV infection and who only have current anti-HBc antibody detected (i.e., they test negative for HBV DNA, HBsAg, and anti-HBs) may have lost immunity to HBV and should be vaccinated.[1] Anti-HBs titers should be obtained 1 to 2 months after the vaccine series is completed in patients with HIV; if anti-HBs titers are below 10 IU/mL, a second vaccine series is recommended.[1,5] 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 ART.[1,5–7] No evidence exists that the HBV vaccine causes adverse effects in developing fetuses or newborns; current vaccines contain noninfectious HBsAg and are recommended for use in pregnancy for women with HIV.[8,9] No consensus exists on how to manage patients whose anti-HBs titers remain below 10 IU/mL following a second HBV vaccine series.[1]

A positive test for anti-HBc alone can be a false positive, especially in regions of low HBV prevalence; alternatively, it may signify remote infection with subsequent loss of anti-HBs antibodies or longstanding chronic HBV infection with loss of surface antigen (this is known as "occult" HBV infection, which can be confirmed by detection of HBV DNA).[10,11] Incidence of HBV viremia with the isolated anti-HBc pattern ranges from 1% to 30% in patients with HIV, depending on the population sampled.[12] The clinical significance of isolated anti-HBc is unknown.[13,14] 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 that have specific activity against HBV.[5] In areas where the prevalence of HBV is low, patients with isolated anti-HBc should be vaccinated with one standard dose of HBV vaccine, and anti-HBs titers should be checked 1 to 2 months after vaccination. If the anti-HBs titer is >100 IU/mL, no further vaccination is needed. If the titer is <100 IU/mL, the patient should receive a complete HBV vaccine series, followed by anti-HBs testing. The cut-off of 100 IU/mL is used in this situation because one study demonstrated that 100% of patients with isolated anti-HBc who achieved a titer of 100 IU/mL after a booster dose maintained an anti-HBs response for >18 months, compared to only 23% of those who achieved a titer of 10 IU/mL to 100 IU/mL.[1] Pregnant women with HIV who have 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.[1,15]

Women who have HBV infection and who have not already received the hepatitis A virus (HAV) vaccine series also should be screened for HAV using antibody testing for immunoglobulin G (IgG) (note that some laboratories provide only a combined IgG and immunoglobulin M [IgM] HAV titer, which is acceptable). Individuals with chronic HBV have an added risk of hepatic decompensation from acute infection with HAV. Women with chronic HBV infection who have not already received the HAV vaccine series and who are not immune to HAV should receive the HAV vaccine series. Responses to the HAV vaccine are reduced in patients with HIV who have CD4 counts <200 cells/mm^3. Antibody response should be assessed in such patients 1 month after the HAV vaccine series is complete. If HAV antibody immunoglobulin (HAV Ab IgG) is negative, patients should be revaccinated when the CD4 count is >200 cells/mm^3.[1] Women who received the HAV vaccine

series when their CD4 count was ≥200 cells/mm³ 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, the HAV vaccine contains inactivated HAV, and the theoretical risk to the developing fetus is expected to be low.[8]

HBV/HIV Coinfection in Pregnancy

A study of 4,236 pregnant women with HIV in France who were followed between 2005 and 2013 found that the prevalence of HBV (HBsAg positive) was 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.[16] HBV/HIV coinfection was not associated with preterm delivery, lower CD4 counts, or detectable HIV viral load in this cohort.[16] In a retrospective analysis of response to ART among Italian women with HIV during 1,462 pregnancies, 12% of women had HBV/HIV coinfection.[17] In a multivariable analysis, women with only HIV had better CD4 responses on ART during pregnancy than women with HBV/HIV coinfection. However, no differences in maternal and infant outcomes were observed between women with HBV/HIV coinfection and women with HIV alone.

Therapy for HIV and HBV 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 immune reconstitution inflammatory syndrome, particularly in patients with high HBV DNA levels and severe liver disease.[1,18] Risk of miscarriage[19] and preterm labor and delivery may increase in people with acute HBV infection;[20] see Hepatitis B Virus Infection in the Adult and Adolescent Opportunistic Infection Guidelines.

The use of ARV drugs with anti-HBV activity during pregnancy in women with HBV mono-infection 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 HBV vaccine (known as passive-active immunoprophylaxis).[21] High maternal HBV DNA levels are strongly correlated with perinatal HBV transmission and with failures of HBV passive-active immunoprophylaxis.[22–25] Several studies and a meta-analysis of women with HBV mono-infection suggest that lamivudine (3TC) and tenofovir 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.[26–36] In addition to HBV viral load, the presence of certain HBV variants is also a risk factor for failure of HBV prophylaxis.[15,37]

3TC, emtricitabine (FTC), tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide (TAF, a prodrug of tenofovir) have activity against both HIV and HBV. All these drugs are preferred nucleoside reverse transcriptase inhibitors (NRTIs) for use during pregnancy in women with HBV/HIV coinfection, except TAF, which is an alternative NRTI, because data about use in pregnancy are more limited (see Table 4). Please see individual drug sections for TDF, TAF, FTC, and 3TC 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 when providing care 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 nucleotide or nucleoside analogues (NAs).

Several other antiviral agents have activity against HBV, including entecavir, adefovir, and telbivudine. However, these drugs have not been well evaluated in pregnancy, with too few exposures to assess overall risk. They **are currently not recommended** for pregnant women with HBV/HIV coinfection.[38]

In a systematic review and meta-analysis of single-drug anti-HBV therapy during pregnancy in women with chronic HBV mono-infection, antiviral therapy reduced perinatal transmission with no significant differences in congenital malformation rate, prematurity rate, and Apgar scores. TDF, 3TC, or telbivudine all improved maternal HBV viral suppression at delivery with no significant increase in the incidence of postpartum hemorrhage or cesarean section, and no significant increase in creatinine kinase levels.[39] For pregnant women with HBV/HIV coinfection, entecavir and telbivudine should be administered only in addition to a fully suppressive ART regimen for HIV and only if the potential benefits outweigh the potential risks. 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 resistance to 3TC and FTC). The Panel on Opportunistic Infections in Adults and Adolescents with HIV 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.[1] (See the Adult and Adolescent Opportunistic Infection Guidelines.)

Interferon alfa and pegylated interferon alfa are also **not recommended** for use during pregnancy, and they 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.[40]

Cases of exposure during pregnancy to any of the ARV drugs and HBV drugs listed above should be reported to the Antiretroviral Pregnancy Registry (online or by telephone at 1-800-258-4263).

Monitoring Women With HBV/HIV Coinfection During Pregnancy

Prior to initiating ARV drugs that are active against HBV, a baseline HBV DNA level should be measured. After initiating 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 Infection Guidelines).

Following initiation of ART, an elevation in hepatic enzymes can occur in women with HBV/HIV coinfection—particularly those with low CD4 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 can also increase the 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 transaminase levels should be assessed 1 month after initiating ARV drugs and at least every 3 months thereafter. If hepatotoxicity 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 should be monitored in pregnant women using the same monitoring schedule as the one recommended for nonpregnant adults.

Once HBV therapy with anti-HBV NAs is initiated, lifelong treatment is recommended.[1,41] Discontinuing anti-HBV agents may lead to reactivation of HBV, resulting in hepatocellular damage. If anti-HBV 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.[1]

Mode of Delivery

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 (see Intrapartum Care for Women with HIV). No data have been published on the role of cesarean delivery in reducing the risk of perinatal transmission of HBV in women with HBV/HIV coinfection. Currently, the guidelines for women with HBV mono-infection do not recommend performing a cesarean delivery to prevent perinatal transmission of HBV.[42–44]

Evaluating and Managing Infants Who Were Exposed to HBV

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 month, 2 to 3 months, and 6 months.[45,46] This regimen is >95% effective in preventing HBV infection in these infants. Maternal ART that includes NAs with anti-HBV activity will result in low or suppressed HBV viral loads near delivery, which should further reduce the risk of perinatal HBV transmission in women with HBV/HIV coinfection.[35,36]

Infant postvaccination testing for anti-HBs and HBsAg should be performed after completing the vaccine series, between the ages of 9 months and 18 months. Serologic testing should not be performed before age 9 months; this delay helps avoid detecting anti-HBs from HBIG that was administered during infancy and maximizes 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 aged ≤24 months who were born to mothers with HBV. 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 single dose of HBV vaccine and receive postvaccination serologic testing 1 to 2 months later. Infants whose anti-HBs levels remain <10 mIU/mL following single-dose re-vaccination should receive two additional doses of HBV vaccine to complete the second series, followed by post-vaccination serologic testing at 1 to 2 months after the final dose.[47]

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Special Populations: Hepatitis C Virus/HIV Coinfection

(Last updated December 29, 2020; last reviewed December 29, 2020)

Panel's Recommendations
• All pregnant women with HIV should be screened during the current pregnancy for hepatitis C virus (HCV) infection **(AIII)**.   • HCV screening should be repeated later in pregnancy in women who initially screen negative for HCV but who have persistent or new risk factors for HCV (e.g., new or ongoing injection or intranasal substance use) **(AIII)**. • All pregnant women with HIV should also be tested for hepatitis B virus (HBV) infection (see Hepatitis B Virus/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 **(AIII)**. If they screen negative for HAV antibodies (either IgG or total antibody (IgG and IgM)), they should receive the HAV vaccine series **(AIII)**. • All pregnant women with HIV (with or without HCV) who screen negative for HBV infection and lack HBV immunity (i.e., HBV surface antigen negative, HBV core antibody negative, and HBV surface antibody negative) should receive the HBV vaccine series **(AII)**. • Currently, treatment of HCV during pregnancy is not recommended (unless part of an approved experimental protocol) because of the lack of safety data on the use of HCV direct-acting antiviral medications in pregnant women. If considering initiating 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 with HIV, including those who have HCV coinfection **(AIII)**. • Pregnant women with HCV/HIV coinfection who are receiving ART should be counseled about the 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)**. • Women with HCV should be strongly considered for HCV treatment with direct-acting antiviral agents (DAAs) postpartum **(AI)**. • In women who have tested positive for HCV, HCV RNA should be evaluated after delivery to assess for spontaneous clearance of HCV infection, particularly as they are being considered for initiation of HCV therapy postpartum **(BII)**. • 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 not otherwise indicated (see Intrapartum Care for Women with HIV) **(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

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** when managing HCV during pregnancy.

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 Antiretroviral Guidelines, and Hepatitis C Virus Infection in the Adult and Adolescent Opportunistic Infection Guidelines). The American Association for the Study of Liver Diseases (AASLD), the Infectious Diseases Society of America (IDSA), and the International Antiviral Society–USA maintain updated information about treating patients with HCV/HIV coinfection. The guidelines are available online at HCVguidelines.org.

Screening and Vaccination

All pregnant women with HIV should be screened at entry into general HIV care and during each pregnancy for the following:

- Hepatitis B virus (HBV), unless they are known to have HBV/HIV coinfection or they have serologic documentation of HBV immunity (see Hepatitis B Virus/HIV Coinfection), *and*
- HCV infection, unless they are known to have HCV/HIV coinfection.

The observed prevalence for HCV infection was 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 among women with HIV in the United States are limited, the prevalence of HCV among women of childbearing age and children aged <2 years in the general population has increased substantially in recent years, partly because of the ongoing opioid epidemic.[3-9]

The Society for Maternal–Fetal Medicine and the American College of Obstetricians and Gynecologists recommend repeating HCV testing later in pregnancy for women who initially screen negative for HCV but who have persistent risk factors for HCV or who develop new risk factors for HCV infection (e.g., new or ongoing use of injected or intranasal substance use).[10] The male partners of all women with HCV/HIV coinfection should be referred for both HIV and hepatitis counseling and testing to prevent the sexual transmission of HIV and HCV; however, HCV is infrequently transmitted via heterosexual sex. 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 benefits of starting oral pre exposure prophylaxis (PrEP) to prevent HIV acquisition (see Preconception Counseling and Care for Women of Childbearing Age Living with HIV).

Newly available DAAs have dramatically improved HCV therapy; it is now possible to cure HCV infection in most patients.[11] Current HCV treatment guidelines recommend therapy for nearly all patients with HCV infection.[11] However, the management of HCV/HIV coinfection during pregnancy is complex. A Phase 1 study is now evaluating the safety and pharmacokinetics (PKs) of ledipasvir/sofosbuvir in pregnancy.[12] Ribavirin is also contraindicated in pregnancy, although it is no longer commonly used for the treatment of HCV.[13] If considering HCV treatment for a pregnant person, consultation with an expert in HIV and HCV is strongly recommended.

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 care system, so that HCV treatment can be offered after delivery (ideally before a subsequent pregnancy);
- To monitor for HCV-related hepatotoxicity, which has been associated with the use of antiretroviral (ARV) drugs in women with HCV/HIV coinfection;[14]
- To monitor for preterm birth, which has been associated with HCV/HIV coinfection in pregnant women;[1,8,15,16]
- To ensure vaccination against other viral hepatitis infections (HAV and HBV) when needed; *and*
- To ensure appropriate follow-up and evaluation of infants who were 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. All pregnant women in the United States should be screened for HCV at each pregnancy, except in settings where the prevalence of HCV infection is <0.1%.[11,17,18] False-negative anti-HCV immunoassay results can occur in individuals with HIV, but this is uncommon with the more sensitive immunoassays. If HCV infection is suspected despite a negative HCV antibody screen, a commercially available diagnostic quantitative plasma HCV RNA assay can be performed.[19,20] Individuals who have a positive HCV antibody test should undergo confirmatory testing for HCV RNA with this quantitative assay. Many laboratories now perform reflex RNA testing for individuals who test positive for HCV antibodies.

Pregnant women should also be tested for HCV RNA when they have indeterminate or negative serologic test results for HCV but are suspected of having HCV infection because of elevated aminotransaminase levels or risk behaviors (e.g., a history of injection drug use).[21]

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 the HAV vaccine should be assessed 1 month after the patient completes the vaccination series; those who are HAV antibody IgG negative should be revaccinated when the CD4 count is >200 cells/mm^3.[22] Women with HCV/HIV coinfection who screen negative for HBV and lack HBV immunity (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 receiving the HBV vaccine series may benefit from revaccination (see Hepatitis B Virus/HIV Coinfection).[23] The hepatitis B vaccination poses no apparent risk to developing fetuses, because current vaccines contain noninfectious HBsAg.[24]

Impact of HCV/HIV Coinfection on Progression and Perinatal Transmission of Both Viruses

Although the HCV viral load tends 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.[25,26]

Hepatitis C Virus Transmission

About 6% of infants born to women with HCV acquire HCV infection.[20] 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 twofold higher among women with HCV/HIV coinfection (10% to 20% transmission risk) than among women with HCV monoinfection.[27-30] These higher transmission rates likely are related to the higher levels of HCV viremia observed in patients with HCV/HIV coinfection and/or other HIV-related impacts on HCV disease activity.[16,31] Early and sustained control of HIV viremia with ART, however, could reduce the risk of HCV transmission to infants.[26,32-34] A European study of perinatal HCV transmission found that the use of effective ART for HIV was associated with a strong trend toward reduced rates of HCV transmission (odds ratio [OR] 0.26; 95% confidence interval [CI], 0.07–1.01).[32] In an Italian cohort, HCV transmission occurred in 9% of infants born to women with HCV/HIV coinfection, most of whom were on ART. No HCV transmissions occurred in infants born to women with HCV viral loads of <5 log IU/mL.[16]

HIV Transmission

In the absence of ART, maternal HCV/HIV coinfection can increase the risk of perinatal HIV transmission.[35,36] The risk of perinatal HIV transmission can 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

Data are limited on the optimal management of pregnant women with HCV/HIV coinfection. Recommendations on the use of ART during pregnancy for treating HIV and preventing perinatal HIV transmission are the same for women who have HCV/HIV coinfection as for those with HIV monoinfection (see General Principles Regarding Use of Antiretroviral Drugs during Pregnancy). 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 recommendations for HIV RNA monitoring during pregnancy.[37]

Hepatitis C Virus–Specific Therapy in Pregnancy

All currently available DAAs lack sufficient safety data to be recommended for use 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.[38] Some DAA regimens are approved for use with ribavirin in specific nonpregnant populations, because of the suboptimal treatment responses observed with the use of DAAs alone. Any treatment regimens that include ribavirin are **contraindicated** in pregnant women because of 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. The risk of teratogenicity persists for up to 6 months following ribavirin cessation and applies also to female partners of men taking ribavirin.[11] Pregnancies that occur in women taking ribavirin should be reported to the Ribavirin Pregnancy Registry (online or by phone at 1-800-593-2214)

Many interferon-free DAA regimens have been approved for the treatment of HCV. When determining the optimal regimen for an individual patient, clinicians must consider many factors, including HCV genotype, prior treatment experience, and stage of liver disease (e.g., compensated or decompensated cirrhosis). The following main classes of DAAs are currently available in the United States:[11,39]

- NS5A inhibitors: elbasvir, ledipasvir, pibrentasvir, velpatasvir
- NS5B nucleoside polymerase inhibitors: sofosbuvir
- NS3/4A protease inhibitors (PIs): glecaprevir, grazoprevir, voxilaprevir

DAAs are not yet recommended for use in pregnancy because of the lack of PKs and safety data; one small PK study that is investigating the use of ledipasvir/sofosbuvir in pregnant women with HCV alone demonstrated 100% virologic suppression and no safety concerns. Similarly, a small case series of 15 pregnant women treated with ledipasvir/sofosbuvir reported 100% virologic suppression at 12 weeks and no early safety concerns in the women or their infants.[40] Women with HCV/HIV coinfection should be strongly considered for HCV treatment with DAAs postpartum.[41] Potential drug interactions exist between the 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 the interactions between ARV drugs and anti-HCV drugs, see the Adult and Adolescent Antiretroviral Guidelines, the Adult and Adolescent Opportunistic Infection Guidelines, HCVGuidelines.org, and the HEP Drug Interaction Checker.

Monitoring Women with HCV/HIV Coinfection During Pregnancy

Hepatic enzyme levels can increase after ART is initiated in women with HCV/HIV coinfection—particularly in those with low CD4 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 coinfection may increase the hepatotoxic risk of certain ARV agents, specifically PIs and nevirapine. HCV monoinfection may increase the risk of intrahepatic cholestasis of pregnancy;[42] this risk also is higher among women with HCV/HIV coinfection than among women with HIV infection alone.[1] Pregnant women with HCV/HIV coinfection should be counseled about the signs and symptoms of liver toxicity, and transaminase levels should be assessed 1 month after initiating ART and then every 3 months. 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 discontinued temporarily. Differentiating between drug toxicity and a flare of HCV disease that is associated with immune reconstitution can be difficult; therefore, consulting an expert in HCV/HIV coinfection is recommended.

HCV RNA levels can fluctuate during pregnancy and postpartum, with frequent increases in HCV RNA levels during pregnancy followed by a drop in the postpartum period.[43] Spontaneous clearance of HCV can occur postpartum. [43-46] As a result, the AASLD and the IDSA recommend that women have their HCV RNA re-evaluated after delivery, particularly if they are being assessed for initiation of therapy with DAA.[41]

Rates of preterm delivery also are high among women with HCV/HIV coinfection. 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 not significantly different among women with lower or higher HCV RNA levels: 29% among women with HCV RNA <5 log IU/mL and 43% among women with HCV RNA >5 log IU/mL. Women with preterm delivery had significantly higher levels of HCV RNA than those who delivered at term.[16] A study of 4,236 pregnant women with HIV reported a higher risk of preterm delivery in women with HCV coinfection (OR 3.0; 95% CI, 1.6–5.7) than in women with HIV alone.[1] Infants born to women with HCV also were more likely to have low birth weights (defined as weighing <2,500 g) than those born to women without HCV (23 vs. 8%, $P < 0.01$).[8]

HCV infection in pregnancy may also be associated with increased risks for gestational diabetes, small for-gestational-age infants, and low birth weight infants.[5,47] Although currently no obstetric guidelines suggest that women with HCV infection should be monitored more frequently for diabetes or for fetal growth,[48] knowledge of these increased risks may inform clinical care.[10]

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 HCV transmission.[32,49-51] Thus, the general recommendations for mode of delivery are the same for women with HCV/HIV coinfection as for those with HIV infection alone (see Intrapartum Care for Women with HIV).

Evaluation of Infants Exposed to Hepatitis C Virus

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.[52] Sensitivity of HCV RNA testing is low at birth, and viremia can be intermittent or infection may resolve spontaneously; [5,53,54] 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.[55] Uptake of HCV testing is very low for infants who were exposed to HCV;[56] therefore, it is important for providers to counsel women about the need for pediatric follow-up and testing during the first few years of life.[8,57-59] The Pediatric Opportunistic Infection Guidelines provide further details about the diagnostic evaluation of infants who were exposed to HCV.

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HIV-2 Infection and Pregnancy

(Last updated December 29, 2020; last reviewed December 29, 2020)

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 virus 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 with HIV-2 should be treated as per guidelines for HIV-1 mono-infection but using antiretroviral (ARV) 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 (NRTIs) 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, darunavir/ritonavir, or lopinavir/ritonavir plus a dual-NRTI backbone of abacavir plus lamivudine (3TC), or tenofovir disoproxil fumarate (TDF) plus emtricitabine or 3TC are recommended for treating HIV-2 mono-infection in pregnant women and in women trying to conceive **(AIII)**. Zidovudine (ZDV) plus 3TC can be used as an alternative dual-NRTI backbone. See Updated Panel Recommendations Regarding the Use of Dolutegravir in Pregnancy in Recommendations for Use of Antiretroviral Drugs During Pregnancy and Appendix C: Antiretroviral Counseling Guide for Health Care Providers: Pregnant Women and Women who are Trying to Conceive.
• As with HIV-1, the possibility of hepatitis B virus/HIV-2 coinfection should be considered when choosing an ARV 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. According to the National HIV Surveillance System, there were 327,700 diagnoses of HIV in the United States from 2010 to 2017, of which 198 (0.06%) met the criteria for HIV-2 (HIV-2 mono-infection, n = 102; dual HIV-1 and HIV-2, n = 11; probable but unconfirmed HIV-2, n = 85).[6] Among these cases, 99 women had diagnoses of confirmed or probable HIV-2, and nine of these women had evidence of pregnancy at or after their diagnosis. No perinatal HIV-2 transmissions were reported. 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, the Centers for Disease Control and Prevention (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 that 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, Wadsworth Center[9] also offer HIV-2 viral load assays. The University of Washington accepts specimens forwarded from laboratories, such as Quest Diagnostics. 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 with HIV-2

Pregnant women 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 antiretroviral (ARV) 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] 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.[25] 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.[26, 27] HIV-2 drug resistance has been documented with various ARV drugs.[28, 29] 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 protease inhibitors (PIs) or INSTIs.[30]

HIV-2 has variable susceptibility to PIs, with lopinavir (LPV), saquinavir, and darunavir (DRV) having the most activity.[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, DRV/r, or LPV/r plus a dual-NRTI backbone of abacavir plus lamivudine (3TC), or tenofovir disoproxil fumarate (TDF) plus emtricitabine or 3TC are the recommended regimens for treating HIV-2 mono-infection in pregnant women and women trying to conceive. See Updated Panel Recommendations Regarding the Use of Dolutegravir in Pregnancy in Recommendations for Use of Antiretroviral Drugs During Pregnancy and Appendix C: Antiretroviral Counseling Guide for Health Care Providers: Pregnant Women and Women who are Trying to Conceive.
- Zidovudine (ZDV) plus 3TC can be used as an alternative dual-NRTI backbone.
- 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.

All infants born to mothers with HIV-2 (who do not have HIV-1) should receive a 4-week ZDV prophylaxis regimen, see Table 8 and Table 9 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 the New York State Department of Health. 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, see Diagnosis of HIV Infection in Infants and Children.[32] 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.

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Prenatal Care, Antiretroviral Therapy, and HIV Management in Women with Perinatal HIV Infection

(Last updated December 24, 2019; last reviewed December 29, 2020)

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, ART treatment 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 **(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

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). The majority of women with PHIV have reached childbearing age, and many are 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 other routes of transmission. However, the reproductive health care needs and the prevention of perinatal transmission in women with PHIV pose unique challenges. Adherence to ART is often 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] However, in some studies, the risk of premature delivery tends to be similar among women with PHIV and women with NPHIV after adjusting for age.[10]

Because women with PHIV have extensive ART experience,[8] optimal ART regimens should be selected using the same guiding principles used for ART-experienced adults; in particular, the ART regimen should be selected on the basis of resistance testing, pill burden, and the woman's specific ART history and preferences. Because individuals who acquired HIV perinatally have the potential to develop complex drug-resistance mutation patterns, clinicians may consider performing phenotypic resistance testing in these women during pregnancy when resistance testing is indicated. Regimens that optimize dosing intervals and minimize pill burden should be considered. 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 experience prolonged HIV infection, have received multiple ART regimens—including suboptimal monotherapy or dual-therapy regimens received as children, and are more likely to harbor drug-resistant virus. As many as 30% to 70% of pregnant women with PHIV have evidence of HIV drug resistance.[8,11-13] 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 achieve viral suppression.[8,11,13-17] However, in an analysis of data from SMARTT PHACS (Surveillance Monitoring for ART Toxicities Study – Pediatric HIV/AIDS Cohort Study) that included 2,123 births from 2007 to 2015, pregnant women with PHIV had a higher perinatal HIV transmission rate (1.1%; 95% confidence interval [CI], 0.3% to 4.3%) than pregnant women with NPHIV (0.4%; 95% CI, 0.2% to 1.0%); this higher rate was associated with a greater likelihood of detectable maternal viral load at delivery.[18] Women with PHIV are more likely to have detectable viral loads at delivery, lower CD4 T lymphocyte counts, and genotypic drug resistance than women with NPHIV; these factors can have implications during labor and delivery.[8,13,16,18,19] 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.[11,16] Cesarean delivery in these young women raises concerns for increased risk of adverse obstetric outcomes if repeated cesarean deliveries are required for future pregnancies.

Evidence from studies is conflicting as to whether women with PHIV have higher rates of preterm and SGA infants than women with NPHIV.[20,21] Several studies have demonstrated no associations between perinatally acquired HIV status and preterm birth, SGA infants, or low birth weight.[8,13,20-22] Other studies with smaller sample sizes have reported conflicting results:

- A case series reported high rates of preterm birth (31%) among women with PHIV.[11]
- 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.[16]

Women with PHIV also have poor rates of retention in care and viral suppression for up to 2 years postpartum.[23] 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. Another study found that, during 4 years of follow-up postpartum, there were four deaths due to AIDS-related complications among women with PHIV but none among the women with NPHIV.[16] 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 adherence interventions after delivery.

Psychosocial challenges in PHIV may be magnified due to the presence of a lifelong chronic illness, high rates of depression,[24] 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 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%.[25] 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.[26] A history of depression has also been associated with nonadherence to ART among pregnant women with PHIV.[27] 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 with HIV in the United Kingdom.[28]

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.[29] 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. There is a need to identify, develop or adapt, and implement culturally sensitive, women-centered interventions for improving HIV care continuum outcomes of pregnant and postpartum women living with HIV.[30] Coordination of care across multiple disciplines, including HIV primary care, OB/GYN, and perinatal case management, is advised.[31] Integration of reproductive health counseling and family planning services, including consistent counseling on condom use, sexually transmitted infection testing and prevention, optimal pregnancy spacing, and developmentally appropriate skill building to support disclosure, as indicated, is recommended.

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Acute HIV Infection

(Last updated February 10, 2021; last reviewed February 10, 2021)

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, who reside in jurisdictions with elevated HIV incidence, or 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 women, irrespective of trimester, and for breastfeeding women with acute HIV (see Table 4, Table 5, Recommendations for Use of Antiretroviral Drugs During Pregnancy, and Appendix C: Antiretroviral Counseling Guide) **(AII)**.
  - Raltegravir plus TDF plus FTC or a ritonavir-boosted protease inhibitor (either atazanavir ATV/r or darunavir/r) plus TDF plus FTC are *Alternative* ART regimens for pregnant and breastfeeding women with acute HIV **(AIII).** See Table 4, Table 5, and 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 with HIV **(AIII)**.
- Providers should inform individuals starting ART of the importance of strict adherence to rapidly achieve and maintain viral suppression **(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 acquiring HIV infection and should receive an ARV regimen that is appropriate for this elevated risk (see Table 6 in Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection) **(AII)**. 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] Women who are at risk for acquiring HIV during pregnancy and the postpartum period should consider using interventions that prevent HIV acquisition, such as oral daily pre-exposure prophylaxis (PrEP).[3] For more information, see Pre-exposure Prophylaxis (PrEP) to Reduce the Risk of Acquiring HIV During Periconception, Antepartum, and Postpartum Periods.

Risk of perinatal transmission after maternal acute HIV infection

Acute or recent HIV infection during pregnancy or breastfeeding is associated with an increased risk of perinatal HIV transmission, and a significant proportion of pediatric infections 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 of 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.

Diagnosis of acute HIV infection in pregnant women

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 still is 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, headache, diarrhea, oral ulcers, 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 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. 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 Mother-Infant Rapid Intervention at Delivery (MIRIAD) 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] Implementation of the recommendation for repeat HIV testing later in pregnancy has varied. 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] At a large, urban tertiary hospital in Florida, 82% of women were retested in the third trimester.[15]

Antiretroviral therapy for women with acute or recent HIV infection during pregnancy

Acute or recent HIV infection during pregnancy and breastfeeding is associated with a high risk of vertical transmission of HIV.[1,4] 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 drugs.[16,17] 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 4, Table 5, and Appendix C: Antiretroviral 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 (or tenofovir alafenamide) plus FTC (or lamivudine) is one of the recommended ARV regimens for treatment of acute and early infection in nonpregnant adults. *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 (either atazanavir/r or darunavir/r) plus TDF plus FTC (see Table 4 and Table 5). 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 the HLA-B*5701 gene variant; this will avoid delays in ART initiation while awaiting HLA-B*5701 test results.

Several studies have demonstrated that the use of integrase strand transfer inhibitor (INSTI)-based regimens is associated with shorter time to viral suppression compared with other ARV regimens.[18–20] Although 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 efavirenz (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 (74% vs. 43%, respectively; adjusted risk ratio 1.66 [95% CI, 1.3–2.1], $P < 0.0001$).[21] Similarly, in the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development P1081 trial, 408 ART-naive, late-presenting pregnant women in South America, Africa, Thailand, and the United States were randomized 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. Overall, 144 women (94%) in the RAL group and 129 (84%) in the EFV group achieved a viral load of < 200 copies/mL at delivery. Furthermore, 131 of 153 women (86%) on RAL-based ART versus 90 of 154 (58%) in the EFV group achieved a viral load below the limit of detection.[22]

Obstetrical and neonatal considerations

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 Counseling and Managing Women 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.

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Intrapartum Care for Women with HIV

(Last updated December 29, 2020; last reviewed December 29, 2020)

Panel's Recommendations

HIV Testing for Women with Unknown HIV Status in Labor

- Women who present in labor with unknown HIV status and women with increased risk of HIV infection who were not retested in the third trimester should undergo expedited antigen/antibody HIV testing **(AII)**. See Maternal HIV Testing and Identification of Perinatal HIV Exposure for more information.
  - If 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 intravenous (IV) zidovudine (ZDV) should be initiated pending the result of the differentiation test **(AII)**.
  - If acute HIV infection is suspected or if a woman has had recent HIV exposure, an HIV RNA assay should be done at the time of expedited antigen/antibody testing (AII). See Acute HIV Infection.

Intrapartum Antiretroviral Therapy (ART), Zidovudine (ZDV) Prophylaxis, and Mode of Delivery for Women with HIV

- See Table 7 Intrapartum Care and Recommended Interventions to Prevent Perinatal HIV Transmission for Women with HIV based on Maternal HIV RNA Levels at the Time of Delivery below.
- Women should continue taking their antepartum ART on schedule, during labor and before scheduled cesarean delivery (AIII).
- **For women with HIV RNA >1,000 copies/mL or unknown HIV RNA near the time of delivery (≥34 to 36 weeks gestation or 4 to 6 weeks before delivery):**
  - Intrapartum IV ZDV should be administered in the following situations based on laboratory and clinical information near the time of delivery: (a) HIV RNA >1,000 copies/mL, (b) unknown HIV RNA, (c) a suspected lack of adherence since the last HIV RNA result, or (d) a positive expedited antigen/antibody HIV test result during labor **(AI)**. Begin IV ZDV when women present in labor or at least 3 hours prior to scheduled cesarean delivery **(AII)**.
  - When HIV RNA is >1,000 copies/mL or is unknown near the time of delivery, scheduled cesarean delivery at 38 weeks gestation is recommended to minimize perinatal HIV transmission, irrespective of administration of antepartum ART **(AII)**.
  - Management of women originally scheduled for cesarean delivery because of HIV RNA >1,000 copies/mL who present in labor or with ruptured membranes must be individualized at the time of presentation **(BII)**. In these circumstances, evidence is insufficient to determine whether cesarean delivery reduces the risk of perinatal HIV transmission. Consultation with an expert in perinatal HIV (e.g., telephone consultation with the National Perinatal HIV/AIDS Clinical Consultation Center at 1-888-448-8765) may be helpful in rapidly developing an individualized delivery plan.
- **For women receiving ART with HIV RNA ≤1,000 copies/mL near the time of delivery (≥34 to 36 weeks gestation or 4 to 6 weeks before delivery):**
  - IV ZDV is not required for women who meet **ALL** of the following three criteria: (1) are receiving ART, (2) have HIV RNA <50 copies/mL at ≥34 to 36 weeks gestation (or 4–6 weeks before delivery), and (3) are adherent to their antiretroviral (ARV) regimen **(BII)**.
  - IV ZDV may be considered for women with HIV RNA ≥50 copies/mL and ≤1,000 copies/mL near delivery (≥34 to 36 weeks gestation) **(BII)**. Data are insufficient to determine whether administration of IV ZDV to women with HIV RNA levels between 50 copies/mL and 1,000 copies/mL provides any additional protection against perinatal HIV transmission. This decision can be made on a case-by-case basis, taking into consideration the woman's recent ART adherence and her preferences and involving expert consultation if needed **(CII)**.
  - Scheduled cesarean delivery performed solely for prevention of perinatal HIV transmission in women receiving ART with HIV RNA ≤1,000 copies/mL near the time of delivery is not 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 of labor is indicated for non-HIV-related reasons, it should be performed at the standard time for obstetric indications **(AII)**. Labor should not be induced to prevent perinatal HIV transmission.

- 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 is not an indication for cesarean delivery to prevent HIV transmission **(BII)**.

Other Intrapartum Management Considerations (see Table 7 below).

- Fetal scalp electrodes for fetal monitoring should be avoided, particularly when maternal HIV RNA is not suppressed (≥50 copies/mL) or is unknown, because of the potential risk of HIV transmission **(BIII)**. See Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV.
- Artificial rupture of membranes (ROM) and operative vaginal delivery with forceps or a vacuum extractor should follow standard obstetric indications but should be avoided if possible in women with HIV RNA ≥50 copies/mL **(BIII)**.
- The ARV regimen a woman is receiving should be taken into consideration when using methergine to treat excessive postpartum bleeding caused by uterine atony.
  - In women who are receiving a cytochrome P450 (CYP) 3A4 enzyme inhibitor (e.g., a protease inhibitor or 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

Overview of Intrapartum Care for Women with HIV

Women with HIV require specialized care during labor and delivery to optimize maternal health outcomes and to prevent perinatal HIV transmission. Documentation of HIV status should be assessed in all women during labor, and HIV testing should be offered to those with unknown or undocumented HIV status, recent HIV exposure, and/or signs of acute HIV (see Maternal Testing and Identification of Perinatal HIV Exposure and Acute HIV Infection). Because maternal HIV RNA level is directly linked to the risk of perinatal HIV transmission,[1] the Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission (Panel) recommends viral load testing throughout pregnancy and specifically at 34 to 36 weeks gestation (or 4–6 weeks before delivery) to inform decisions about intrapartum care. The risk of perinatal HIV transmission is reduced to very low levels in pregnant women receiving antiretroviral therapy (ART) who have documented viral suppression (<50 copies/mL) near delivery.[1-3] Panel recommendations about intrapartum care to prevent HIV transmission are based on maternal HIV RNA levels and encompass continuation of maternal ART, intrapartum intravenous (IV) zidovudine (ZDV) during labor and delivery, scheduled cesarean delivery, and other intrapartum management considerations. Table 7 provides an overview of the Perinatal Panel recommendations for intrapartum care based on maternal HIV RNA, but these recommendations are discussed in the following sections.

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) (see Maternal HIV Testing and Identification of Perinatal HIV Exposure). Expedited repeat HIV testing is also recommended for women who present in labor and 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.[4,5] Factors that may increase the risk of infection include diagnosis of a sexually transmitted infection, illicit drug use, exchange of sex for money or drugs, multiple sexual partners during pregnancy, a

sexual partner who is at risk of HIV infection or who is known to have HIV, signs or symptoms of acute HIV infection, or living in a region with an elevated incidence of HIV in women of childbearing age.[4] Women who test positive on the initial HIV test during labor should be presumed to have HIV until follow-up testing clarifies their HIV status. To prevent perinatal HIV transmission, intrapartum IV ZDV should be started immediately, as discussed below, and women should not initiate breastfeeding until HIV infection is definitively ruled out. For additional information, see Postpartum Follow-up of Women with HIV Infection and Care, Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection, and Table 9.

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. No further testing is required for specimens that are nonreactive on the initial immunoassay, unless the woman has had recent HIV exposure or acute infection is suspected, in which case, an HIV RNA assay should be obtained (see Maternal HIV Testing and Identification of Perinatal HIV Exposure). Women with an initial positive antigen/antibody combination immunoassay result should be tested with an FDA-approved antibody immunoassay that differentiates HIV-1 antibodies from HIV-2 antibodies and an HIV RNA assay to screen for both acute and chronic HIV-1 infection (see Revised Recommendations for HIV Testing of Adults, Adolescents, and Pregnant Women in Health-Care Settings and the resource page for laboratory testing for HIV from the Centers for Disease Control and Prevention). If the follow-up antibody test result is negative, results of the HIV RNA test should be reviewed to rule out acute infection as a cause of the initial positive test result before ART is stopped (see Acute HIV Infection). Those with a high level of HIV-1 RNA and a negative confirmatory HIV assay most likely have acute HIV infection. If both the HIV-1 RNA and the confirmatory HIV assay are negative, the initial HIV test result may have been a false positive.

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 and State Laws That Address High-Impact HIV Prevention Efforts).

Intrapartum Continuation of Antenatal Antiretroviral Drugs

ART is recommended for the treatment of HIV and prevention of perinatal HIV transmission in all pregnant women with HIV, regardless of CD4 T lymphocyte (CD4) cell count and HIV RNA (viral load). Women should continue their antepartum ARV regimen on schedule as much as possible during the intrapartum period to maintain maximal virologic suppression and to minimize the chance of developing drug resistance. When cesarean delivery is planned, oral medications can be administered preoperatively with sips of water. Medications that must be taken with food 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.

Decisions Regarding the Use of Intrapartum Intravenous Zidovudine

Intrapartum administration of IV ZDV provides antiretroviral pre-exposure prophylaxis at a time when infants are at increased risk of exposure to maternal blood and body fluids. Although the PACTG 076 ZDV regimen included a continuous IV infusion of ZDV during labor for all women, decisions regarding the use of IV ZDV during labor are now based on maternal ART, HIV RNA level, and adherence considerations (see Table 7 below). IV ZDV is also recommended for women with an initial diagnosis of HIV during labor and women with HIV whose HIV RNA level is unknown.

Current evidence indicates that intrapartum IV ZDV reduces perinatal HIV transmission for women with HIV RNA >1,000 copies/mL who are on ART, but the benefits for women with HIV RNA ≤1,000 copies/mL are less clear. Using data from 1997 to 2010, the French Perinatal Cohort Study evaluated the association between

IV ZDV and perinatal HIV transmission based on HIV RNA levels in >11,000 pregnant women with HIV who were on ART (72% of the women recieved triple-ARV regimens). The majority of the women (95%) received IV intrapartum ZDV.[6] Among women with HIV RNA ≥1,000 copies/mL whose infants received only ZDV for prophylaxis, the risk of perinatal HIV transmission was significantly higher without maternal IV ZDV (10.2%) than with maternal IV ZDV (2.5%; $P < 0.01$), but this difference was not observed if the neonate received a combination prophylaxis of two or more ARV drugs (4.8% with IV ZDV vs. 4.1% without IV ZDV, $P = 0.83$). Among women with HIV RNA <1,000 copies/mL at delivery, transmission rates did not differ significantly between those who received IV ZDV (0.6%, 47 of 8,132 infants) and those who did not (0 of 369 infants, $P > 0.20$).

In a European cohort of infants who were considered to be at high risk of perinatal HIV transmission, lack of IV ZDV during labor was associated with transmission on univariate analysis but not after the results were adjusted for maternal HIV RNA and other factors (adjusted odds ratio with IV ZDV was 0.79; 95% confidence interval, 0.55–1.15; $P = 0.23$).[7] In a cohort of 717 women who delivered between 1996 and 2008 in Miami, not receiving IV ZDV during labor (n = 67) was not associated with an increased risk of perinatal HIV transmission.[8] The majority of these women were receiving ART (89%) and had HIV RNA <1,000 copies/mL (75%) at delivery.

Based on available data, the Panel recommends that IV ZDV should continue to be administered to women with HIV RNA >1,000 copies/mL near delivery (or to women with HIV who have unknown HIV RNA levels), regardless of a woman's antepartum ARV regimen. Though not required, administration of intrapartum IV ZDV may be considered for women with HIV RNA levels ≥50 copies/mL and ≤1,000 copies/mL or in women for whom there are concerns about adherence to or tolerance of their ARV regimens in late pregnancy. Many experts think the data are insufficient to determine whether administration of intrapartum IV ZDV to women with HIV RNA between 50 copies/mL and 1,000 copies/mL provides any additional protection against perinatal transmission. However, the transmission risk is slightly higher (approximately 1% to 2%) when HIV RNA is in the range of 50 copies/mL to 999 copies/mL than when it is <50 copies/mL (transmission risk is ≤1%).[1,6,9]

IV ZDV is **not** required for women who meet ALL of the following three criteria: (1) are receiving ART, (2) have HIV RNA <50 copies/mL at ≥34 to 36 weeks gestation (or 4–6 weeks before delivery), and (3) are adherent to their ARV regimen. However, a study showing that 6 percent of women with suppressed HIV RNA levels during pregnancy had viral load rebound near delivery[10] highlights the importance of using clinical judgement when making the decision to use intrapartum IV ZDV, regardless of the patient's viral load. The additional benefit of IV ZDV in women who are receiving ART and are virally suppressed (HIV RNA <50 copies/mL) has not been evaluated in randomized clinical trials.

If a patient has known or suspected ZDV resistance, intrapartum use of IV ZDV 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 its proven record in reducing the risk of perinatal HIV transmission, even in the presence of maternal resistance to the drug (see Antiretroviral Drug Resistance and Resistance Testing in Pregnancy).

Administration of Intrapartum IV ZDV

Intrapartum IV ZDV is recommended for women with HIV RNA >1,000 copies/mL or unknown HIV RNA near the time of delivery or when they present in labor. In women with HIV RNA >1,000 copies/mL who are undergoing a scheduled cesarean delivery for prevention of perinatal HIV transmission, IV ZDV administration should begin at least 3 hours before the scheduled cesarean delivery; **women should receive a 1-hour loading dose of ZDV at 2 mg/kg followed by a continuous IV ZDV infusion of 1 mg/kg for 2 hours (minimum of 3 hours total)**. This recommendation is based on a pharmacokinetic (PK) study in which ZDV was administered orally during pregnancy and as a continuous infusion during labor. Maternal ZDV levels were measured at

baseline, after the initial IV loading dose, and then every 3 to 4 hours until delivery. ZDV levels were also measured in cord blood.[11] Systemic and intracellular ZDV levels increased from baseline but appeared to stabilize after 3 hours of infusion; cord blood ZDV 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, administering IV ZDV is not required.

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 ZDV administration and delivery. For example, some experts recommend administering the 1-hour loading dose of IV ZDV and not waiting to complete additional administration before proceeding with delivery when an expedited delivery is indicated.

Use of Oral Intrapartum ZDV

In some international studies, oral (rather than IV) ZDV has been administered during labor. Data are limited on the PKs of oral versus IV ZDV during labor. In studies of oral dosing in labor, ZDV levels were lower than they were with IV dosing, and PK parameters suggested erratic absorption during labor.[12,13] Therefore, IV administration is recommended over oral administration in the United States for women with HIV RNA >1,000 copies/mL near delivery. In situations where IV administration is not possible, clinicians can consider administering oral ZDV using a 600-mg loading dose and then ZDV 400 mg every 3 hours,[13] although no benefit of using this approach has been proven.

Transmission and Mode of Delivery

Current Recommendations *on Mode of Delivery*

Scheduled cesarean delivery, defined as cesarean delivery performed before the onset of labor and before rupture of membranes, is recommended at 38 weeks gestation for prevention of perinatal HIV transmission in women with HIV RNA levels >1,000 copies/mL near delivery and for women with unknown HIV RNA levels. Although 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 to 36 weeks gestation (4–6 weeks before delivery) to inform decisions about mode of delivery and optimal treatment of the newborn. The American College 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.[14]

Recommendations for cesarean delivery to prevent perinatal HIV transmission were initially based on findings from a multicenter, randomized clinical trial[15] and from a large individual patient data meta-analysis[16] that were conducted before the availability of viral load information, when most women with HIV received either no ARV drugs or ZDV as a single drug. The HIV RNA threshold of 1,000 copies/mL for decisions about mode of delivery was based largely on data from a 1999 report of the Women and Infants Transmission Study, a large prospective cohort study that reported no cases of perinatal HIV transmission among 57 women with HIV RNA levels <1,000 copies/mL.[17] Results of studies conducted since then have been extrapolated to make current recommendations about the mode of delivery in an era when ART recommended for all pregnant women and viral load information is readily available.

In a report on births to women with HIV in 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 of 3,544; 0.3%) were not significantly different from those in women who had a planned vaginal delivery (6 of 2,238; 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 with suppressed viral loads on ART (0.3% in both groups of women).[18] Among 290 deliveries in women with HIV in Finland from 1993 to

2013, 75.4 percent of women delivered vaginally, 12.5 percent delivered by elective cesarean, and 12.5 percent delivered by emergency cesarean; 80 percent had HIV RNA <50 copies/mL. No perinatal HIV transmissions occurred across the delivery methods.[19] For preterm deliveries in women with HIV RNA <1,000 copies/mL, an analysis of data from the French Perinatal Cohort found that 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.[18]

Given the low perinatal HIV transmission rates achievable with the use of maternal ART, the benefit of scheduled cesarean delivery is difficult to evaluate for women who are virally suppressed. It is unclear whether scheduled cesarean delivery confers any additional benefit in reducing transmission. No evidence to date suggests any benefit from scheduled cesarean delivery in women who have been receiving ART for several weeks and who are virally suppressed at or near delivery. Furthermore, evidence exists that complication rates for cesarean deliveries are higher in women with HIV than in women without HIV.[20] 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 no evidence indicates that a scheduled cesarean delivery performed solely for prevention of perinatal HIV 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.

Timing of 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.[21,22] 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.[14] 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.

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) ($P < 0.001$). No statistically significant association existed between mode of delivery and infant RDS in an adjusted model that included infant gestational age and birth weight.[23] Although newborn complications may be increased with planned cesarean delivery at <39 weeks gestation, the benefits of planned cesarean delivery at 38 weeks are generally thought to outweigh the risks if the procedure is performed to prevent HIV transmission.

In women with HIV RNA ≤1,000 copies/mL, cesarean delivery is not recommended to prevent perinatal HIV transmission. The Panel recommends that women should be delivered according to standard obstetric indications; **labor should not be induced at 38 weeks for prevention of perinatal HIV transmission**. When scheduled cesarean delivery is performed in women with HIV RNA ≤1,000 copies/mL for an indication other than preventing HIV transmission, cesarean delivery should be scheduled based on ACOG guidelines for women without HIV. A comparison of 613 women (with HIV RNA levels <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 obstetric indications.[24]

Cesarean Delivery for 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 (see Recommendations of Use of ARVs During Pregnancy and Women Who Have Not Achieved Viral Suppression on Antiretroviral Therapy).[25-29] In this instance, scheduled cesarean delivery is likely to provide additional benefit in reducing the risk of perinatal transmission of HIV, 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 <1,000 copies/mL by the day of delivery. No data are available to address the management of an elite controller (i.e., someone who has previously maintained an undetectable HIV RNA level without ART) who presents in labor and is not receiving ART; however, in this setting, it would appear reasonable to administer IV ZDV and allow for vaginal delivery **(CIII)**.

Risk of Maternal Complications *with Cesarean Delivery*

Administration of perioperative antimicrobial prophylaxis is recommended for all women to decrease maternal infectious morbidity associated with cesarean delivery. Most studies performed in the era before routine ART was recommended 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.[30-35] 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.[36,37] Complication rates in women with HIV in most studies[15,38-42] 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.[20] 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 (odds ratio [OR] 3.12) and no reduction in perinatal HIV transmission among the mothers on ART.[43] 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 without clear evidence of benefit, especially in younger women who are likely to have additional pregnancies and perhaps multiple cesarean deliveries. The risks of abnormal placentation (e.g., placenta previa, placenta accreta, placenta increta, placenta percreta), bowel and bladder injury, and intrapartum hemorrhage increase as the number of cesarean deliveries a woman has had increases. These risks should be considered and discussed with the woman before proceeding with a cesarean delivery.[44,45]

Managing Women Who Present in Early Labor or with Ruptured Membranes

Most studies have shown a similar risk of perinatal 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).[2] Although a 2001 meta-analysis found that a longer duration of ruptured membranes was associated with an increased risk of perinatal HIV transmission,[46] it is not clear how soon after the onset of labor or the rupture of membranes the benefit of cesarean delivery is lost for women with HIV RNA >1,000 copies/mL.[47] Later data on the association between the duration of rupture of membranes (ROM) and

perinatal HIV transmission in the era of ART and viral load measurement are reassuring. A prospective cohort study of 707 pregnant women in Ireland showed that among 493 women on ART with HIV RNA levels <1,000 copies/mL, no cases of perinatal transmission occurred among those 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.[8]

In a large, prospective, population-based surveillance study in the United Kingdom and Ireland that evaluated data on 2,116 pregnancies between 2007 to 2012, there was no difference in perinatal HIV transmission between women with a ROM duration of ≥4 hours (0.64%) and those with a ROM duration of <4 hours (0.34%). Among women with HIV RNA <50 copies/mL, the transmission rate for a ROM duration ≥4 hours was 0.14% and did not differ from the rate for a ROM duration of <4 hours (0.12%). The median duration of ROM was 3 hours 30 minutes (interquartile range [IQR] 1–8 hours).The infants in this study were delivered at term, vaginally or by emergency cesarean delivery, to women with HIV who were on ART; the majority of women (89%) had HIV RNA <50 copies/mL and only 1 percent of them had HIV RNA ≥1,000 copies/mL. Among preterm infants, no transmissions occurred during 163 deliveries where the maternal viral load was <50 copies/mL.[48]

Because it is not clear whether cesarean delivery after onset of labor reduces the risk of perinatal HIV transmission in women with HIV RNA >1,000 copies/mL, management of women originally scheduled for cesarean delivery who present in labor or with ruptured membranes 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 [1 888-448-8765]) may provide assistance in rapidly developing an individualized plan.

If spontaneous ROM occurs at >34 weeks gestation before labor or early in labor in women whose HIV RNA level is ≤1,000 copies/mL, interventions to decrease the interval to delivery (e.g., administration of oxytocin) should be considered based on obstetric considerations. When membrane rupture occurs before 34 weeks gestation, decisions about timing of delivery should be based on best obstetric 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.

Other Intrapartum Management

Obstetric Procedures

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 in some studies, primarily those performed in the pre-ART era.[49-52] Data are limited on the use of fetal scalp electrodes during labor in women who are receiving suppressive ART and who have an undetectable viral load. The use of fetal scalp electrodes for fetal monitoring is an additional source of perinatal HIV exposure for the infant and should be avoided in the setting of maternal HIV infection when possible. If a fetal scalp electrode is used, some Panel members would manage the infant as being at high risk of perinatal HIV transmission even when the mother is virally suppressed (HIV RNA <50 copies/mL). See Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV.

Based on data discussed in the previous section (see Managing Women Who Present in Early Labor or with Ruptured Membranes), artificial ROM can be performed for standard obstetric indications in women with HIV RNA <50 copies/mL who are on ART and are virally suppressed. Artificial ROM should be avoided in women with HIV RNA ≥50 copies/mL, unless there is a clear obstetric indication. Although no data exist about the risks of perinatal HIV transmission with intrauterine pressure catheters, clinicians may use them with caution when indicated.

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. ACOG now recommends delaying cord clamping for 30 to 60 seconds after birth in vigorous term and preterm infants.[53-55] In the setting of HIV infection, a recent study of 64 mother-infant pairs in which 32 infants had early cord clamping (performed <30 seconds after birth) and 32 infants had delayed cord clamping (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 ARV regimens. During 18 months of follow up, there were no HIV transmissions and no increased risk of jaundice or polycythemia in infants with delayed cord clamping.[56]

Intrapartum Epidural Use and Pharmacologic Interactions with ARV Drugs

Ritonavir (RTV) inhibition of cytochrome P450 (CYP) 3A4 decreases the elimination of fentanyl by 67 percent. This raises concerns about a possible increased risk of respiratory depression, particularly with patient-controlled analgesia during labor, in women who are receiving regimens that contain RTV. However, a pharmacokinetic simulation study suggested that even with maximal clinical dosing regimens of epidural fentanyl over 24 hours, RTV-induced CYP3A4 inhibition is unlikely to produce the plasma fentanyl concentrations that are associated with a decrease in minute ventilation.[57] This suggests that epidural anesthesia can be used safely regardless of a patient's ARV regimen.

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 device. Peters et al. reviewed the deliveries of 9,072 women with HIV in the United Kingdom between 2008 and 2016. The percentage of women with viral suppression was 80 percent for the deliveries from 2007 through 2011 and 90 percent for those from 2012 through 2014. Among the 3,023 of 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 one 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.[58] Based on these data, the Panel recommends that operative delivery with forceps or a vacuum extractor should follow standard obstetric indications but should be avoided, if possible, when HIV RNA is ≥50 copies/mL. No data from the ART era address the risk of perinatal HIV transmission associated with episiotomy or with vaginal or perineal tears 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).

Postpartum Hemorrhage, ARV 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 (COBI) has been associated with exaggerated vasoconstrictive responses.[59] When uterine atony results in excessive postpartum bleeding in women who are receiving PIs or COBI, 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. No known drug-drug interactions limit the adjunctive use of tranexamic acid in this setting.

Table 7. Intrapartum Care and Recommended Interventions to Prevent Perinatal HIV Transmission for Women with HIV, Based on Maternal HIV RNA Levels at the Time of Delivery

All women with HIV should be receiving antiretroviral therapy (ART) or initiate ART in pregnancy as early as possible to suppress HIV RNA to undetectable levels (<50 copies/mL).

Maternal HIV RNA at Time of Delivery Assessed at ≥34 to 36 Weeks Gestation (or 4–6 Weeks Before Delivery) with No Concerns Regarding ART Adherence[a]				
	<50 copies/mL and on ART with No Concerns About Adherence	**≥50 to ≤1,000 copies/mL**	**>1,000 copies/mL**	• **Unknown HIV RNA** • **ART Adherence Concerns** • **Not Receiving ART** • **HIV Diagnosis in Labor**
Intrapartum ART	Women should take their prescribed ART on schedule as much as possible during labor and before scheduled cesarean delivery **(CIII)**. In general, ARV regimens are initiated postpartum for women diagnosed with HIV during labor.			
Intrapartum IV ZDV	Not required **(BII)**.	Not required but may be considered **(CII)**; many experts recommend.	Yes, recommended **(AI)**.[b] IV ZDV: 1-hour loading dose at 2 mg/kg followed by a continuous ZDV infusion of 1 mg/kg for 2 hours (at least 3 hours total) **(AII)**.	
Mode of delivery	Normal vaginal delivery[c] **(AII)**.	Normal vaginal delivery[c] **(AII)**.	Scheduled cesarean delivery at 38 weeks[d] **(AII)**.	Individualized care, see footnote.[d]
Artificial rupture of membranes[e]	Per standard obstetric indications **(BII)**.	Avoid if possible **(BIII)**.	Not applicable, cesarean delivery recommended.	Avoid if possible in women with detectable or unknown viral load who are not receiving a cesarean delivery **(BIII)**.
Induction of labor	Per standard obstetric indications, including use of pitocin. **Women with HIV RNA ≤1,000 copies/mL should NOT be routinely induced at 38 weeks.**		Not applicable, scheduled cesarean delivery recommended.	Avoid if possible **(BIII)**.
IUPC	Data not available for women with HIV; use IUPC with caution and only if there are clear obstetric indications.			

Maternal HIV RNA at Time of Delivery Assessed at ≥34 to 36 Weeks Gestation (or 4–6 Weeks Before Delivery) with No Concerns Regarding ART Adherence[a]				
	<50 copies/mL and on ART with No Concerns About Adherence	**≥50 to ≤1,000 copies/mL**	**>1,000 copies/mL**	• **Unknown HIV RNA** • **ART Adherence Concerns** • **Not Receiving ART** • **HIV Diagnosis in Labor**
Fetal scalp electrodes for fetal monitoring	Avoid, particularly when maternal viral load is not suppressed (≥50 copies/mL) or is unknown, because of the potential risk of HIV transmission **(BIII)**. See Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV.			
Operative delivery with forceps or a vacuum extractor	Per standard obstetric indications **(BIII)**.	Avoid for women in the setting of viremia if possible **(BIII)**.		
Delayed cord clamping	Per standard obstetric indications and care.			
Use of methergine for postpartum hemorrhage	Because of potential drug interactions with some ARV drugs, consider a woman's ARV regimen when treating postpartum bleeding caused by uterine atony **(BIII)**.[f]			
Infant ARVs and infant feeding	See Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV, Table 8, Table 9, Postpartum Care, and Guidelines for Counseling and Managing Women with HIV in the United States Who Desire to Breastfeed.			

Key: ART = antiretroviral therapy; CYP3A4 = cytochrome P450 3A4; HIV = human immunodeficiency virus; IUPC = intrauterine pressure catheter; IV = intravenous; RNA = ribonucleic acid; ZDV = zidovudine

[a] Assess ART adherence at every visit and upon presentation for delivery.
[b] Begin IV ZDV when women present in labor or at least 3 hours before a cesarean delivery using a 1-hour loading dose of ZDV at 2 mg/kg followed by a continuous ZDV infusion of 1 mg/kg for at least 2 hours **(AII)**.
[c] Scheduled cesarean delivery performed solely for prevention of perinatal HIV transmission in women receiving ART with HIV RNA ≤1,000 copies/mL **is not 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 obstetric indications **(AII)**.
[d] Provide individualized care. If HIV RNA is >1,000 copies/mL or unknown, evidence is insufficient to determine whether cesarean delivery reduces the risk of perinatal HIV transmission for women who present in spontaneous labor or with ruptured membranes. 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 1-888-448-8765) may be helpful in rapidly developing an individualized plan.
[e] In women on ART with suppressed viral load (HIV RNA <50 copies/mL), duration of ruptured membranes is not associated with an increased risk of perinatal transmission and is not an indication for cesarean delivery to prevent HIV transmission **(BII)**.

[f] Consider drug interactions with ART when treating postpartum bleeding caused by uterine atony. In women who are receiving a cytochrome P450 3A4 enzyme inhibitor (e.g., a protease 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 if, 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

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Postpartum Follow-Up of Women With HIV

(Last updated December 29, 2020; last reviewed December 29, 2020)

Panel's Recommendations
• Antiretroviral therapy (ART) is currently recommended for all individuals with HIV to reduce the risk of disease progression and to prevent the sexual transmission of HIV **(AI)**. • ART should be continued after delivery **(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)** and plans for future pregnancies. • Because the immediate postpartum period poses unique challenges to ART adherence, arrangements for new or continued supportive services should be made before hospital discharge **(AII)**. • Women with a positive rapid HIV antibody test during labor require immediate linkage to HIV care and comprehensive follow-up, including for confirmation of HIV infection **(AII)**. • Prior to hospital discharge, the woman should be given ART for herself and her newborn to take at home (AIII). • Breastfeeding is not recommended for women in the United States who have confirmed HIV or are presumed to have HIV, because safer infant feeding alternatives are available **(AI).** Women who desire to breastfeed should receive evidence-based counseling on infant feeding options **(AIII)**, see Counseling and Managing Women with HIV in the United States Who Desire to Breastfeed. • 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)**. • Clinicians should discuss future reproductive plans and timing, as well as the risks and benefits of conceiving on specific antiretroviral (ARV) medications and the use of appropriate contraceptive options to prevent unintended pregnancy **(AIII)**. • Contraceptive counseling should involve shared decision-making and should start during the prenatal period; a contraceptive plan should be developed prior to hospital discharge, as desired by the patient **(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

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 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;
- Supportive services;
- Coordination of care through case management for the woman, her child (or children), and other family members; *and*
- Prevention of secondary transmission for partners with differing HIV status, including counseling on the use of condoms, antiretroviral therapy (ART) to maintain virologic suppression in the partner who has HIV (i.e., treatment as prevention), and the potential use of pre-exposure prophylaxis (PrEP) by the partner who does not have HIV (see Pre-exposure Prophylaxis (PrEP) to Reduce the Risk of Acquiring HIV During Periconception, Antepartum, and Postpartum Periods).

Supportive services should be tailored to the individual woman's needs and can include screening for intimate partner violence; case management; child care; respite care; assistance with basic needs, such as housing, food, and transportation; peer counseling; and legal and advocacy services. Ideally, these services 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 within 3 weeks postpartum and that postpartum care be provided as an ongoing process based on a woman's individual needs, rather than as a single postpartum visit.[1] Women with HIV, particularly those who struggle with ART adherence, 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 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 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 hospital discharge, the mother should receive ART for herself and her newborn. Special hospital programs may need to be established to support dispensing ART to mothers before discharge.

Postpartum Maternal Antiretroviral Therapy

ART should be continued postpartum. Decisions about any changes to an ART regimen after delivery should be made after discussion between the woman and her HIV care provider, ideally prior to delivery. When providing counseling about postpartum ART, health care providers should consider the woman's desire for future planned or potential for unplanned pregnancies in the context of the woman's anticipated ART regimen, choice of contraceptive, and the potential for any drug-drug interactions during the postpartum period that were not an issue during pregnancy (see Preconception Counseling and Care for Women of Childbearing Age with HIV and Appendix C: Antiretroviral Counseling Guide for Health Care Providers: Pregnant Women and Women who are Trying to Conceive). Some ART regimens that are recommended for nonpregnant adults (see the Adult and Adolescent Guidelines) may not be recommended for use during pregnancy or in women who are trying to conceive, because insufficient data exist regarding pharmacokinetics or safety concerns. See Recommendations for Use of Antiretroviral Drugs During Pregnancy, Table 4, Table 5, Teratogenicity, and Combination Antiretroviral Drug Regimens and Maternal and Neonatal Outcomes for additional information and 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 secondary transmission of HIV.[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 of HIV to a discordant partner by 93%.[4] According to the Centers for Disease Control and Prevention, people with HIV who take ART as prescribed and achieve and maintain an undetectable viral load have effectively no risk of transmitting HIV through sex (i.e., Undetectable = Untransmittable).[5]

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.[6–10] During the postpartum period, women may have difficulty with medical appointment follow-up, including appointment adherence, which can affect ART adherence. Systematic monitoring of retention in HIV care is recommended for all individuals with HIV, but special attention is warranted for postpartum women.

Maternal Adherence to ART and Postpartum Depression

A number of studies have suggested that postpartum depression is common among women with HIV.[11–19] The U.S. Preventive Services Task Force recommends screening all postpartum women for postpartum depression[20] using a validated tool (e.g., the Edinburgh Postnatal Depression Scale); such screening is especially important for women 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.[2,21–24]

Poor adherence has been shown to be associated with virologic failure, development of ARV drug resistance, and decreased long-term effectiveness of ART.[25–27] In women who achieve viral suppression by the time of delivery, postpartum ART simplification to once-daily, co-formulated 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 Antiretroviral Guidelines). For women who are continuing ART and who received increased protease inhibitor (PI) doses during pregnancy, available data suggest that doses can be reduced to standard doses immediately after delivery.

Secondary Sexual Transmission and Contraception

The postpartum period is a critical time for addressing safer sex practices to reduce secondary transmission of HIV to partners,[28] and clinicians should begin discussing these practices with the patient during the prenatal period. Topics for discussion during counseling on prevention of secondary transmission to the partner without HIV should include condom use, ART for the partner with HIV to maintain viral suppression below the limit of detection, and the potential use of PrEP by the partner who does not have HIV. With full, sustained viral suppression in the woman—with or without reliable PrEP use by her partner—HIV is untransmittable (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 soon after delivery.[29] 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 routine postpartum visit. If the insertion of a LARC is postponed until the postpartum visit, medroxyprogesterone acetate (DMPA-IM) is a contraceptive option that can be given to avoid unplanned pregnancy in the interim, particularly if the postpartum appointment is missed or delayed. Interpregnancy intervals of <18 months have been associated with an increased risk of poor perinatal and maternal outcomes in women without HIV.[1,30] Given the stresses and demands of caring for 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.[31]

The potential for drug-drug interactions between several ARV drugs and hormonal contraceptives is discussed in Preconception Counseling and Care for Women of Childbearing Age 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.[32,33] This is consistent with the Centers for Disease Control and Prevention (CDC) recommendations advocating access to a broad range of effective contraceptive methods, including combined hormonal contraceptives, progestin-only pills, depot medroxyprogesterone acetate (DMPA), and implants.[34]

Infant Feeding

Avoidance of breastfeeding has been and continues to be a standard recommendation for women living with HIV in the United States, because maternal ART dramatically reduces but does not eliminate the risk of HIV transmission via breast milk, and safe infant feeding alternatives are readily available. Other concerns include 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 breast milk. However, clinicians should be aware that women may face social, familial, and personal pressures to consider breastfeeding despite this recommendation; such pressures may be particularly problematic for women from cultures where breastfeeding is important, because they may fear that formula feeding would reveal their HIV status.[35,36] It is therefore important to address these possible barriers to formula feeding during the antenatal period (see Guidelines for Counseling and Managing Women 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 of infant food (i.e., by a mother prechewing or prewarming the food in her mouth).[37] 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.

Lactation Inhibition

For women who do not breastfeed (as recommended for women with HIV), symptoms related to breast engorgement can be very unpleasant in the days following labor and delivery. Supportive measures—such as using acetaminophen or ibuprofen for pain control, alternating hot and cold compresses on the breasts, or wearing a tight-fitting bra—can help relieve symptoms related to breast engorgement.[1] Although pharmacologic options for lactation inhibition are not generally used in the United States, recent data suggest cabergoline may be appropriate for some women.[38,39] Cabergoline is a dopamine agonist/ergot derivative that reduces the production of prolactin; however, it is not approved by the Food and Drug Administration for lactation inhibition. Bromocriptine, another dopamine agonist, is no longer used for lactation inhibition because of serious cardiovascular and neurologic complications associated with its use.[40]

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Counseling and Managing Women with HIV in the United States Who Desire to Breastfeed (Last updated, February 10, 2021; last reviewed February 10, 2021)

Panel's Recommendations
• In the United States, formula feeding is the strategy least likely to result in HIV transmission, because breastfeeding presents an ongoing risk of HIV exposure after birth, and because suppressive maternal antiretroviral therapy significantly reduces but does not eliminate the risk of transmitting HIV through breastfeeding. Therefore, breastfeeding is not recommended for women 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, they should be supported in risk-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

The standard recommendation for women living with HIV in the United States is to avoid breastfeeding, 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;
- The postpartum period can be a challenging time to be fully adherent to ART; *and*
- There is a paucity of safety data on most modern ARV regimens during breastfeeding.

The recommendations for infant feeding in the United States differ from those in many low-income 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 in some areas of the United States may also have limited access to safe water. Infant replacement feeding using formula (or formula powder mixed with safe water), banked breast milk, or a properly screened HIV-negative surrogate remains the only way to eliminate the risk of breast milk–associated HIV transmission. However, women may face environmental, social, familial, and personal pressures to consider breastfeeding, despite the risk of HIV transmission via breast milk.[2-7] A survey of 93 U.S. clinicians who provide specialty care to women with HIV revealed that one-third of the providers were aware that women in their care had breastfed their infants after being advised not to do so.[8]

A qualitative study of mothers with HIV in Canada found that many factors affected a woman's decision to breastfeed her infant; these included social, cultural, and emotional factors and concerns about 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] Breastfeeding has maternal and infant benefits; thus, an exclusive focus on the risk of perinatal HIV transmission via breastfeeding fails to acknowledge the advantages that may be lost by prohibiting breastfeeding for women with HIV. Hence, multiple experts and community organizations have called for a patient-centered risk-reduction approach to shared decision-making on infant feeding options for women with HIV in high-income countries.[2,9-13]

This section of the guidelines is intended to provide tools to help providers counsel women with HIV on the potential risks of HIV transmission that are associated with breastfeeding and to provide a risk-reduction approach for women who choose to breastfeed, despite intensive counseling. **It is not intended to be an endorsement of breastfeeding, nor to imply that breastfeeding is recommended for women with HIV in the United States.**

Breastfeeding and Strategies to Reduce Risk of HIV Transmission

Both the evidence regarding the risk of HIV transmission via breastfeeding and the strategies to reduce this type of transmission come from studies conducted in low-income 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 breastfeeding infant acquiring HIV from a mother with HIV is 15% to 20% over 2 years.[14,15]

Studies have shown that maternal ART throughout pregnancy and breastfeeding and infant ARV prophylaxis during breastfeeding can reduce, but not eliminate, the risk of breast milk–associated HIV transmission.[16-20] 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 evaluated HIV transmission during breastfeeding among women who initiated ART earlier in pregnancy and who continued ART longer than women in previous studies. Among more than 500 mothers who were on ART in the Mma Bana study, two cases of HIV transmission via breastfeeding occurred. In these cases, maternal plasma and breast milk HIV RNA levels were <50 copies/mL at 1 month and 3 months postpartum.[21] The PROMISE trial, which included more than 2,400 women with CD4 T lymphocyte cell counts ≥350 cells/mm³, compared the efficacy of prolonged infant prophylaxis to maternal ART in preventing HIV transmission during breastfeeding. Both treatments continued through cessation of breastfeeding or 18 months postpartum, whichever came first. This study reported estimated transmission rates of 0.3% at 6 months and 0.6% at 12 months in both arms.[22] Two cases of HIV transmission during breastfeeding were reported among 186 infants born during a study in Tanzania; the first occurred in the infant of a mother who had a high viral load 1 month after delivery, and the second occurred after a mother discontinued ART. No cases of HIV transmission were reported among infants who were born to virally suppressed mothers who remained in care.[23]

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 rates of HIV transmission than mixed feeding (a term used to describe infants fed breast milk plus other liquid or solid foods, including formula).[24,25] 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, because increased HIV shedding into breast milk and an increased rate of HIV transmission during rapid weaning were observed in studies from low-income countries that were conducted before ART was widely accessible for breastfeeding women.[26-28] Currently, not enough data exist to determine whether exclusive breastfeeding or mixed feeding has an impact on perinatal transmission in the context of effective ART.

Safety of Maternal and Infant Use of Antiretroviral Drugs During Breastfeeding

The non-nucleoside reverse transcriptase inhibitors (NNRTIs) nevirapine (NVP), efavirenz, and etravirine have been detected in breast milk; however, the levels of these ARV drugs that have been detected in breast milk are lower than those seen in maternal plasma. Among protease inhibitors (PIs), lopinavir, nelfinavir, ritonavir, indinavir, and atazanavir have been found in very low concentrations in breast milk, with little to no drug detectable in the blood of the breastfed infant.[29] Nucleoside reverse transcriptase inhibitors (NRTIs) show more variability than PIs and NNRTIs. Tenofovir disoproxil fumarate (TDF) concentrations are very low in breast milk, and the drug is undetectable in the blood of the breastfed infant.[29-31] Emtricitabine and lamivudine (3TC) have more accumulation in breast milk and can sometimes be detected in the blood of the breastfed infant (in 19% and 36% of infants, respectively).[29] A sub-analysis of the Breastfeeding, Antiretrovirals, and Nutrition (BAN) study confirmed higher levels of the NRTIs zidovudine and lamivudine in breast milk than in plasma, in contrast to NNRTIs and PIs. The study demonstrated that higher drug concentrations in the maternal plasma and breast milk compartments were associated with lower levels of the virus in both compartments and a lower

incidence of viral transmission during breastfeeding.[32] Data on the transfer of integrase strand transfer inhibitors to breast milk in humans are limited; data do show that dolutegravir is found in breast milk at levels that are about 3% of those seen in maternal plasma.[33] For more details on the passage of ARV drugs into breast milk, see the individual drug sections in Appendix B.

One study showed a decrease in maternal bone mineral content among breastfeeding mothers who were receiving TDF-based ART compared to mothers who received no ART, but whether this condition persists after discontinuation of breastfeeding is not known.[34]

In infants, serious adverse events that are associated with the use of ART by breastfeeding mothers appear to be relatively uncommon. In two studies that compared the efficacy of maternal ART (zidovudine [ZDV]-based ART in one study and TDF-based ART in the other) to infant NVP prophylaxis with no maternal ART during breastfeeding for prevention of postnatal HIV transmission, no significant differences in adverse events were observed between study arms.[17,22] One study reported that anemia occurred more frequently among infants who were exposed to ZDV-based ART during breastfeeding than among infants who were not exposed to ART.[35] An infant who acquires HIV while breastfeeding is at risk for developing ARV drug resistance due to subtherapeutic drug levels in breast milk.[36,37]

Likewise, the rates of serious adverse events among infants who receive extended ARV prophylaxis during breastfeeding are low. In one study, the rate of adverse events in infants receiving 6 months of NVP was not significantly different from the rate in infants receiving placebo. A second study that compared two infant ARV prophylaxis regimens (lopinavir/ritonavir vs. 3TC) found no significant difference between the rates of adverse events among infants receiving the two regimens.[17-19,22] Studies to date have only examined short-term adverse events, and few data are available 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 surrogate 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 (the Panel) recommends that women with HIV in the United States not breastfeed their infants. However, patient-centered counseling on infant feeding must balance maternal psychosocial concerns, the health benefits of breastfeeding for the infant, and the risk of HIV transmission. Similarly, the British HIV guidelines recommend using formula as the safest approach to infant feeding, but they suggest supporting women who opt to breastfeed.[12] Providers should 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, "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, the Panel recommends engaging each woman privately in a nonjudgmental conversation about the motivation behind her desire to breastfeed and potential barriers to formula feeding, e.g., lack of disclosure or cultural issues, as well as consulting with the clinician(s) who will be managing the infant's care. Infant feeding intentions should be assessed throughout pregnancy among women who have expressed interest or uncertainty about breastfeeding.

If, despite counseling, a woman decides to breastfeed, risk-reduction measures should be taken to reduce the possibility of HIV transmission. Ideally, the woman should be adherent to her ARV regimen, she should maintain a suppressed viral load during pregnancy, and she should be fully engaged in her own care. Risk-reduction measures may include the following:

- Supporting maternal ART adherence and engagement in care during pregnancy and throughout breastfeeding, as well as early identification of antenatal or postpartum depression.

- 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. Plasma viral loads should also be monitored whenever nonadherence to ART is suspected. If maternal viral load becomes detectable, consult an expert immediately and consider weaning the infant.
- Breastfeeding exclusively for up to 6 months postpartum, followed by breastfeeding in combination with the introduction of complementary foods. However, this recommendation is based on studies of exclusive breastfeeding and nonexclusive breastfeeding that were completed before effective ART was widely available.
- Developing a plan for weaning with input from the family and providers. Rapid weaning over a few days **is not recommended**, but data on weaning are lacking for infants born to women who are receiving ART and who are virologically suppressed. Administering at least 6 weeks of ARV prophylaxis with ZDV and/or NVP to infants. In non-breastfeeding infants, high-quality evidence indicates that 4 to 6 weeks of infant prophylaxis with ZDV prevents HIV transmission (see Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection). The most extensively studied prophylaxis in breastfeeding infants is daily NVP, which has been shown to be safe and effective when used for extended prophylaxis in infants whose mothers are **not** receiving ART.[18,22]
- Discontinuing infant ARV prophylaxis after 6 weeks, if the mother is receiving ART. Among mothers who were enrolled in the HPTN 046 trial and who received suppressive ART, no difference was observed between the rates of postnatal transmission for infants who received NVP and infants who received placebo.[18] No data exist to support the added benefit of giving ARV drugs for more than 4 weeks to 6 weeks to infants of mothers who are on suppressive ART. However, some experts have felt more comfortable continuing infant ARV prophylaxis for 1 week to 4 weeks after cessation of weaning, even when the mother is receiving suppressive ART.[38]
- Monitoring the infant for HIV acquisition during breastfeeding and for a period of time after cessation of breastfeeding.[39] A proposed 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.
- Promptly initiating a full ARV regimen for the infant in the unlikely event of HIV transmission via breastfeeding. Resistance testing should be done on the infant viral isolate. If resistance is identified, the treatment regimen can be adjusted appropriately.
- Promptly identifying and treating maternal mastitis and infant thrush. Both conditions increase the risk of HIV transmission through breastfeeding.[40-42] Experts in the United States recommend that milk from the affected breast be pumped and discarded until mastitis resolves.

The immediate postpartum period poses unique challenges to adherence to medical care and ART. Although it has been shown that people with undetectable viral loads cannot transmit HIV through sexual contact, currently not enough data exist to say the same for transmission during breastfeeding. Many questions remain as to the mechanism for breast milk–associated HIV transmission in the cases where it has occurred. HIV RNA in cell-free breast milk may be controlled with ART, but cell-associated HIV (usually measured by HIV DNA) may provide a latent reservoir of HIV that is capable of causing perinatal infection via breastfeeding, even among women on ART.[43-45] Close follow-up and enhanced support services should be considered for women who are planning to breastfeed (see Postpartum Follow-Up of Women with HIV).

Clinicians who are 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).

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Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection

(Last updated December 29, 2020; last reviewed December 29, 2020)

Panel's Recommendations

• All newborns who were exposed perinatally to HIV should receive postpartum antiretroviral (ARV) drugs to reduce the risk of perinatal transmission of HIV **(AI)**.
• Newborn ARV regimens administered at doses that are appropriate for the infant's gestational age should be initiated as close to the time of birth as possible, preferably within 6 hours of delivery **(AII)**.
• A newborn's ARV regimen should be determined based on maternal and infant factors that influence the risk of perinatal transmission of HIV **(AII)**. 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.
  • **Presumptive HIV Therapy:** The administration of a three-drug ARV regimen to newborns who are at highest risk of perinatal acquisition of HIV. Presumptive HIV therapy is intended to be preliminary treatment for a newborn who is later documented to have HIV, but it 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 doses (called antiretroviral therapy [ART]) to newborns with documented HIV infection (see Diagnosis of HIV Infection in Infants and Children).
• A 4-week zidovudine (ZDV) ARV prophylaxis regimen can be used in newborns whose mothers received ART during pregnancy and had viral suppression near delivery (defined as a confirmed HIV RNA level <50 copies/mL) and for whom maternal adherence is not of concern **(BII)**.
• Newborns at high risk of perinatal acquisition of HIV should begin presumptive HIV therapy (see Table 9 for recommended regimens). Newborns at high 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 who did not achieve viral suppression (defined as a confirmed HIV RNA level <50 copies/mL) near delivery **(AII)**, *or*
  • Have primary or acute HIV infection during pregnancy **(AII)**, *or*
  • Have primary or acute HIV infection while breastfeeding **(AII)**.
• If a woman presents with unknown HIV status and has a positive expedited HIV test during labor or shortly after delivery, the infant should begin presumptive HIV therapy **(AII)**. If supplemental maternal testing is negative, the infant's ARV regimen should be discontinued **(AII)**.
• For newborns with HIV infection, ART should be initiated **(AI)**.
• The use of ARV drugs other than ZDV, lamivudine, and nevirapine cannot be recommended for any indication in premature newborns (<37 weeks gestational age) because of the lack of dosing and safety data **(BII)**.
• 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 during the neonatal period to reduce the risk of perinatal HIV transmission, with selection of the appropriate ARV regimen guided by the level of transmission risk. HIV transmission can occur *in utero*, intrapartum, or during breastfeeding.

Maternal viral load is the most important risk factor for HIV transmission to a newborn. Newborns are at an increased risk for transmission when their mothers do not receive antiretroviral therapy (ART) during pregnancy, when mothers start antepartum treatment late in pregnancy, or when antepartum treatment does not

result in virologic suppression (defined as a confirmed HIV RNA level <50 copies/mL). Higher maternal viral load, especially in late pregnancy, correlates with higher risk of transmission. A spectrum of transmission risk depends on these and other maternal and infant factors, including mode of delivery, gestational age at delivery, and maternal health status.

Historically, the use of ARV drugs in the newborn period was referred to as ARV prophylaxis because 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 presumptive treatment of HIV. In this section, 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 (ZDV)—as well as combinations of two or three ARV drugs.
- **Presumptive HIV Therapy:** The administration of a three-drug ARV regimen to newborns at highest risk of HIV acquisition. Presumptive HIV therapy is intended to be early treatment for a newborn who is later documented to have acquired HIV, but it 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 regimen to newborns with documented HIV infection (see Diagnosis of HIV Infection in Infants and Children).

The terms ARV prophylaxis and presumptive HIV therapy describe the clinician's intent when prescribing ARV drugs, which may lead to an overlap between these two terms. For example, a presumptive HIV therapy regimen also provides ARV prophylaxis for a newborn. However, two-drug (or sometimes three-drug) ARV prophylaxis regimens, notably those that use prophylactic doses rather than therapeutic doses of nevirapine (NVP), are not considered presumptive HIV therapy.

The interval during which newborn ARV prophylaxis or presumptive HIV therapy can be initiated and still be beneficial is undefined; however, most studies support providing ARV drugs as early as possible after delivery.[1–6]

Table 8 provides an overview of neonatal ARV management recommendations according to the risk of perinatal HIV transmission to the newborn, and Table 9 summarizes the recommendations for ARV drug dosing in newborns. Additional information about dose selection for newborns, including premature infants (<37 weeks' gestational age), can be found in the Pediatric Antiretroviral Guidelines. Information about infants born to women with HIV-2 infection is available in HIV-2 Infection and Pregnancy and Table 8. In addition, the National Perinatal HIV Hotline (1-888-448-8765) is a federally funded service that provides free clinical consultation on difficult cases to providers who are caring for pregnant women with HIV and their newborns, and consultants can provide referrals to local or regional pediatric HIV specialists.

Table 8. Neonatal 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 (1-888-448-8765).

Level of Perinatal HIV Transmission Risk	Description	Neonatal ARV Management
Low Risk of Perinatal HIV Transmission	Mothers who received ART during pregnancy with viral suppression (defined as a confirmed HIV RNA level <50 copies/mL) near delivery and no concerns related to adherence	ZDV for 4 weeks[a]
High Risk of Perinatal HIV Transmission[a,b]	Mothers who did not receive antepartum or intrapartum ARV drugs Mothers who received only intrapartum ARV drugs Mothers who received antepartum and intrapartum ARV drugs but did not have viral suppression (defined as a confirmed HIV RNA level <50 copies/mL) near delivery Mothers with acute or primary HIV infection during pregnancy or breastfeeding (in which case, the mother **should immediately discontinue breastfeeding**)[c]	Presumptive HIV therapy using either ZDV, 3TC, and NVP (treatment dose) *or* ZDV, 3TC, and RAL administered from birth up to 6 weeks.[d]
Presumed Newborn HIV Exposure	Mothers with unconfirmed HIV status who have at least one positive HIV test at delivery or postpartum *or* Mothers whose newborns have a positive HIV antibody test	ARV management as described above for newborns with a high risk of perinatal HIV transmission Infant ARV drugs 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	Three-drug ARV regimen using treatment doses

[a] A 4-week ZDV prophylaxis regimen is recommended for infants born to mothers with HIV-2 mono-infection, see HIV-2 Infection and Pregnancy. If the mother has HIV-1 and HIV-2 infection, the infant ARV regimen should be based on the determination of low or high risk of HIV-1 transmission as described in the above table. Because HIV-2 is not susceptible to NVP, RAL should be considered.

See text for evidence that supports the use of presumptive HIV therapy and a two-drug ARV prophylaxis regimen.

[b] See Intrapartum Care 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 presumptive 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, the mother should immediately discontinue nursing.

[d] The optimal duration of presumptive HIV therapy in newborns who are at a high risk for perinatal HIV transmission is unknown. If possible, newborns who are at a high risk for HIV acquisition should receive ZDV for 6 weeks. Additional medications, such as 3TC, RAL, or NVP, may need to administered for 2 to 6 weeks; the recommended duration for these drugs varies depending on HIV NAT results, maternal viral load at the time of delivery, and additional risk factors for HIV transmission. Consultation with an expert in pediatric HIV is recommended when selecting a therapy duration because this decision should be based on case-specific risk factors and interim HIV NAT results. The two-drug regimen used in the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD)-HIV Prevention Trials Network (HPTN) 040/ Pediatric AIDS Clinical Trials Group (PACTG) 1043 for infants who were at a high risk for HIV acquisition is described in the text (see the Two-Drug Antiretroviral Prophylaxis section).

[e] Most Panel members strongly recommend initiating ART without waiting for the results of confirmatory HIV NAT testing, given the 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 hours of delivery. See Table 9 for dosing specifics.

Key: 3TC = lamivudine; ART = antiretroviral therapy; ARV =antiretroviral; IV = intravenous; NAT = nucleic acid test; NVP = nevirapine; Panel = Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission; RAL = raltegravir; ZDV = zidovudine

Table 9. Antiretroviral Drug Dosing Recommendations for Newborns

Newborns at Low Risk of Perinatal HIV Transmission	
Recommended Regimen	**Recommended Duration**
ZDV	ZDV administered for 4 weeks at the doses listed below
Newborns at High Risk of Perinatal HIV Transmission	
Recommended Regimen	**Recommended Duration**
Three-drug HIV therapy: ZDV plus 3TC plus (NVP *or* RAL)	ZDV administered for 6 weeks, with no increase to the 12 mg/kg dose unless the infant has confirmed HIV infection. Dosing for 3TC, NVP, and RAL is described below. Duration for these three drugs may vary; see the guidance in footnote.[a]
Newborns with HIV Infection	
Recommended Regimen	**Lifelong Duration Recommended**[b]
Three-drug HIV therapy: ZDV plus 3TC plus (NVP *or* RAL)	Lifelong therapy in accordance with current treatment guidelines. The ARV regimen should be individualized based on the infant's age and clinical determinants. RAL can be used in infants who were born at a postmenstrual age of ≥37 weeks (defined as the time from the first day of the mother's last menstrual period to birth plus the time elapsed after birth) and who weigh ≥2 kg. LPV/r can be used when the infant reaches a postmenstrual age of ≥42 weeks and a postnatal age ≥14 days. DTG tablets for oral suspension (dispersible tablets) can replace LPV/r, NVP, or RAL in infants at least 4 weeks of age and weighing at least 3 kg.

<table>
<tr><th>Drug</th><th>Drug Doses by Gestational Age at Birth</th></tr>
<tr><td>ZDV

Note: For newborns who are unable to tolerate oral agents, the IV dose is 75% of the oral dose while maintaining the same dosing interval.</td><td>≥35 Weeks' Gestation at Birth
Birth to Age 4 Weeks:
• ZDV 4 mg/kg per dose orally twice daily

Age >4 Weeks:
• ZDV 12 mg/kg per dose orally twice daily; only make this dose increase for infants with confirmed HIV infection.

Simplified Weight-Band Dosing for Newborns Aged ≥35 Weeks' Gestation from Birth to 4 Weeks
<table>
<tr><th>Weight Band</th><th>Volume of 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>
</table>

<table>
<tr><td></td><td>≥30 to <35 Weeks' Gestation at Birth
Birth to Age 2 Weeks:
• ZDV 2 mg/kg per dose orally twice daily

Age 2 Weeks to 6 to 8 Weeks:
• ZDV 3 mg/kg per dose orally twice daily

Age >6 to 8 Weeks:
• ZDV 12 mg/kg per dose orally twice daily; only make this dose increase for infants with confirmed HIV infection.</td></tr>
<tr><td></td><td><30 Weeks' Gestation at Birth
Birth to Age 4 Weeks:
• ZDV 2 mg/kg per dose orally twice daily
Age 4 to 8–10 Weeks:
• ZDV 3 mg/kg per dose orally twice daily
Age >8 to 10 Weeks:
• ZDV 12 mg/kg per dose orally twice daily; only make this dose increase for infants with confirmed HIV infection</td></tr>
<tr><td>3TC</td><td>≥32 Weeks' Gestation at Birth
Birth to Age 4 Weeks:
• 3TC 2 mg/kg per dose orally twice daily

Age >4 Weeks:
• 3TC 4 mg/kg per dose orally twice daily</td></tr>
<tr><td>NVP</td><td>≥37 Weeks' Gestation at Birth
Birth to Age 4 Weeks:
• NVP 6 mg/kg per dose orally twice dailyc

Age >4 Weeks:
• NVP 200 mg/m^2 BSA per dose orally twice daily; only make this dose increase for infants with confirmed HIV infection.</td></tr>
<tr><td></td><td>≥34 to <37 Weeks' Gestation at Birth
Birth to Age 1 Week:
• NVP 4 mg/kg per dose orally twice daily
Age 1 to 4 Weeks:
• NVP 6 mg/kg per dose orally twice daily
Age >4 Weeks:
• NVP 200 mg/m^2 BSA per dose orally twice daily; only make this dose increase for infants with confirmed HIV infection.</td></tr>
<tr><td>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</td><td>≥37 Weeks' Gestation at Birth and Weighing ≥2 kg[d]
Birth to Age 6 Weeks:
<table><tr><th>Body Weight</th><th>Volume (Dose) of RAL 10 mg/mL Suspension</th></tr><tr><td>Birth to 1 Week: Once-Daily Dosing</td><td>Approximately 1.5 mg/kg per dose</td></tr><tr><td>2 to <3 kg</td><td>0.4 mL (4 mg) once daily</td></tr></table></td></tr>
</table>

<table>
<tr><td>birth; additional ARV drugs should be started as soon as possible.[7]</td><td>
<table>
<tr><td>3 to <4 kg</td><td>0.5 mL (5 mg) once daily</td></tr>
<tr><td>4 to <5 kg</td><td>0.7 mL (7 mg) once daily</td></tr>
<tr><td>1 to 4 Weeks: Twice-Daily Dosing</td><td>Approximately 3 mg/kg per dose</td></tr>
<tr><td>2 to <3 kg</td><td>0.8 mL (8 mg) twice daily</td></tr>
<tr><td>3 to <4 kg</td><td>1 mL (10 mg) twice daily</td></tr>
<tr><td>4 to <5 kg</td><td>1.5 mL (15 mg) twice daily</td></tr>
<tr><td>4 to 6 Weeks: Twice-Daily Dosing</td><td>Approximately 6 mg/kg per dose</td></tr>
<tr><td>3 to <4 kg</td><td>2.5 mL (25 mg) twice daily</td></tr>
<tr><td>4 to <6 kg</td><td>3 mL (30 mg) twice daily</td></tr>
<tr><td>6 to <8 kg</td><td>4 mL (40 mg) twice daily</td></tr>
</table>
</td></tr>
<tr><td>DTG

Note: Only tablets for oral suspension (dispersible tablets) are approved for use in infants > 4 weeks of age and > 3 kg</td><td>
Age > 4 weeks of age AND > 3 kg:
<table>
<tr><th>Pediatric

Body Weight</th><th>Recommended Dose[e]

Dolutegravir Dispersible Tablets</th><th>Number of tablets</th></tr>
<tr><td>3 to <6 kg</td><td>5 mg once daily</td><td>1</td></tr>
<tr><td>6 to <10 kg</td><td>15 mg once daily</td><td>3</td></tr>
<tr><td>10 to <14 kg</td><td>20 mg once daily</td><td>4</td></tr>
<tr><td>14 to <20 kg</td><td>25 mg once daily</td><td>5</td></tr>
<tr><td>≥20 kg</td><td>30 mg once daily</td><td>6</td></tr>
</table>
</td></tr>
</table>

[a] The optimal duration of presumptive HIV therapy in newborns who are at a high risk for perinatal HIV transmission is unknown. If possible, newborns who are at a high risk for HIV acquisition should receive ZDV for 6 weeks. Additional medications, such as 3TC, RAL, or NVP, may need to administered for 2 to 6 weeks; the recommended duration for these drugs varies based on HIV NAT results, maternal viral load at the time of delivery, and additional risk factors for HIV transmission. Consultation with an expert in pediatric HIV is recommended when selecting a therapy duration because this decision should be based on case-specific risk factors and interim HIV NAT results. The two-drug regimen used in NICHD-HPTN 040/PACTG 1043 for infants who were at a high risk for HIV acquisition is described in the text (see the Two-Drug Antiretroviral Prophylaxis section).
[b] For ARV management after the newborn period, see the Pediatric Antiretroviral Guidelines.
[c] This dose is an investigational NVP treatment dose recommended by the Panel; the FDA has not approved a dose of NVP for infants aged <1 month. See the Two-Drug Antiretroviral Prophylaxis section in the text for prophylactic NVP dosing if using the NICHD-HPTN 040/PACTG 1043 prophylaxis regimen.
[d] 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 4–6 weeks of life. No dosing information is available for preterm infants or infants weighing <2 kg at birth.
[e] If certain UGT1A or CYP3A inducers are coadministered, then administer twice daily.

Key: 3TC = lamivudine; ARV =antiretroviral; BSA = body surface area; DTG = dolutegravir; FDA = Food and Drug Administration; IV = intravenous; LPV/r = lopinavir/ritonavir; 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; UGT = uridine diphosphate glucotransferase; ZDV = zidovudine

Recommendations for Antiretroviral Drugs in Specific Clinical Situations

In this section 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 and achieved effective viral suppression (defined as a confirmed HIV RNA level <50 copies/mL)
- Are at high risk for transmitting HIV to their newborns, including mothers who—
  - Received neither antepartum nor intrapartum ARV drugs, *or*
  - Received only intrapartum ARV drugs, *or*
  - Received antepartum and intrapartum ARV drugs but who do not have effective viral suppression (defined as a confirmed HIV RNA level <50 copies/mL) near delivery
- Had acute or primary HIV infection during pregnancy or breastfeeding
- Have unknown HIV status
- Have known ARV drug-resistant virus

Newborns Born to Mothers Who Achieved Viral Suppression on Antepartum/ Intrapartum Antiretroviral Drugs

The risk of HIV acquisition in newborns born to women who received ART during pregnancy and labor and who had undetectable viral load near or at the time of delivery is <1 percent. In the PACTG 076 study, ZDV alone reduced the incidence of perinatal HIV transmission by 66 percent, and ZDV is recommended as prophylaxis for neonates whose mothers received ART that resulted in consistent virologic suppression during pregnancy.[8] The optimal minimum duration of neonatal ZDV prophylaxis has not been established in clinical trials. A 6-week ZDV regimen was studied in newborns in PACTG 076. However, the evidence that supports a reduced duration of ZDV prophylaxis in infants born to women who were suppressed virologically during pregnancy and at time of delivery is mounting.[9–11] In the United Kingdom and many other European countries, a 2-week neonatal ZDV prophylaxis regimen is recommended for infants born to women who have been on ART for longer than 10 weeks **and** have had at least two documented maternal HIV viral loads <50 copies/mL at least 4 weeks apart **and** have viral loads <50 copies/mL at or after 36 weeks' gestation. A 4-week course of ZDV is recommended[12] if any of these criteria are not fulfilled but the maternal viral load is <50 copies/mL at or after 36 weeks' gestation. Compared with the 6-week ZDV regimen, 2 to 4 weeks on this regimen has been reported to allow earlier recovery from anemia in otherwise healthy newborns.[13,14]

Currently, the Panel recommends a 4-week neonatal ZDV prophylaxis regimen for newborns if the mother achieved viral suppression on ART during pregnancy (defined as a confirmed HIV RNA level <50 copies/mL) at or after 36 weeks' gestation and maternal adherence is not of concern. Dosing recommendations for ZDV are available for premature newborns, and an intravenous preparation of ZDV is available. Table 9 shows recommended neonatal ZDV dosing based on gestational age and birth weight.

Newborns Born to Mothers Who Received No Antepartum or Intrapartum Antiretroviral Drugs, Who Received Intrapartum Antiretroviral Drugs Only, Who Received Antiretroviral Drugs and Were Not Virally Suppressed Near Delivery, or Who Acquired HIV During Pregnancy or Breastfeeding

The Panel recommends that all newborns born to mothers who do not have viral suppression (defined as a confirmed HIV RNA level <50 copies/mL) near delivery, who received only intrapartum ARV drugs, or who received no ARV drugs during pregnancy or delivery are at high risk for HIV acquisition and **should receive**

presumptive HIV therapy.[5,15–19] Primary or acute HIV infection during pregnancy also is associated with an increased risk of perinatal transmission of HIV. Infants born to women who acquired HIV during pregnancy **should receive presumptive HIV therapy** (see Acute HIV Infection). The experience with these two strategies is described below.

Presumptive HIV Therapy

Early effective treatment of HIV infection in infants restricts the viral reservoir size, reduces HIV genetic variability, and modifies the immune response.[20–28] Because of these potential benefits of early ART, the Panel recommends a three-drug ARV presumptive HIV therapy regimen consisting of ZDV, lamivudine (3TC), and either NVP (at treatment dose) or raltegravir (RAL) for newborns at high risk of perinatal acquisition of HIV.

Although no clinical trials have compared the safety and efficacy of presumptive ART with single-drug or two-drug regimens, emerging data suggest that early presumptive HIV therapy has not been associated with serious adverse events. Many infants develop anemia or neutropenia that may be drug-related regardless of whether the ARV drugs are administered as prophylaxis or treatment.[29–33] In a prospective cohort in Thailand, infants who received a presumptive HIV therapy regimen that contained ZDV, 3TC, and NVP were more likely to have Grade 2 or higher anemia at 1 and 2 months of life compared with infants who received ZDV alone (48.5% vs. 32.3%; $P = 0.02$). However, no difference was found in the incidence of severe anemia (Grade 3) between the two groups.[34] Additionally, in a Canadian study, nonspecific signs and symptoms (e.g., vomiting, diarrhea, rash, jitteriness, irritability) that were potentially attributable to medication-related adverse effects were reported among the newborns who received presumptive HIV therapy but not among those who received ZDV only (10.2% vs. 0%; $P < 0.001$). Infants were more likely to discontinue presumptive HIV therapy prematurely than a regimen of ZDV alone (9.5% vs. 2.1%; $P = 0.01$).[30]

The Centers for Disease Control and Prevention recommend a three-drug ARV regimen for HIV-postexposure prophylaxis following occupational and nonoccupational HIV exposure. HIV acquisition risk in these circumstances is often lower than for newborns who are at high risk for HIV acquisition.[35,36] The pharmacokinetic (PK) and safety data of presumptive HIV therapy have provided reassuring evidence for its use in the neonatal period. Although the use of NVP to prevent perinatal HIV transmission has been found to be safe in neonates and newborns of low birthweight, these prophylaxis-dose regimens target trough drug levels that are ≥10-fold lower than targeted therapeutic levels. However, recent studies of therapeutic doses of NVP and RAL have established safe doses that achieve targeted PK parameters.[37–42]

At this time, if a presumptive HIV therapy regimen is required, the Panel recommends using a combination of ZDV, 3TC, and NVP (treatment dose) or ZDV, 3TC, and RAL (see Tables 6 and 7). The optimal duration of presumptive HIV therapy in newborns at high risk of perinatal HIV transmission is unknown. Some Panel members opt to discontinue additional medications if birth nucleic acid test (NAT) results are negative, whereas others would continue presumptive HIV therapy for 2 to 6 weeks depending on the risk of HIV transmission. In all cases, ZDV should be continued for 6 weeks. If HIV infection is confirmed and the infant is receiving NVP, a switch from NVP to lopinavir/ritonavir (LPV/r) is recommended when the infant reaches a postmenstrual age (defined as the time from the 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; when a switch to dolutegravir (DTG) can be made at 4 weeks of age; and when a switch to RAL can be made at any age (see What to Start in the Pediatric Antiretroviral Guidelines). Consulting an expert in pediatric HIV is recommended when selecting a therapy duration based on case-specific risk factors and interim HIV NAT results.

Two-Drug Antiretroviral Prophylaxis

To date, the NICHD-HPTN 040/PACTG 1043 trial is the only randomized clinical trial of multi-ARV prophylaxis in newborns at high risk of HIV acquisition.[5] 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 receive one of three newborn prophylaxis regimens: the standard 6-week ZDV regimen; 6 weeks of ZDV plus three doses of NVP given during the first week of life (first dose given at birth or within 48 hours of birth, second dose 48 hours after the first dose, and third dose 96 hours after the second dose); and 6 weeks of ZDV plus 2 weeks of 3TC plus nelfinavir (NFV).

Forty-one percent of the mothers received ZDV during labor. The risk of intrapartum transmission was significantly lower in the two-drug and three-drug arms (2.2% and 2.5%, respectively, vs. 4.9% for 6 weeks of ZDV alone; $P = 0.046$ for each experimental arm vs. ZDV alone).[5] The NICHD-HPTN 040/PACTG 1043 regimen was associated with nucleoside reverse transcriptase inhibitor (NRTI) resistance in three of 53 participants (5.7%) with *in utero* infection who were treated with ZDV alone and in six of 33 participants (18.2%) who were treated with ZDV plus NVP ($P > 0.05$). In addition, the third drug in the three-arm regimen was NFV, which has highly variable PKs in this age group and did not reach the NFV target plasma concentration in 46 percent of study participants.[43]

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 ZDV-alone regimens (27.5% vs. 14.9% vs. 16.4%; $P < 0.001$ for both comparisons). For newborns who are at a high risk for HIV acquisition, the two-drug regimen used in NICHD-HPTN 040/PACTG 1043 is an option for preventing HIV transmission in infants aged ≥32 weeks' gestation with a birthweight of ≥1.5 kg. This two-drug regimen consists of 6 weeks of ZDV plus three doses of the prophylactic dose of NVP, with the NVP doses given within 48 hours of birth, 48 hours after the first dose, and 96 hours after the second dose. The prophylactic doses are NVP 12 mg per dose orally for infants weighing >2 kg and NVP 8 mg per dose orally for infants weighing 1.5 kg to 2 kg. **These are the actual doses, not the milligram per kilogram doses**. ZDV dosing is shown in Table 9.

Choosing between Presumptive HIV Therapy and Two-Drug Antiretroviral Prophylaxis

Because a spectrum of transmission risk depends on maternal viral load **and** other maternal and infant factors **and** no randomized trials have compared the safety and efficacy of presumptive HIV therapy and two-drug ARV prophylaxis, experts have differing opinions about when to initiate presumptive HIV therapy and when to initiate two-drug prophylaxis. For instance, among women who received ARV drugs during pregnancy but who have a detectable viral load near delivery (on or after 36 weeks' gestation), the level of maternal viremia that would prompt the use of a two-drug ARV prophylaxis regimen or presumptive HIV therapy is not definitively known.

In two large observational studies of women on combination antenatal ARV drugs, perinatal transmission rates were 0.05 percent and 0.3 percent when the mother had a viral load <50 copies/mL at delivery. Rates of transmission in these studies increased to 1.1 percent and 1.5 percent when viral load was 50 to 399 copies/mL and 2.8 percent and 4.1 percent when viral load was >400 copies/mL.[44,45] Although most Panel members would recommend initiating presumptive HIV therapy with any detectable level of viremia near delivery, others may opt for a two-drug prophylaxis regimen if maternal viral load was less than 200 to 400 copies/mL. Emerging data about the lack of serious safety issues associated with presumptive HIV therapy in newborns is reassuring, even though mild-to-moderate adverse events may occur more frequently.

In summary, in scenarios where the infant is at high risk for HIV transmission, most Panel members recommend presumptive HIV therapy. In some situations, a two-drug ARV prophylaxis regimen may be considered (see Two-Drug Antiretroviral Prophylaxis in the text). Choosing between these regimens will depend on the clinician's assessment of the likelihood of HIV transmission, and a decision should be made after weighing the risks and benefits of the proposed regimen and discussing these transmission prevention strategies with the parents.

Consulting an expert in pediatric HIV or the National Perinatal HIV Hotline (1-888-448-8765) is recommended when selecting a regimen based on case-specific risk factors.

Newborns Born to Mothers with Unknown HIV Status Who Present in Labor

Expedited HIV testing is recommended during labor for women with unknown HIV status; if testing is not performed during labor, it should be performed as soon as possible after birth for the mothers and/or their newborns (see Maternal HIV Testing and Identification of Perinatal HIV Exposure). Expedited test results should be available within 60 minutes. If maternal or infant expedited testing is positive, the newborn **should begin presumptive HIV therapy immediately** 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 because not all states allow HIV testing in infants without parental consent.

A nursing mother who is suspected of having HIV based on an initial positive antibody or antibody/antigen test result should discontinue breastfeeding immediately 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.[46]

Newborns Born to Mothers with Antiretroviral Drug-Resistant Virus

The optimal ARV regimen for newborns born to women with ARV drug-resistant virus is unknown. Although some studies have suggested that ARV drug-resistant virus may have decreased replicative capacity (reduced viral fitness) and transmissibility,[47] perinatal transmission of multidrug-resistant virus does occur.[48–53] Whether resistant virus in the mother increases the antepartum/intrapartum risk of HIV acquisition by the infant also is unknown. A recently reported secondary analysis of data from the NICHD-HPTN 040/PACTG 1043 study demonstrated that the risk of perinatal transmission was not related to the presence of drug resistance mutations in mothers who had not received ARV drugs before the start of the study (adjusted odds ratio 0.8; 95% confidence interval, 0.4–1.5).[53] Maraviroc (MVC) was approved recently for infants ≥2 kg and may provide an additional treatment option for newborns of women carrying multidrug resistant HIV-1 that remains CCR5-trophic. However, the lack of data about MVC as prophylaxis or treatment in infants weighing <10 kg and the risk of drug interactions will limit its role for routine use in neonates. 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 (1-888-448-8765). Additionally, no evidence exists that shows that neonatal prophylaxis regimens customized based on presence of maternal drug resistance are more effective than standard neonatal prophylaxis regimens.

Newborns with HIV Infection

Until recently, neonatal ARV regimens were designed for prophylaxis against perinatal HIV transmission and were intended to be as simple as possible for practical use. There was little reason to develop ARV regimens for the treatment of neonates, because the long turnaround times to receive HIV NAT results meant that neonatal infections, in general, were not diagnosed during 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 in many centers. 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 early treatment (before age 2 weeks) will lead conclusively to prolonged remission or better outcomes in newborns with HIV is lacking.

Information regarding the safety of early treatment of HIV in newborns has been reported from two studies. In the International Maternal, Pediatric, Adolescent AIDS Clinical Trials (IMPAACT) P1115 study, 54 infants with HIV began presumptive HIV therapy between 0.4 and 40 hours of life. Grade 3 or 4 related events—most of which were hematologic—occurred in 22 of 54 infants (41%) through 52 weeks of the study.[31] Forty infants with HIV in Botswana began treatment with NVP plus ZDV plus 3TC at a median age of 2 days (range 1–5 days) and transitioned to LPV/r plus ZDV plus 3TC at approximately 2 weeks of age. These infants had minimal toxicity during the first 12 weeks of treatment. Only one instance of Grade 3 neutropenia was reported, and no instances of Grade 3 or 4 anemia were reported.[33]

Earlier diagnosis of HIV in newborns and the increasing use of presumptive HIV therapy in newborns at high risk for HIV acquisition have necessitated the investigation of dosing and the safety of ARV drugs in term and preterm newborns. Although data are 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 NVP (see the Pediatric Antiretroviral Guidelines).

Sufficient data exist to provide dosing recommendations for the treatment of HIV in neonates using the following medications (see the Pediatric Antiretroviral Guidelines):

- From birth in term and preterm newborns: ZDV, 3TC, NVP
- From birth in term newborns: emtricitabine, RAL, MVC
- From age 2 weeks in term newborns: LPV/r
- From age 4 weeks in term newborns: DTG

Dosing recommendations for *premature* newborns are available for ZDV, 3TC, and NVP only. Neonatal dosing advice, including dosing advice for premature newborns, is summarized in Table 9. For more detailed information about neonatal dosing recommendations and considerations when using these drugs, please see the Pediatric Antiretroviral Guidelines.

Newborns of Mothers Who Receive an HIV Diagnosis while Breastfeeding

Women with suspected HIV (e.g., a positive initial screening test) should discontinue breastfeeding immediately 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 Counseling and Managing Women Living with HIV in the United States Who Desire to Breastfeed).[54]

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.[55] Newborns of women who develop acute HIV while breastfeeding are at greater risk of acquiring HIV than those whose mothers have chronic HIV infection[56] because acute HIV infection is accompanied by a rapid increase in viral load and a corresponding decrease in CD4 count.[57]

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 postexposure prophylaxis in newborns for 4 to 6 weeks after cessation of breastfeeding. Postexposure prophylaxis, however, is less likely to be effective in this circumstance

than with other nonoccupational exposures because the exposure to breast milk is likely to have occurred over a prolonged period rather than during a single exposure to the virus.[58]

Several studies of newborns who were breastfed by women with chronic HIV infection in low-resource settings have shown that a newborn's daily regimen of NVP, 3TC, LPV/r, or NVP plus ZDV can reduce the risk of postnatal infection during breastfeeding.[59–63] No trials have evaluated the use of multidrug 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 is to offer presumptive HIV therapy until the infant's HIV status can be determined. If the infant's initial HIV NAT is negative, the optimal duration of presumptive HIV therapy is unknown. A 28-day course may be reasonable based on current recommendations for nonoccupational HIV exposure.[58] When making decisions about ARV management, clinicians should consult a pediatric HIV specialist and counsel the parents on the potential risks and benefits of a particular treatment strategy. The National Perinatal HIV Hotline (1-888-448-8765) can provide referrals to local or regional pediatric HIV specialists.

Newborns exposed to HIV during breastfeeding should be tested for HIV infection prior to initiating presumptive HIV therapy, as well as 4 to 6 weeks and 4 to 6 months after diagnosis of maternal HIV infection and cessation of breastfeeding. An additional virologic test should be performed 2 to 4 weeks after discontinuing presumptive HIV therapy (see Diagnosis of HIV Infection in Infants and Children). If an HIV-exposed newborn is already receiving an ARV prophylaxis regimen other than presumptive HIV therapy and is found to have HIV, prophylaxis should be discontinued and treatment for HIV should be initiated. Resistance testing should be performed, and the ART should be modified if needed (see the Pediatric Antiretroviral Guidelines).

Short-Term Antiretroviral Drug Safety

Newborn prophylaxis with ZDV has been associated with only minimal toxicity, primarily transient hematologic toxicity (mainly anemia), which generally resolves by age 12 weeks (see Initial Postnatal Management of the Neonate Exposed to HIV). Data on toxicities in newborns who were exposed to multiple ARV drugs are limited.

Other than ZDV, 3TC is the NRTI with the most clinical experience for neonatal prophylaxis. In early studies, neonatal exposure to combination ZDV/3TC therapy was limited, in general, to [118,64,65] or 2 weeks.[5] Six weeks of ZDV/3TC exposure in newborns also has been reported. These studies suggest that hematologic toxicity may be greater with ZDV/3TC than with ZDV 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 cases of severe anemia and neutropenia were observed in newborns who were exposed to 6 weeks of ZDV/3TC prophylaxis plus maternal antepartum ZDV/3TC than in a historical cohort of newborns who were exposed only to maternal and newborn ZDV. Anemia was reported in 15 percent of newborns, and neutropenia was reported in 18 percent of newborns who were exposed to ZDV/3TC, with 2 percent of newborns requiring blood transfusion and 4 percent requiring treatment discontinuation for toxicity.[66] Similarly, in a Brazilian study of maternal antepartum ZDV/3TC and 6 week newborn ZDV/3TC prophylaxis, neonatal hematologic toxicity was common, with anemia seen in 69 percent and neutropenia seen in 13 percent of newborns.[67]

Experience with other NRTI drugs for neonatal prophylaxis is more limited.[68,69] Hematologic and mitochondrial toxicity may be more common with exposure to multiple NRTI drugs than with exposure to a single NRTI.[66,70–73]

In rare cases, chronic multiple-dose NVP prophylaxis in pregnant women has been associated with severe and potentially life-threatening rash and hepatic toxicity.[74] These toxicities have not been observed in newborns receiving prophylactic dosing with single-dose NVP or the two-drug ZDV regimen plus three doses of NVP in the first week of life used in NICHD-HPTN 040/PACTG 1043 or in breastfeeding newborns receiving NVP prophylaxis daily for 6 weeks to 18 months to prevent transmission of HIV via breast milk.[5,59–61,63,75]

The U.S. Food and Drug Administration (FDA) recently approved infant dosing of RAL for term neonates aged ≥37 weeks' gestation at birth and weighing ≥2 kg. Dosing information for RAL is not available for preterm or low-birthweight infants. Infant RAL dosing needs to be increased at 1 week and 4 weeks of age. RAL is metabolized by uridine diphosphate glucuronosyltransferase (UGT) 1A1, the same enzyme responsible for the elimination of bilirubin. UGT enzyme activity is low at birth, and RAL elimination is prolonged in neonates. In addition, bilirubin and RAL may compete for albumin binding sites, and extremely elevated neonatal plasma RAL concentrations could pose a risk of kernicterus.[40] IMPAACT P1110 is a Phase 1, multicenter trial that enrolled full-term neonates who were exposed to HIV and who were at risk for acquiring perinatal HIV-1 infection, with or without *in utero* RAL exposure. Daily RAL 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. No drug-related clinical adverse reactions were observed, and only three laboratory adverse reactions were observed: one case of Grade 4 transient neutropenia in an infant receiving a ZDV-containing regimen; and two cases of bilirubin elevations (one Grade 1 and one Grade 2) that were considered nonserious and did not require specific therapy[76] (see the Raltegravir section of the Pediatric Antiretroviral Guidelines for additional information).

The safety and PK data on daily dosing from P1110 are from RAL-naive infants whose mothers did not receive RAL; data collection from infants born to mothers who were receiving RAL is ongoing. However, the FDA currently recommends delaying the first dose of RAL in infants for 24 to 48 hours after birth if the mother received RAL 2 to 24 hours before delivery, and the Panel believes that this recommendation is reasonable based on current data about clearance of the drug in RAL-exposed infants.

DTG tablets for oral suspension recently have been approved by the FDA for use in term infants at least 4 weeks of age and weighing at least 3 kg. Safety profiles were favorable with no Grade 3 or 4 toxicities reported and no drug-related discontinuations. It is important to note that DTG tablets for oral suspension and DTG tablets are not bioequivalent and are not interchangeable on a milligram-per-milligram basis.

Of the protease inhibitors, pediatric drug formulations are available for LPV/r, ritonavir (RTV), darunavir, tipranavir, and fosamprenavir; however, the use of these drugs in neonates during the first 2 weeks of life **is not recommended**, given the lack of dosing and safety information. In addition, LPV/r oral solution contains 42.4 percent alcohol and 15.3 percent propylene glycol. The enzymes that metabolize these compounds are immature in neonates, particularly preterm newborns. Four premature newborns (two sets of twins) who were given LPV/r at birth developed heart block that resolved after drug discontinuation.[77,78] In studies of adults, both RTV and LPV/r caused 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 also has been associated with administering LPV/r during the neonatal period, an association not found with ZDV. The levels of 17-hydroxyprogesterone were greater in newborns who also were exposed to LPV/r *in utero* than in those exposed only during 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.[79] Additional studies by these investigators also have demonstrated that LPV was associated with dose-dependent adrenal dysfunction in infants who received LPV/r as prophylaxis during breastfeeding compared with infants who received 3TC and may require further investigation.[80]

On the basis of these and other postmarketing 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[81] predominantly in preterm neonates, the FDA now recommends that LPV/r oral solution **not be administered** to neonates before the infant reaches a postmenstrual age (defined as time from the 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.[82] However, the ANRS 12174 study randomized 1,273 newborns to receive either LPV/r (n = 615) or 3TC (n = 621) 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 weighing >2 kg were randomized. The frequency of clinical and biological severe adverse events did not differ between the groups, suggesting that LPV/r is safe to use in term newborns aged 7 days and older.[83] 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.

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Diagnosis of HIV Infection in Infants and Children

(Last updated December 29, 2020; last reviewed December 29, 2020)

Panel's Recommendations

- Virologic assays (i.e., HIV RNA or 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)**.
- Plasma HIV RNA or cell-associated HIV DNA NATs are generally equally recommended **(AII)**. However, the results of plasma HIV RNA NAT or plasma HIV RNA/DNA NAT can be affected by antiretroviral therapy (ART).
- 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)**. If a mother of an infant acquired HIV outside of the United States and has had repeated undetectable HIV RNA by standard testing, consultation with a clinical virologist on more sensitive HIV nucleic acid testing may be indicated.
- Virologic diagnostic testing (see Figure 1 and 2) 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 who are at high risk of perinatal HIV infection, additional virologic diagnostic testing is recommended at birth **(AII)** and at 2 to 6 weeks after antiretroviral (ARV) drugs are discontinued **(BII)**.
- A positive virologic test should be confirmed as soon as possible by repeat virologic testing **(AII)**.
- Definitive exclusion of HIV infection in non-breastfed 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 that were obtained at age ≥6 months **(AII)**.
- Some experts confirm the absence of HIV at age 12 to 18 months 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 remain HIV antibody-positive should be based on an HIV NAT **(AII)**.
- Diagnostic testing in children with non-perinatal exposure only or in 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 infection **(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/adolescents, but not studies limited to post-pubertal adolescents

Diagnosis of HIV in Infants and Children

HIV can be definitively diagnosed by virologic testing in most non-breastfed infants with perinatal HIV exposure by age 1 to 2 months and in virtually all infants with HIV by age 4 to 6 months. Antibody tests, including the 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. Plasma HIV RNA or cell-associated HIV DNA NATs are generally equally recommended—although the results of a plasma HIV RNA NAT or plasma HIV RNA/DNA NAT can be affected by antiretroviral therapy (ART)—through transplacental transfer of antiretrovirals (ARVs) administered to pregnant women or their newborns. In contrast, qualitative HIV proviral DNA PCR assays from whole blood detect cell-associated virus and should be less affected by ARVs.

A positive HIV test result should be confirmed as soon as possible by repeat virologic testing, because false-positive results can occur with both RNA and DNA assays.[3] For additional information on the diagnosis of Group M non-subtype B, Group O HIV-1 infections, and HIV-2 infections, see the relevant sections below. Newer real-time HIV RNA PCR assays and the qualitative diagnostic RNA assay are better at detecting non-subtype B HIV infection and Group O strains than older RNA assays.[4–9] (See Clinical and Laboratory Monitoring of Pediatric HIV Infection.) One example is the COBAS® AmpliPrep/COBAS® TaqMan HIV-1 qualitative test (a dual-target DNA/RNA test), which also can identify non-subtype B and Group O infections.[10,11]

Antigen/antibody combination immunoassays that detect HIV-1/2 antibodies as well as HIV-1 p24 antigen **are not recommended** for diagnosis of HIV infection in infants. In the first months of life, the antigen component of antigen/antibody tests is less sensitive than an HIV NAT, and antibody tests should not be used for HIV diagnosis in infants and children <18 months of age.[12–14] 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 remain HIV antibody–positive should be based on a NAT (see the section below titled 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 the section below titled Diagnostic Testing in Children with Non-perinatal 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[15] and receive antiretroviral (ARV) prophylaxis or presumptive HIV therapy as soon as possible. For ARV management of newborns who have been exposed to HIV and newborns with HIV infection (including those who do not yet have confirmed infection), see Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV.[16,17]

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. Figures 1 and 2 summarize the timing of recommended virologic diagnostic testing for infants based on HIV transmission risk. Infants at high risk on presumptive HIV therapy may require testing at additional time points (see Figure 1) compared to infants at low risk of transmission (see Figure 2). The risk of transmission is determined based on whether a mother is receiving ART and virally suppressed.

HIV infection can be **presumptively** excluded in non-breastfed infants with two or more negative virologic tests (one at age ≥2 weeks 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.[1,15]

Definitive exclusion of HIV infection in a non-breastfed 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 must 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.[18] Thus, PCP prophylaxis can be avoided or discontinued if HIV infection is presumptively excluded (see Initial Postnatal Management of the Neonate Exposed to HIV and the Pediatric Opportunistic Infection Guidelines).

The case definition for indeterminate HIV infection status is a child who has been exposed to HIV, who is 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 not having acquired HIV. This includes infants who do not meet the minimum requirement for presumptively uninfected.

Virologic Testing at Birth for Newborns at High Risk of Perinatal HIV Transmission

Virologic testing at birth should be considered for newborns who are at high risk of perinatal HIV transmission,[19–24] such as infants born to women with HIV who—

- Did not receive prenatal care;
- Received no antepartum ARVs or only intrapartum ARV drugs;
- Initiated ART late in pregnancy (during the late second or third trimester);
- Received a diagnosis of acute HIV infection during pregnancy or in labor; and/or
- Had detectable HIV viral loads (≥50 copies/mL) close to the time of delivery, including those who received ART and did not have sustained viral suppression.

All infants at high risk of perinatal HIV transmission should be tested at birth before initiating an ARV drug regimen; however, presumptive HIV therapy should not be delayed.

Blood samples from the umbilical cord should not be used for diagnostic evaluation because of the potential for contamination with maternal blood.

Virologic testing at birth is critical for early HIV diagnosis (see When to Initiate Therapy in Antiretroviral-Naive Children in the Pediatric Antiretroviral Guidelines). Infants who have a positive virologic test result at or before age 48 hours are considered to have early (intrauterine) infection, whereas infants who have a negative virologic test result during the first week of life and subsequently have positive test results are considered to have late (intrapartum) infection.[19,20,25] Testing at birth might also be considered in instances when there are concerns that a newborn at low risk of perinatal HIV transmission may be lost to follow-up without testing.

Virologic Testing at Age 14 to 21 Days

The diagnostic sensitivity of virologic testing increases rapidly by age 2 weeks,[15] and early identification of infection permits transition from presumptive HIV therapy to treatment doses of ART (see When to Initiate Therapy in Antiretroviral-Naive Children in the Pediatric Antiretroviral Guidelines.

Virologic Testing at Age 1 to 3 Months

Testing performed at age 1 to 2 months is intended to maximize the likelihood of detecting HIV infection in infants. In the HPTN 040 study, 93 of 140 infants with HIV (66.4%) were identified at birth. Infants who received 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.[26] For infants at high risk of perinatal HIV transmission, the Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission suggests performing an additional virologic test 2 to 6 weeks after ARV drugs are discontinued (i.e., at age 8–12 weeks), given the increased risk of infection and concern that ARV prophylaxis, particularly combination ARV prophylaxis or presumptive HIV therapy, may reduce the sensitivity of diagnostic testing.[15,26,27] In these situations, many experts recommend one test at age 4 to 6 weeks to allow prompt recognition of infants with HIV, with an additional test at 8 to 12 weeks of life (i.e., 2–6 weeks after cessation of prophylaxis or presumptive HIV therapy) to capture additional cases (see Figure 1). 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 (see Figure 2).

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, and is not breastfed.

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, who have no clinical evidence of HIV infection, and who are not breastfed should be retested at age 4 to 6 months for definitive exclusion of HIV infection.

Figure 1. Recommended Virologic Testing Schedules for Infants Who Were Exposed to HIV and Who Are at High Risk of Perinatal HIV Transmission

High Risk: Infants born to mothers with HIV who—

- Did not receive prenatal care;
- Received no antepartum ARVs or only intrapartum ARV drugs;
- Initiated ART late in pregnancy (during the late second or third trimester);
- Received a diagnosis of acute HIV infection during pregnancy or in labor; and/or
- Had detectable HIV viral loads (≥50 copies/mL) close to the time of delivery, including those who received ART but did not achieve sustained viral suppression.

All infants at high risk should be tested at birth before initiating an ARV drug regimen; however, presumptive HIV therapy should not be delayed.

Age at NAT testing	Birth	14–21 days	1–2 months	2–3 months[a]	4–6 months

[a] For high-risk infants, additional virologic diagnostic testing is recommended at birth and 2 to 6 weeks after ARV drugs are discontinued (i.e., at 8–12 weeks of life).

Key: ART = antiretroviral therapy; ARV = antiretroviral; NAT = nucleic acid test

Figure 2. Recommended Virologic Testing Schedules for Infants Who Were Exposed to HIV and Who Are at Low Risk of Perinatal HIV Transmission

Low Risk: Infants born to mothers with HIV who—

- Received ART during pregnancy;
- Had sustained viral suppression (usually defined as <50 copies/mL); *and*
- Were adherent to their ARV regimens.

Age at NAT testing	14–21 days	1–2 months[a]	4–6 months

[a] Test may be timed to occur at least 2 weeks after cessation of ARV prophylaxis.

Key: ART = antiretroviral therapy; ARV = antiretroviral; NAT = nucleic acid test

Antibody Testing at Age 6 Months and Older

Two or more negative results of HIV antibody tests that were performed in non-breastfed 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.[28,29]

Antibody Testing at Age 12 to 18 Months to Document Seroreversion

In cases where an infant or child has not previously received two negative antibody test results, some experts confirm the absence of HIV infection with negative virologic test results by repeating serologic testing between 12 months and 18 months of age to confirm that the maternal HIV antibodies that transferred *in utero* have cleared.[1] In a study from 2012, the median age at seroreversion was 13.9 months.[30] Although the majority of infants who do not have 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.[30–33]

Diagnostic Testing in Children with Perinatal HIV Exposure in Special Situations

Late Seroreversion (Aged ≤24 Months)

Non-breastfed children with perinatal HIV exposure, no other HIV transmission risk factor, 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.[30–33] In one study, 14% of children with HIV exposure who did not have HIV seroreverted after age 18 months.[30] More recent data from Thailand associated late seroreversion with the antenatal use of protease inhibitors in pregnant women with HIV. In this study, late seroreversion was also associated with the use of fourth-generation combination antigen/antibody immunoassays.[34] These children may have had positive immunoassay results, but supplemental antibody test results 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 have a positive HIV antibody (or antigen/antibody) test at age 18 months to 24 months. Virologic testing will distinguish late-seroreverting children who do not have HIV but have residual antibodies from children who have antibodies due to underlying HIV infection.

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 test results. 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 below).

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.[35–37] 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 Non-perinatal HIV Exposure or Children with Perinatal HIV Exposure Aged >24 Months

Breastfeeding

Women with HIV should be encouraged to avoid breastfeeding. Monitoring of infants born to women with HIV who opt to breastfeed after comprehensive counseling should include immediate HIV diagnostic virologic testing with a NAT at standard time points (see Figure 1). 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 (1-888-448-8765). See Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV and Counseling and Managing Women Living with HIV in the United States Who Desire to Breastfeed.[38–40]

Premastication

Receipt of solid food that has been premasticated or prewarmed (in the mouth) by a caregiver with HIV is associated with risk of HIV transmission.[41–46] If this occurs in children with perinatal HIV exposure aged ≤24 months 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 above).

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 mother's 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 reported cases of HIV transmission from these activities have been documented.[47]

Diagnostic Testing

Diagnosis of HIV-1 infection in infants and children with nonperinatal HIV exposure only or children with perinatal HIV exposure who are aged >24 months relies primarily on HIV antibody and antigen/antibody tests.[1,48] 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. These tests are 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.[49] Recent data suggest that the use of immunoassays and rapid diagnostic test combination algorithms that have limited HIV antigen breadth may not be adequate for diagnosis of HIV infection in children following early treatment with ART.[50]

- HIV-1/HIV-2 antibody differentiation immunoassay, which differentiates HIV-1 antibodies from HIV-2 antibodies. This immunoassay is recommended for supplemental testing.
- HIV-1 NAT. A NAT is always indicated as an additional test to diagnose acute HIV infection.
- HIV-1 Western blot and HIV-1 indirect IFAs (first-generation tests). These tests are alternatives for supplemental testing, but they will not detect HIV during acute infection. These tests are rarely performed and **not recommended** by the Centers for Disease Control and Prevention (CDC) for HIV screening in the United States.

The diagnosis of HIV-2 in children with nonperinatal exposure only or children with perinatal exposure aged >24 months relies on the 2014 CDC/Association of Public Health Laboratories laboratory testing guidelines. These guidelines recommend using an HIV-1/HIV-2 antibody differentiation immunoassay that distinguishes between HIV-1 and HIV-2 antibodies for supplemental testing. When used as a supplemental test, the results of the HIV-1 Western blot are more ambiguous than those of the HIV-1/HIV-2 antibody differentiation immunoassay; >60% of individuals with HIV-2 are misclassified as having HIV-1 by the HIV-1 Western blot.[1,51] 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 by CDC if an HIV-1/HIV-2 antibody differentiation immunoassay is inconclusive. HIV-2 DNA PCR testing may be necessary for definitive diagnosis, although this assay is not commercially available.[52,53]

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 ages 1 month, 3 months, and 6 months and is comparable to the specificity of HIV DNA PCR.[27] 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.[54,55] Testing at birth will detect HIV RNA in infants who acquire HIV *in utero* and not in those who acquire HIV from exposure during delivery or immediately prior to delivery (i.e., during 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. These results are similar to the results of HIV DNA PCR for early diagnosis of HIV.[3,15,27,56]

HIV RNA undergoes reverse transcription in the cytoplasm to double-stranded DNA, which persists in the nucleus of an infected cell. The sensitivity of HIV RNA assays is affected by maternal antenatal ART or infant combination ARV prophylaxis.[57] In one study, the sensitivity of HIV RNA assays was 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 who were receiving multidrug prophylaxis (n = 9; median HIV RNA 2.5 $\log_{10}$ copies/mL) than those in infants who were receiving single-drug zidovudine (ZDV) prophylaxis (n = 47; median HIV RNA 5.4 $\log_{10}$ copies/mL). In contrast, the median HIV RNA levels were high (median HIV RNA 5.6 $\log_{10}$ copies/mL) by age 3 months in both groups after stopping prophylaxis.[27] 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 (WHO).[58] Further studies are necessary to evaluate the sensitivity of HIV RNA assays during receipt of multidrug ARV prophylaxis or presumptive HIV therapy in infants whose mothers also received antenatal ART.

An HIV quantitative RNA assay can be used as a confirmatory 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 to 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 below).

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.[25,59–62]

HIV DNA PCR and Related Assays

HIV DNA PCR is a sensitive technique that is 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 detects only *in utero* HIV infection and not infection in those infants who acquire HIV during the intrapartum period. This percentage increases to >90% by age 2 weeks to 4 weeks and to 100% at ages 3 months and 6 months.[15,25,27,56]

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 who were 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 that consisted of 6 weeks of ZDV 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 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.[26]

A study from Cape Town evaluated the sensitivity of HIV DNA assays within 8 days of life, during and after initiating ART in infants with HIV. The infants had been exposed to a combination of maternal ART *in utero* and ARV drugs for prophylaxis and treatment. The authors noted that one infant had undetectable HIV DNA after 6 days on treatment, another had undetectable HIV DNA after 3 months, and a third had undetectable HIV DNA after 4 months. In seven infants who achieved 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.[63] More recent studies from the same authors suggest that ART initiation within the first week of life reduces persistence of long-lived infected cells and that delaying ART initiation is associated with slower decay of infected cells.[64] 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 showed that infants who received the WHO Option B+ regimen had fewer indeterminate DNA PCR results than infants who were receiving older regimens. These findings should be regarded with a high index of suspicion because many patients had positive results that were representative of true HIV infections on subsequent samples. These findings point to the need for additional virologic testing to establish definitive diagnosis.[65] Another group of South African investigators reported similar conclusions in a study of a cohort of 5,743 neonates from Johannesburg who were exposed to HIV.[66]

The AMPLICOR® HIV-1 DNA test has been widely used for diagnosis of HIV in infants born to mothers with HIV-1 infection since it was introduced in 1992. However, it is no longer commercially available in the United States. The sensitivity and specificity of noncommercial HIV-1 DNA tests that use individual laboratory

reagents may differ from the sensitivity and specificity of an FDA-approved commercial test. The COBAS® AmpliPrep/COBAS® TaqMan® HIV-1 version 2.0 qualitative test (which detects both HIV-1 RNA and proviral DNA in plasma, whole blood, and dried blood spots) may be used for HIV diagnosis in infants, but it is not approved by the FDA.[10,11,66] The sensitivity of these DNA assays may be lower than the sensitivity of RNA assays in children who are not currently being treated with ARV drugs.

These considerations underscore the importance of testing with HIV NATs at 4 months—well after neonatal prophylaxis or presumptive HIV therapy has stopped—and highlight the utility of antibody retesting at 24 months of life.

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 also found in the United States.[67] 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.[68] In an evaluation of infants who 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.[69] Among a group of 40 children who visited a pediatric HIV clinic in Rhode Island between 1991 and 2012, 14 (35%) acquired HIV with non-B HIV-1 subtypes. All 14 children were either born outside the United States or their parents were of foreign origin.[70] 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 participants with non-B subtypes formed transmission clusters, including individuals with perinatally acquired infection.[71] In an analysis of 3,895 HIV-1 sequences that were collected between July 2011 and June 2012 in the United States, 5.3% were determined to be non-B subtypes (including recombinant forms).

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.[72] Non-subtype B and Group O strains may be seen in countries with links to these geographical regions.[73–77] The geographical distribution of HIV groups is available at the HIV Sequence Database.

Real-time HIV RNA PCR assays and the qualitative diagnostic RNA assay are better at detecting non-subtype B HIV infection and the less-common Group O strains than older RNA assays.[4–9] (see Clinical and Laboratory Monitoring of Pediatric HIV Infection). An example includes the COBAS® AmpliPrep/COBAS® TaqMan® HIV-1 qualitative test (a dual-target DNA/RNA test), which also can identify non-subtype B and Group O infections.[10,11]

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 that is 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 test results 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 CDC may be able to assist in obtaining referrals for diagnostic testing.

Chimeric Antigen Receptor T Cell (CAR-T Cell) and Lentiviral-Based Gene Therapy May Give Rise to False-Positive HIV NAT Tests

Chimeric antigen receptor (CAR) T-cell immunotherapy is a major advancement in cancer therapeutics, including for pediatric B-cell acute lymphoblastic leukemia (B-ALL). Reprogramming of T cells is achieved by using gammaretroviral or lentiviral vectors. Recent reports indicate that these vectors may interfere with long terminal repeat (LTR) genomes in HIV NAT tests and, thus, produce false-positive results. As CAR T-cell therapy becomes more widely available for multiple indications, it will be important for clinicians to recognize that routine HIV-1 NAT tests may give rise to false results. In addition, lentiviral vector-based gene therapy as treatment for severe combined immunodeficiency can give rise to false-positive HIV NAT tests. Laboratories should, therefore, have appropriate alternate HIV-1 NAT testing platforms made available for this emerging patient population.[78–82]

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, Sao Tome, Senegal, and Togo; and parts of India.[83–85] HIV-2 infection is also well documented in France and Portugal, which have large numbers of immigrants from these regions.[86,87] HIV-1 and HIV-2 coinfection may occur, but this is rarely described 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 that were developed to suppress HIV-1.[88–90] (See HIV-2 Infection and Pregnancy.)

A mother should be suspected of having HIV-2 if her infection is linked to an area that is 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 is to use an HIV-1/HIV-2 antibody differentiation immunoassay for supplemental testing, as the results of this test are less ambiguous than the results of the HIV-1 Western blot when it is used as a supplemental test.[1,91] Between 2010 and 2017, an increase in the number of HIV-1/HIV-2 differentiation test results was reported to the CDC's National HIV Surveillance System (NHSS). More than 99.9% of all HIV infections identified in the United States were categorized as HIV-1, and the number of HIV-2 diagnoses (mono-infection or dual-infection) remained extremely low (<0.03% of all HIV infections).[92]

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. HIV-2 DNA PCR testing can be arranged by the HIV surveillance program of the state, local health department through their public health laboratory, or the CDC, because this assay is not commercially available.[52,53] Clinicians should consult with an expert in pediatric HIV infection when caring for infants with suspected or known exposure to HIV-2.[83,93]

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Initial Postnatal Management of the Neonate Exposed to HIV

(Last updated December 29, 2020; last reviewed December 29, 2020)

Panel's Recommendations
• All newborns who were perinatally exposed to HIV should receive appropriate antiretroviral (ARV) drugs as soon as possible after delivery (see Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV) **(AI)**. • A complete blood count and differential should be performed on newborns as a baseline evaluation **(BIII)**. • Infants who are found to have hematologic abnormalities may need to discontinue ARV drugs. Clinicians should base the decision to discontinue ARV drugs on the individual needs of the patient. Consultation with an expert in pediatric HIV infection is advised if early discontinuation of ARV drugs is considered **(CIII)**. • When determining the timing for subsequent monitoring of hematologic parameters in infants, clinicians need to consider the infant's baseline hematologic values, gestational age at birth, and clinical condition; whether the infant is receiving zidovudine (ZDV), other ARV drugs, or certain concomitant medications; and the specific ARV drugs used in the mother's antepartum drug regimen **(CIII)**. • Hemoglobin and neutrophil counts should be remeasured 4 weeks after initiating an ARV regimen that contains ZDV and lamivudine **(AI).** • 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 or an empiric HIV therapy regimen, unless there is adequate test information to presumptively exclude HIV infection (see the Pediatric Opportunistic Infection Guidelines) **(AII)**. • Health care providers should routinely inquire about infant feeding plans and/or breastfeeding desires, as well as the use of premasticated (prechewed or prewarmed) food. Counseling against premastication and discussion of safe infant feeding options should be provided (see Counseling and Managing Women Living with HIV in the United States Who Desire to Breastfeed) **(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

Postnatal Management of the Neonate Exposed to HIV

Following birth, infants who were 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 the appropriate evaluations to exclude the possibility of transmission of additional infectious agents. The routine primary immunization schedule for children should be followed for infants born to women with HIV. The schedule may need to be modified for infants with known HIV infection (see the Pediatric Opportunistic Infection Guidelines for more information).

Infants should be monitored for the toxicities that are associated with the antiretroviral (ARV) drugs they were exposed to *in utero* or the ARV drugs that they are receiving for the prevention of perinatal HIV transmission (see Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV). Comprehensive care also includes appropriate HIV diagnostic testing and infant feeding support to assist mothers in abstaining 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 initiating ARV drugs in newborns who were exposed to HIV (see Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV). Decisions about the timing of hematologic monitoring after birth depend on several factors, including the infant's baseline hematologic values, gestational age at birth, and clinical condition; the infant's ARV drugs and concomitant medications; and the maternal antepartum ARV drug regimen.

Older studies have shown that anemia is the primary complication seen in neonates who received a 6-week postnatal prophylaxis regimen with zidovudine (ZDV).[1] Some experts remeasure hemoglobin and neutrophil counts routinely after 4 weeks of ZDV prophylaxis and/or when the results of diagnostic HIV polymerase chain reaction (PCR) tests are obtained. Data are limited and somewhat mixed on infants who received ZDV in combination with other ARV drugs. Higher rates of hematologic toxicity have been observed in infants who received ZDV plus lamivudine (3TC) and other combination infant ARV regimens, such as ZDV plus 3TC plus nevirapine (NVP), than in those who received ZDV alone.[2-6] Although a recent study from Thailand observed significantly higher Grade 2 anemia at age 1 month in high-risk infants who received ZDV plus 3TC plus NVP compared to low-risk infants who received ZDV alone, these differences did not persist past 2 months of age. In addition, a recent study from the European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC) evaluated 1,836 infants who were exposed to HIV but uninfected (HEU) and who were receiving ARV drugs. The presence of Grade 3 or 4 anemia in the first 6 months of life was not associated with the infants' ARV regimens (adjusted odds ratio [aOR] 1.04 for one-drug regimens, $P = 0.879$; aOR 1.60 for three-drug vs. two-drug regimens, $P = 0.277$). Likewise, the presence of Grade 3 or 4 neutropenia in the first 6 months of life was not associated with the infants' ARV regimens (aOR 1.33 for one-drug regimens, $P = 0.330$; aOR 1.98 for three-drug vs. two-drug regimens, $P = 0.113$).[7] Hemoglobin level and neutrophil count testing should be repeated 4 weeks after initiating ARV drugs and/or at the time that diagnostic HIV PCR testing is done in infants who receive regimens that contain ZDV and 3TC.[5,6]

Older studies previously have shown that the association between *in utero* exposure to maternal ARV drugs and anemia and/or neutropenia in infants was greater in infants with *in utero* exposure to combination ARV drug regimens than in infants with exposure to ZDV alone.[8-10] In the Pediatric AIDS Clinical Trials Group, Protocol 316 (PACTG 316), where 77% of mothers received antenatal combination therapy, significant Grade 3 or higher anemia was noted in 13% of infants, and significant Grade 3 or higher neutropenia was noted in 12% of infants. Some experts recommend more intensive hematologic monitoring in infants who were exposed to combination ARV drug regimens *in utero* or during the neonatal period. These tests should be performed at birth and when diagnostic HIV PCR tests are also obtained.

Infants who are found to have hematologic abnormalities may need to discontinue ARV drugs. Clinicians should base the decision to discontinue ARV drugs on the individual needs of the patient. Considerations include the extent of the abnormality, whether related symptoms are present, the duration of ARV drugs received by the infant, and the risk of HIV infection (as assessed by maternal history of ARV drugs, maternal viral load near delivery, and mode of delivery). A 4-week ZDV regimen has been reported to result in earlier recovery from anemia in HIV-exposed but otherwise healthy infants than the 6-week ZDV regimen.[11] A 4-week (instead of a 6-week) ZDV neonatal regimen is recommended when the mother has received standard antiretroviral therapy (ART) during pregnancy and has had consistent viral suppression and appropriate adherence; the shorter regimen may mitigate the risk of anemia in HEU (see Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV).[12]

Hyperbilirubinemia

Hyperbilirubinemia has been observed in HIV-exposed infants receiving raltegravir (RAL) through 6 weeks of life.[13] The International Maternal Pediatric Adolescent AIDS Clinical trials Network (IMPAACT) P1110 study reported Grade 3–4 levels of increased bilirubin in 3 of 52 infants. However, no bilirubin levels exceeded 16 mg/dL, and no infants required phototherapy or other clinical treatment for hyperbilirubinemia. RAL at extremely high levels may displace unconjugated bilirubin from albumin, increasing the potential risk of bilirubin-induced neurologic dysfunction.[14] Due to the possible risk of hyperbilirubinemia, serum total and direct bilirubin measurement may be considered in infants receiving RAL.

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.[15,16] 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 to be poor.[15,16] However, serum lactate measurement should be considered for infants who develop severe clinical symptoms of unknown etiology, particularly neurologic symptoms. ARV drugs should be discontinued in cases where infants develop symptoms or when serum lactate levels are significantly abnormal (i.e., levels >5 mmol/L). An expert in pediatric HIV infection should be consulted about initiating alternative ARV regimens or the discontinuation of ARV drugs.

Prophylaxis Against Pneumocystis jirovecii Pneumonia

To prevent *Pneumocystis jirovecii* pneumonia, all infants born to women with HIV should begin trimethoprim-sulfamethoxazole prophylaxis at age 4 to 6 weeks, after completing the infant ARV regimen, unless there is adequate virologic test information to presumptively exclude HIV infection (see the Pediatric Opportunistic Infection Guidelines).[17] With appropriate follow-up to support the recommended diagnostic testing schedule, most infants with perinatal HIV exposure do not require trimethoprim-sulfamethoxazole prophylaxis, because HIV can be presumptively excluded by the time their infant ARV regimen is completed (see Diagnosis of HIV Infection in Infants and Children).

HIV Testing of the Infant

All infants who were perinatally exposed to HIV require virologic HIV testing (i.e., HIV RNA and HIV DNA nucleic acid tests) to diagnose or exclude HIV infection. For a detailed discussion of HIV testing, including types of tests and the 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, it is recommended that women with HIV refrain from breastfeeding their infants, because safe infant feeding alternatives are available.[18] Maternal ART is likely to reduce free virus in breast milk, but cell-associated virus (intracellular HIV DNA) remains unaffected and may continue to pose a transmission risk.[19] However, clinicians should be aware that some women may face considerable social, familial, and personal pressures to breastfeed despite this recommendation (see Counseling and Managing Women Living with HIV in the United States Who Desire to Breastfeed). It is important to address a woman's desire to breastfeed and potential barriers to formula feeding as early as possible in the antenatal period.

Some HIV transmission events that occurred in later infancy are thought to have resulted from infants' being fed solid food that had been premasticated (prechewed or prewarmed) by caregivers with HIV. Phylogenetic comparisons of virus from cases and suspected sources, as well as supporting clinical history, 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 with HIV not to perform this feeding practice, and advise on safer feeding options.[20,21]

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Long-Term Follow-Up of Infants Exposed to Antiretroviral Drugs

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Panel's Recommendations
• 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 and outcomes studies, as well as ongoing 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 studies include children without HIV infection who are born to women with HIV (e.g., the Pediatric AIDS Clinical Trial Group [PACTG] Late Outcomes Study and the Surveillance Monitoring for ART Toxicities [SMARTT] study from the Pediatric HIV/AIDS Cohort Study [PHACS]). Participation of children and their parents in observational studies provides an essential contribution to the research needed to monitor and identify long-term health outcomes following *in utero* HIV and ARV exposure. Available evidence does not permit definitive conclusions about whether *in utero* exposure to HIV and ARV agents might affect immune function, infectious morbidity, growth, cardiometabolic health, neurodevelopment, mitochondrial function, or cancer risk from infancy through adulthood. Further, long-term investigation of potential HIV- and/or ARV-related toxicities is required, especially as new antiretroviral therapy (ART) for pregnant women with HIV evolves. It is important to include information about perinatal exposure to HIV and ARV agents in the long-term medical record of a child without HIV 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.[1–3]

Potential Increased Morbidity and Mortality

In general, the risks for increased morbidity and mortality are greater in infants who are HIV exposed but uninfected (HEU) than in infants who are HIV unexposed and uninfected (HUU). These differences are more pronounced in infants from low- and middle-income countries than in infants from high-income countries.[4] Higher rates of morbidity and mortality were observed in infants and children in Botswana who were HEU than in those who were HUU, with the strongest predictors of 24-month mortality being HEU status and formula feeding.[5,6] In a meta-analysis, all-cause mortality risk was higher in infants and children who were HEU than in those who were HUU.[7] Further research is needed to confirm these results and to elucidate an immunologic basis for the increased susceptibility of infants and children who were HEU to invasive infections.[8]

Potential Immunologic Dysfunction and Infectious Morbidity

The potential long-term impact of HIV/ARV exposure on the immune system of an infant without HIV is unclear. In a recent meta-analysis, infants who were HEU had a 50% and 70% increased risk for diarrhea and pneumonia, respectively, compared with infants who are HUU in the first 6 months of life.[9] The French Perinatal Cohort Group has observed an increased risk of serious bacterial infections with encapsulated organisms in HEU infants born to women with HIV with low CD4 T lymphocyte (CD4) cell counts near the time of delivery.[10] In a U.S. study, the rates of infection-related hospitalizations in the first 2 years of life were higher among infants who were HEU than in infants who were HUU.[11] A South African study reported higher

rates of lower respiratory tract and diarrheal illnesses in the first 6 months of life in breastfed infants who were HEU compared with breastfed infants who were HUU.[12] A potential association between maternal viral load at delivery and infant immunity also was documented previously. Here, infants who were HEU born to mothers with a viral load >1,000 copies/mL had lower CD4 counts than those born to mothers whose viral load was <50 copies/mL at delivery.[13] Immune phenotyping suggests that exposure to HIV *in utero* may be associated with perturbations in infant CD4 and CD8 cell-mediated immune responses, resulting in T-cell dysfunction and altered vaccine responses in infants who were HEU.[14,15] These observations have been supported by data showing increased monocyte activation and proinflammatory responses with downregulation of genes involved in neutrophil-mediated immunity in infants who were HEU compared with infants who were HUU.[16–23]

Potential Adverse Growth and Metabolic Outcomes

Similar to patterns of overall morbidity and mortality in infants who were HEU, the effect of *in utero* HIV/ARV exposure on infant and child growth largely has differed between low- and high-income settings.[24–29] Among studies that compared growth in children who were HEU with those who were HUU, a Nigerian study reported compromised growth in those who were HEU. Studies from South Africa and Malawi documented persistently lower weight-for-age z-scores (WAZ) in early childhood and higher rates of stunting in those who were HEU.[27,30,31] The Sanitation Hygiene Infant Nutrition Efficacy (SHINE) trial from Zimbabwe reported a similar trend of increased stunting in infants who were HEU.[28] These changes may reflect disruption to the growth hormone axis in infants who were HEU compared with infants who were HUU.[28] However, in a large Danish study of postnatal growth through 5 years of life, no significant differences in WAZ after 2 weeks of life or length-for-age z-scores after 6 months of life were noted between children who were HEU and a matched comparator group of children who were HUU.[32] Furthermore, the Surveillance Monitoring for ART Toxicities (SMARTT) study of the Pediatric HIV/AIDS Cohort (PHACS) in the United States noted above-average weight in children who were HEU compared with children in the general pediatric population.[25] This positive relationship may carry potential long-term cardiometabolic risk for children from high-income settings who were HEU. PHACS SMARTT has found high rates of obesity in children and adolescents who were HEU,[33] and obese children and adolescents who were HEU have a greater risk for systolic and diastolic hypertension than obese children and adolescents in the general pediatric population.[34] Although early derangements in fuel utilization and intermediary metabolism have been described in infants who were HEU in the United States and Africa, the significance of these findings on long-term metabolic health remains unclear.[35,36]

Potential Neurodevelopmental Outcomes

Studies investigating whether the risk for poor neurodevelopmental outcomes is higher in children who were HEU than in those who were HUU have not been conclusive.[37] The heterogeneity of study populations and study designs may further complicate the interpretation of conflicting results from different studies. Several studies found no differences in early neurodevelopment between children who were HEU and those who were HUU. However, some studies reported an increased risk for poorer neurodevelopmental outcomes in children who were HEU.[38–42] Some studies evaluated whether maternal factors or *in utero* ARV drug exposure contributed to adverse neurodevelopmental outcomes among children who were HEU. Although worse infant neurodevelopment was associated with maternal viremia in one study[43] and with *in utero* efavirenz exposure in another,[44] many studies have not identified associations between maternal ARV use and infant neurodevelopment.[40,43,45–47] In the PHACS SMARTT study, children who were HEU with *in utero* exposure to efavirenz had a greater risk of microcephaly than those without *in utero* efavirenz exposure (see Teratogenicity). Neurodevelopmental assessments at ages 1 and 5 years demonstrated that children who were HEU with microcephaly had lower mean scores and a higher prevalence of neurodevelopmental impairment than children who were HEU without microcephaly.[48,49] At present, no definitive evidence shows an association between *in utero* exposure to specific ARV drugs and poorer neurodevelopmental outcomes.[50]

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.[51–53] 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 nonhuman primates and neonates exposed *in utero* to NRTI drugs.[2,54–59] The degree to which these documented mitochondrial abnormalities are clinically relevant is unknown, but they are significantly outweighed by the robust, proven efficacy of maternal and infant ARV prophylaxis in preventing perinatal HIV transmission.[2,60]

Evidence of clinically apparent effects of mitochondrial toxicity also is conflicting. Although 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 (12 of 2,644 infants vs. 0 of 1,748 infants with and without exposure to *in utero* ARV drugs, respectively, $P = 0.002$)[61,62]—low rates of hyperlactatemia (3.4%) have been documented among infants who were HEU, born to women with HIV in the United States who were receiving ART during pregnancy.[63] In addition, further clinical studies from the United States and Europe did not corroborate findings from the French studies.[64–70] Some small alterations in mtDNA and oxidative phosphorylation enzyme activities were documented in stored specimens from children who were HEU in the U.S. PACTG 219/219C trial, but the clinical significance of these observations is unknown.[71,72]

Mitochondrial dysfunction should be considered in children without HIV but with perinatal exposure to ARV drugs who present with clinical findings of unknown etiology, particularly neurologic findings.

Potential Cancer Risk and Exposure to Nucleoside Reverse Transcriptase Inhibitor Drugs

Animal studies have reported potential transplacental genotoxicity of nucleoside analogue therapy in monkeys, and micro-nucleated erythrocytes have been identified in infants with *in utero* nucleoside analogue exposure.[73,74] A report from the French Perinatal Cohort described 21 cancers among 15,163 children without HIV (median age 9.9 years) exposed in utero to HIV and ≥1 NRTI drug.[75,76] Among the NRTIs studied, didanosine (which **is no longer recommended**) was potentially associated with risk of cancer. In a study in the United States, four cancer diagnoses occurred among 3,087 children exposed to HIV; the number of cancer cases did not differ significantly from the number of cases expected based on national reference rates.[77] Continued follow-up of children who were HIV and ARV exposed but uninfected is needed to evaluate the potential risk of cancer as these children age into adulthood.

Conclusion

In the United States, ongoing evaluation of the early and late effects of *in utero* exposure to ARV drugs and of infant feeding practices is occurring in the PHACS SMARTT study, natural history studies, and HIV/AIDS surveillance conducted by state health departments, as well as the Centers for Disease Control and Prevention. It is critical that studies to evaluate potential adverse effects of *in utero* drug exposure continue to be supported given the fast pace at which newly developed ARV drugs are being made available to pregnant women who have HIV. 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, the data from these confidential registries can be compared with information from birth defects and cancer registries to identify potential adverse outcomes of *in utero* ARV drug exposure.

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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 HIV Infection).

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

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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

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**[a]	**Use in Pregnancy**	**Last Reviewed**
NRTIs NRTIs interfere with HIV reverse transcriptase by competitive inhibition. Nucleoside analogue drugs require three intracellular phosphorylation steps to form the triphosphate nucleoside, which is the active drug moiety. The nucleotide analogue tenofovir contains a monophosphate component attached to the adenine base and requires only two phosphorylation steps to form the active moiety.				
Abacavir (ABC) *Ziagen* (ABC/3TC) *Epzicom* (ABC/DTG/3TC) *Triumeq* (ABC/3TC/ZDV) *Trizivir* **Note:** Generic products are available for some formulations.	**ABC (Ziagen):**[d] *Tablet:* • 300 mg *Oral Solution:* • 20 mg/mL **ABC/3TC (Epzicom):**[d] • ABC 600 mg/3TC 300 mg tablet **ABC/DTG/3TC (Triumeq):** • ABC 600 mg/DTG 50 mg/3TC 300 mg tablet **ABC/3TC/ZDV (Trizivir):**[d] • ABC 300 mg/3TC 150 mg/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):* • One tablet once daily without regard to food *ABC/DTG/3TC (Triumeq):* • One tablet once daily without regard to food *ABC/3TC/ZDV (Trizivir):* • One tablet twice daily without regard to food **Pregnancy** *PKs in Pregnancy:* • PKs 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., 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 a patient's status **should be documented as negative** before initiating ABC. Patients should be educated regarding symptoms of HSR.	December 29, 2020

Table 10. Antiretroviral Drug Use in Pregnant Women with HIV: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations[a]	Use in Pregnancy	Last Reviewed
Emtricitabine (FTC) *Emtriva* (FTC/EFV/TDF) *Atripla* (FTC/BIC/TAF) *Biktarvy* (FTC/RPV/TDF) *Complera* (FTC/TAF) *Descovy* (FTC/EVG/c/TAF) *Genvoya* (FTC/RPV/TAF) *Odefsey* (FTC/EVG/c/TDF) *Stribild* (FTC/DRV/c/TAF) *Symtuza* (FTC/TDF) *Truvada*	**FTC (Emtriva)** *Capsule*:[d] • 200 mg *Oral Solution:* • 10 mg/mL **FTC/EFV/TDF (Atripla):**[d] • FTC 200 mg/EFV 600 mg/TDF 300-mg tablet **FTC/BIC/TAF (Biktarvy):** • FTC 200 mg/BIC 50 mg/TAF 25-mg tablet **FTC/RPV/TDF (Complera):** • FTC 200 mg/RPV 25 mg/TDF 300-mg tablet **FTC/TAF (Descovy):** • FTC 200 mg/TAF 25 mg tablet	**Standard Adult Doses** *FTC (Emtriva)* Capsule: • FTC 200 mg once daily without regard to food Oral Solution: • FTC 240 mg (24 mL) once daily without regard to food *FTC/EFV/TDF (Atripla):* • One tablet once daily at or before bedtime • Take on an empty stomach to reduce or mitigate side effects. *FTC/BIC/TAF (Biktarvy):* • One tablet once daily with or without food *FTC/RPV/TDF (Complera):* • One tablet once daily with food *FTC/TAF (Descovy):* • One tablet once daily with or without food *FTC/EVG/c/TAF (Genvoya):* • One tablet once daily with food *FTC/RPV/TAF (Odefsey):* • One tablet once daily with food *FTC/EVG/c/TDF (Stribild):* • One tablet once daily with food	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 HBV/HIV coinfection, it is possible that a HBV flare may occur if the drug is stopped; see Hepatitis B Virus/HIV Coinfection.	December 29, 2020

Table 10. Antiretroviral Drug Use in Pregnant Women with HIV: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy

Generic Name (Abbreviation) *Trade Name*	**Formulation**	**Dosing Recommendations**[a]	**Use in Pregnancy**	**Last Reviewed**
Note: Generic products are available for some formulations.	**FTC/EVG/c/TAF (Genvoya):** • FTC 200 mg/EVG 150 mg/COBI 150 mg/TAF 10-mg tablet **FTC/RPV/TAF (Odefsey):** • FTC 200 mg/RPV 25 mg/TAF 25 mg tablet **FTC/EVG/c/TDF (Stribild)**: • FTC 200 mg/EVG 150 mg/COBI 150 mg/TDF 300-mg tablet **FTC/DRV/c/TAF (Symtuza):** • FTC 200 mg/DRV 800 mg/COBI 150 mg/TAF 10-mg tablet **FTC/TDF (Truvada):**[d] • FTC 200 mg/TDF 300-mg tablet	*FTC/DRV/c/TAF (Symtuza):* • One tablet once daily with food *FTC/TDF (Truvada):* • One tablet once daily without regard to food **Pregnancy** *PKs in Pregnancy:* • PKs of FTC are not significantly altered in pregnancy. *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., TDF, TAF, EFV, RPV, DRV, EVG, BIC, COBI).		

Table 10. Antiretroviral Drug Use in Pregnant Women with HIV: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations[a]	Use in Pregnancy	Last Reviewed
Lamivudine (3TC) *Epivir* (3TC/TDF) *Cimduo* (3TC/ZDV) *Combivir* (3TC/DOR/TDF) *Delstrigo* (3TC/DTG) *Dovato* (3TC/ABC) *Epzicom* (3TC/EFV/TDF) (3TC/EFV/TDF) (3TC/TDF) *Temixys* (3TC/ABC/DTG) *Triumeq*	**3TC (Epivir)[d]** *Tablets:* • 150 mg • 300 mg *Oral Solution:* • 10 mg/mL **3TC/TDF (Cimduo):** • 3TC 300 mg/TDF 300 mg tablet **3TC/ZDV (Combivir):[d]** • 3TC 150 mg/ZDV 300 mg tablet **3TC/DOR/TDF (Delstrigo):** • 3TC 300 mg/DOR 100 mg/TDF 300 mg tablet **3TC/DTG (Dovato):** • 3TC 300 mg/DTG 50 mg tablet **3TC/ABC (Epzicom):[d]** • 3TC 300 mg/ABC 600 mg tablet	**Standard Adult Doses** *3TC (Epivir):* • 3TC 150 mg twice daily or 300 mg once daily, without regard to food *3TC/TDF (Cimduo):* • One tablet once daily without regard to food *3TC/ZDV (Combivir):* • One tablet twice daily without regard to food *3TC/DOR/TDF (Delstrigo):* • One tablet once daily without regard to food *3TC/DTG (Dovato):* • One tablet once daily without regard to food *3TC/ABC (Epzicom):* • One tablet once daily without regard to food • One tablet once daily on an empty stomach and preferably at bedtime *3TC/TDF (Temixys):* • One tablet once daily without regard to food *3TC/ABC/DTG (Triumeq):* • One 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). If patient has HBV/HIV coinfection, it is possible that an HBV flare may occur if the drug is stopped; see Hepatitis B Virus/HIV Coinfection. 3TC products that were 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 29, 2020

Table 10. Antiretroviral Drug Use in Pregnant Women with HIV: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy

Generic Name (Abbreviation) *Trade Name*	**Formulation**	**Dosing Recommendations**[a]	**Use in Pregnancy**	**Last Reviewed**
(3TC/ABC/ZDV) *Trizivir* **Note:** Generic products are available for some formulations.	**3TC/EFV/TDF (Symfi):** • 3TC 300 mg/EFV 600 mg plus TDF 300 mg tablet **3TC/EFV/TDF (Symfi Lo):** • 3TC 300 mg/ EFV 400 mg/TDF 300 mg tablet **3TC/TDF (Temixys):** • 3TC 300 mg/TDF 300 mg tablet **3TC/ABC/DTG (Triumeq):** • 3TC 300 mg/ABC 600 mg/DTG 50 mg tablet **3TC/ABC/ZDV (Trizivir):**[d] • 3TC 150 mg/ABC 300 mg/ZDV 300 mg tablet	*3TC/ABC/ZDV (Trizivir):* • One tablet twice daily without regard to food **Pregnancy** *PKs in Pregnancy:* • PKs not significantly altered in pregnancy. *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, DOR, DTG, EFV, TDF, ZDV)		

Table 10. Antiretroviral Drug Use in Pregnant Women with HIV: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy

Generic Name (Abbreviation) *Trade Name*	**Formulation**	**Dosing Recommendations**[a]	**Use in Pregnancy**	**Last Reviewed**
Tenofovir Alafenamide (TAF) *Vemlidy* (TAF/BIC/FTC) *Biktarvy* (TAF/FTC) *Descovy* (TAF/EVG/c/FTC) *Genvoya* (TAF/FTC/RPV) *Odefsey* (TAF/DRV/c/FTC) *Symtuza*	**TAF (Vemlidy)** *Tablet:* • 25 mg **TAF/BIC/FTC (Biktarvy):** • TAF 25 mg/BIC 50 mg/FTC 200 mg tablet **TAF/FTC (Descovy):** • TAF 25 mg/FTC 200 mg tablet **TAF/EVG/c/FTC (Genvoya):** • TAF 10 mg/EVG 150 mg/COBI 150 mg/FTC 200 mg tablet **TAF/FTC/RPV (Odefsey):** • TAF 25 mg/FTC 200 mg/RPV 25 mg tablet **TAF/DRV/c/FTC (Symtuza):** • TAF 10 mg/DRV 800 mg/COBI 150 mg/FTC 200 mg tablet	**Standard Adult Doses** *TAF (Vemlidy)*: • One tablet once daily with food *TAF/BIC/FTC(Biktarvy)*: • One tablet once daily with or without food *TAF/FTC (Descovy):* • One tablet once daily with or without food • Same dose (TAF 25 mg) can be used with or without PK enhancers. *TAF/EVG/c/FTC (Genvoya)*: • One tablet once daily with food *TAF/FTC/RPV (Odefsey)*: • One tablet once daily with food *TAF/DRV/c/FTC (Symtuza)*: • One tablet once daily with food **Pregnancy** *PKs in Pregnancy:* • Plasma PKs not significantly altered in pregnancy. *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., 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 the potential for renal toxicity.	December 29, 2020

Table 10. Antiretroviral Drug Use in Pregnant Women with HIV: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy

Generic Name (Abbreviation) *Trade Name*	**Formulation**	**Dosing Recommendations**[a]	**Use in Pregnancy**	**Last Reviewed**
Tenofovir Disoproxil Fumarate (TDF) *Viread* (TDF/EFV/FTC) *Atripla* (TDF/3TC) *Cimduo* (TDF/FTC/RPV) *Complera* (TDF/DOR/3TC) *Delstrigo* (TDF/EVG/c/FTC) *Stribild* (TDF/EFV/3TC) (TDF/EFV/3TC) (TDF/3TC) *Temixys* (TDF/FTC) *Truvada*	**TDF (Viread)** *Tablet*:[d] • 300 mg *Powder*: • 40 mg/1 g oral powder **TDF/EFV/FTC (Atripla):** • TDF 300 mg/ EFV 600 mg/ FTC 200 mg tablet **TDF/3TC (Cimduo):** • TDF 300 mg/ 3TC 300 mg tablet **TDF/FTC/RPV (Complera):** • TDF 300 mg/ FTC 200 mg/ RPV 25 mg tablet **TDF/DOR/3TC (Delstrigo):** • TDF 300 mg/ DOR 100 mg/ 3TC 300 mg tablet	**Standard Adult Doses** *TDF (Viread)* Tablet: • TDF 300 mg once daily without regard to food Powder: • TDF 8 mg/kg daily (up to a maximum of TDF 300 mg). Take with food. *TDF/EFV/FTC (Atripla):* • One tablet once daily at or before bedtime. Take on an empty stomach to reduce side effects. *TDF/3TC (Cimduo):* • One tablet once daily without regard to food *TDF/FTC/RPV (Complera):* • One tablet once daily with food *TDF/DOR/3TC (Delstrigo):* • One tablet once daily without regard to food *TDF/EVG/c/FTC (Stribild):* • One tablet once daily with food • One tablet once daily on an empty stomach and preferably at bedtime *TDF/3TC (Temixys):* • One 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 twofold 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 has HBV/HIV coinfection, it is possible that an HBV flare may occur if TDF is stopped; see Hepatitis B Virus/ HIV Coinfection. Renal function should be monitored because of potential for renal toxicity.	December 29, 2020

Table 10. Antiretroviral Drug Use in Pregnant Women with HIV: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy

Generic Name (Abbreviation) *Trade Name*	**Formulation**	**Dosing Recommendations**[a]	**Use in Pregnancy**	**Last Reviewed**
Note: Generic products are available for some formulations.	**TDF/EVG/c/FTC (Stribild):** • TDF 300 mg/ EVG 150 mg/ COBI 150 mg/ FTC 200 mg tablet **TDF/EFV/3TC (Symfi):** • TDF 300 mg/ EFV 600 mg/ 3TC 300 mg tablet **TDF/EFV/3TC (Symfi Lo):** • TDF 300 mg/EFV 400 mg/3TC 300 mg tablet **TDF/3TC (Temixys):** • TDF 300 mg/3TC 300 mg tablet **TDF/FTC (Truvada):** • TDF 300 mg/FTC 200 mg tablet	*TDF/FTC (Truvada):* • One tablet once daily without regard to food **Pregnancy** *PKs in Pregnancy:* • AUC is lower in third trimester than postpartum, but trough levels are adequate. *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., 3TC, COBI, DOR, EFV, EVG, FTC, RPV)		

Table 10. Antiretroviral Drug Use in Pregnant Women with HIV: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy

Generic Name (Abbreviation) *Trade Name*	**Formulation**	**Dosing Recommendations**[a]	**Use in Pregnancy**	**Last Reviewed**
Zidovudine (ZDV) *Retrovir* (ZDV/3TC) *Combivir* (ZDV/ABC/3TC) *Trizivir* **Note:** Generic products are available for all formulations.	**ZDV (Retrovir)** *Capsule:* • 100 mg *Tablet:* • 300 mg *Oral Solution:* • 10 mg/mL *IV Solution:* • 10 mg/mL **ZDV/3TC (Combivir):** • ZDV 300 mg/3TC 150 mg tablet **ZDV/ABC/3TC (Trizivir):** • ZDV 300 mg/ABC 300 mg/3TC 150 mg tablet	**Standard Adult Doses** *ZDV (Retrovir):* • ZDV 300 mg twice daily or ZDV 200 mg three times a day without regard to food • Patients in active labor should receive ZDV 2 mg/kg IV as a loading dose, followed by ZDV 1 mg/kg/hour continuous infusion from beginning of active labor until delivery. *ZDV/3TC (Combivir):* • One tablet twice daily without regard to food *ZDV/ABC/3TC (Trizivir):* • One tablet twice daily without regard to food **Pregnancy** *PKs in Pregnancy:* • PKs not significantly altered in pregnancy. *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).	High placental transfer to fetus.[b] No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects).	December 29, 2020

Table 10. Antiretroviral Drug Use in Pregnant Women with HIV: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy

Generic Name (Abbreviation) *Trade Name*	**Formulation**	**Dosing Recommendations**[a]	**Use in Pregnancy**	**Last Reviewed**
NNRTI NNRTIs interfere with HIV reverse transcriptase by binding directly to the enzyme.				
Doravirine (DOR) *Pifeltro* (DOR/3TC/TDF) *Delstrigo*	**DOR (Pifeltro):** • 100 mg tablet **DOR/3TC/TDF (Delstrigo):** • DOR 100 mg/3TC 300 mg/TDF 300 mg tablet	**Standard Adult Doses** *DOR* (*Pifeltro*): • DOR 100 mg once daily with or without food *DOR/3TC/TDF* (*Delstrigo*): • One tablet once daily with or without food **Pregnancy** *PKs in Pregnancy:* • No PK studies in human pregnancy. *Dosing in Pregnancy:* • Insufficient data to make dosing recommendations. For guidance about use of combination products in pregnancy, please see the specific sections on other components (i.e., 3TC, TDF).	No data are available on the placental transfer of DOR in humans, 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 29, 2020
Efavirenz (EFV) *Sustiva* (EFV/FTC/TDF) *Atripla* (EFV/3TC/TDF)	**EFV (Sustiva)**[d] *Capsules:* • *50 mg* • *200 mg* *Tablet:* • *600 mg*	**Standard Adult Doses** *EFV (Sustiva):* • EFV 600 mg once daily at or before bedtime • Take on an empty stomach to reduce side effects. *EFV/FTC/TDF (Atripla)*: • One tablet once daily at or before bedtime • Take on an empty stomach to reduce side effects.	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. However, the data on more than 7,900	December 29, 2020

Table 10. Antiretroviral Drug Use in Pregnant Women with HIV: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy

Generic Name (Abbreviation) *Trade Name*	**Formulation**	**Dosing Recommendations**[a]	**Use in Pregnancy**	**Last Reviewed**
(EFV/3TC/TDF) **Note:** Generic products are available for some formulations.	**EFV/FTC/TDF (Atripla):** • EFV 600 mg/FTC 200 mg/TDF 300 mg tablet **EFV/3TC/TDF (Symfi):** • EFV 600 mg/3TC 300 mg/TDF 300 mg tablet **EFV/3TC/TDF (Symfi Lo):** • EFV 400 mg/3TC 300 mg/TDF 300 mg tablet	• One tablet once daily on an empty stomach and preferably at bedtime **Pregnancy** *PKs 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 the use of combination products in pregnancy, please see the specific sections on other components (i.e., 3TC, FTC, TDF).	periconception EFV exposures from Botswana rule out a threefold or greater increased risk of NTDs. 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 virally 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).	

Table 10. Antiretroviral Drug Use in Pregnant Women with HIV: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations[a]	Use in Pregnancy	Last Reviewed
Etravirine (ETR) *Intelence*	**Tablets:** • 25 mg • 100 mg • 200 mg For patients who are unable to swallow tablets whole, the tablets may be dispersed in a glass of water.	**Standard Adult Doses** • 200 mg twice daily with food **Pregnancy** *PK in Pregnancy:* • PK data in pregnancy suggest 1.2-fold to 1.6-fold increases in ETR exposure during pregnancy. *Dosing in Pregnancy:* • No change in dose indicated.	Placental transfer varies; it is usually in the moderate-to-high categories, ranging 0.19–4.25.[b] Insufficient data to assess for teratogenicity in humans. No evidence of teratogenicity in rats or rabbits.	December 29, 2020
Nevirapine (NVP) *Viramune* *Viramune XR* **Note:** Generic products are available for some formulations.	**NVP (Viramune)** *Tablet:* • 200 mg[d] *Oral Suspension:* • 50 mg/5 mL[d] **Viramune XR** *Tablets:* • 100 mg • 400 mg[d]	**Standard Adult Doses** • NVP 200 mg once daily (using Viramune immediate release) for a 14-day lead-in period; thereafter, NVP 200 mg twice daily or 400 mg (using 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 the lead-in period, continue lead-in dosing until rash resolves, but administer for ≤28 days total. **Pregnancy** *PKs in Pregnancy:* • PKs of immediate-release tablets not significantly altered in pregnancy. • No data available on extended-release formulations 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 twofold increase in cardiovascular and genitourinary defects). There is an increased risk of symptomatic liver toxicity when first initiating therapy in women with CD4 counts ≥250/mm^3. Liver toxicity is often associated with a rash and can be fatal. Pregnancy does not appear to increase this risk.	December 29, 2020

Table 10. Antiretroviral Drug Use in Pregnant Women with HIV: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy

Generic Name (Abbreviation) *Trade Name*	**Formulation**	**Dosing Recommendations**[a]	**Use in Pregnancy**	**Last Reviewed**
		Dosing in Pregnancy: • No change in dose indicated.	NVP should be initiated in pregnant women with CD4 counts ≥250 cells/mm³ only if benefit clearly outweighs risk. There is a potential increased risk of life-threatening hepatotoxicity in women with high CD4 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 taking those regimens, regardless of their CD4 counts.	
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/FTC 200 mg/TDF 300 mg tablet **RPV/DTG (Juluca):** • RPV 25 mg/ DTG 50 mg tablet	**Standard Adult Doses** *RPV (Edurant):* • RPV 25 mg once daily with a meal *RPV/FTC/TDF (Complera):* • One tablet once daily with a meal *RPV/DTG (Juluca):* • One tablet once daily with a meal *RPV/FTC/TAF (Odefsey):* • One tablet once daily with food	Moderate-to-high placental transfer to fetus.[b] No evidence of human teratogenicity (can rule out twofold increase in overall birth defects). Two-drug regimens (e.g., the RPV/DTG FDC) **are not recommended** for use in pregnancy.	December 29, 2020

Table 10. Antiretroviral Drug Use in Pregnant Women with HIV: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy

Generic Name (Abbreviation) *Trade Name*	**Formulation**	**Dosing Recommendations**[a]	**Use in Pregnancy**	**Last Reviewed**
	RPV/FTC/TAF (Odefsey): • RPV 25 mg/ FTC 200 mg/ TAF 25 mg tablet	**Pregnancy** *PKs in Pregnancy:* • RPV PKs are highly variable during pregnancy. RPV AUC and trough concentrations are 20% to 50% lower in pregnancy than postpartum. Although most pregnant women exceeded target exposure, those with detectable viral loads had lower RPV troughs. *Dosing in Pregnancy:* • Although RPV plasma concentration is reduced during pregnancy, higher-than-standard doses have not been studied, and not enough data are available to recommend a dosing change during pregnancy. Pregnant women receiving standard dosing should have their viral loads monitored more frequently than women who are not receiving RPV. For guidance about the use of combination products in pregnancy, please see the specific sections on other components (i.e., DTG, FTC, TAF, TDF).		

Table 10. Antiretroviral Drug Use in Pregnant Women with HIV: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations[a]	Use in Pregnancy	Last Reviewed
PIs PIs block the activity of the protease enzyme, which is required to assemble new HIV viral particles that are capable of infecting new cells.				
Atazanavir (ATV) *Reyataz* **Note:** Generic products are available for some formulations. **Note:** ATV must be combined with low-dose RTV boosting in pregnancy. (ATV/c) *Evotaz*	**ATV (Reyataz)** *Capsules:* • 100 mg (generic product only) • 150 mg[d] • 200 mg[d] • 300 mg[d] *Oral Powder:* • 50 mg packet **ATV/c (Evotaz):** • ATV 300 mg/COBI 150-mg tablet	**Standard Adult Doses** *In 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. *In ARV-Naive Patients With RTV Boosting:* • ATV/r 300 mg/100 mg once daily with food • When combined with EFV in ARV-naive patients: ATV/r 400 mg/100 mg once daily with food *In ARV-Experienced Patients:* • ATV 300 mg plus RTV 100 mg once daily with food • **Do not use** with PPIs or EFV. *In ARV-Experienced Patients Who Are Receiving an H2-Receptor Antagonist:* • ATV/r 300/100 mg once daily with food *In ARV-Experienced Patients Who Are Receiving an H2-Receptor Antagonist and TDF:* • ATV/r 400 mg/100 mg once 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). Must be given with RTV boosting in pregnancy. Effect of *in utero* ATV exposure on infant indirect bilirubin levels is unclear. Nonpathologic elevations of neonatal bilirubin 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. Use of ATV/c **is not recommended** during pregnancy. See Recommendations for Use of Antiretroviral Drugs During Pregnancy, Table 4 and Table 5 for discussions about avoiding-the use of ATV/c during pregnancy.	December 29, 2020

Table 10. Antiretroviral Drug Use in Pregnant Women with HIV: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy

Generic Name (Abbreviation) *Trade Name*	**Formulation**	**Dosing Recommendations**[a]	**Use in Pregnancy**	**Last Reviewed**
		Powder Formulation: • Oral powder is taken with RTV once daily with food at the same recommended adult dose as the capsules. *ATV/c (Evotaz):* • One tablet once daily with food **Pregnancy** *PKs in Pregnancy* *ATV (Reyataz):* • ATV concentrations are reduced during pregnancy, and they are further reduced when ATV is given concomitantly with TDF or an H2-receptor antagonist. *ATV/c (Evotaz):* • Use of ATV/c **is not recommended** during pregnancy, because ATV trough concentrations are 80% to 85% lower than the ATV concentrations seen in nonpregnant adults. *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 who are taking TDF and an H2-receptor antagonist. • Use of an increased dose (ATV/r 400 mg/100 mg once daily with food) during the second and -		

Table 10. Antiretroviral Drug Use in Pregnant Women with HIV: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy

Generic Name (Abbreviation) *Trade Name*	**Formulation**	**Dosing Recommendations**[a]	**Use in Pregnancy**	**Last Reviewed**
		third trimesters results in plasma ATV concentrations equivalent to those seen in nonpregnant adults receiving 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/c (Evotaz)*: • Insufficient data to make dosing recommendation in pregnancy (see COBI). For guidance about the use of combination products in pregnancy, please see the specific sections on other components (i.e., COBI).		

Table 10. Antiretroviral Drug Use in Pregnant Women with HIV: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy

Generic Name (Abbreviation) *Trade Name*	**Formulation**	**Dosing Recommendations**[a]	**Use in Pregnancy**	**Last Reviewed**
Darunavir (DRV) *Prezista* **Note:** Must be combined with low-dose RTV or COBI boosting. (DRV/c) *Prezcobix* (DRV/c/FTC/TAF) *Symtuza*	**DRV (Prezista)** *Tablet:* • 75 mg • 150 mg • 600 mg • 800 mg *Oral Suspension:* • 100 mg/mL **DRV/c (Prezcobix):** • DRV/c 800 mg/ 150 mg tablet **DRV/c/FTC/TAF (Symtuza):** • DRV 800 mg/ COBI 150 mg/ FTC 200 mg/ TAF 10 mg tablet	**Standard Adult Doses** *ARV-Naive Patients*: • DRV/r 800 mg/ 100 mg once daily with food • DRV/c 800 mg/ 150 mg once daily with food *ARV-Experienced Patients* If Patient Has No DRV Resistance Mutations: • DRV/r 800 mg/ 100 mg once daily with food • DRV/c 800 mg/ 150 mg once daily with food If Any DRV Resistance Mutations Are Present: • DRV/r 600 mg/ 100 mg twice daily with food *DRV/c (Prezcobix):* • One tablet once daily with food *DRV/c/FTC/TAF (Symtuza)*: • One tablet once daily with food **Pregnancy** *PKs in Pregnancy:* • Decreased exposure in pregnancy with use of DRV/r.	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/r during pregnancy or the use of DRV/c during pregnancy. If a DRV/c regimen is continued during pregnancy, viral load should be monitored frequently.	December 29, 2020

Table 10. Antiretroviral Drug Use in Pregnant Women with HIV: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy

Generic Name (Abbreviation) *Trade Name*	**Formulation**	**Dosing Recommendations**[a]	**Use in Pregnancy**	**Last Reviewed**
		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/r 600 mg/100 mg with food) is recommended for all pregnant women. • Increased, twice-daily DRV dose (DRV/r 800 mg/100 mg with food) during pregnancy does not result in an increase in DRV exposure and **is not recommended.** For guidance about the use of combination products in pregnancy, please see the specific sections on other components (i.e., COBI, FTC, TAF).		
Lopinavir/ Ritonavir (LPV/r) *Kaletra*	**LPV/r (Kaletra)** *Tablets:* • LPV/r 200 mg/50 mg • LPV/r 100 mg/25 mg *Oral Solution:* • Each 5 mL contains LPV/r 400 mg/100 mg	**Standard Adult Doses** • 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 in PI-Naive or PI-Experienced Patients:* • LPV/r 500 mg/125 mg tablets twice daily without regard to meals (use a combination of two LPV/r 200 mg/50 mg tablets and one LPV/r 100 mg/25 mg tablet), *or*	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 29, 2020

Table 10. Antiretroviral Drug Use in Pregnant Women with HIV: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy

Generic Name (Abbreviation) *Trade Name*	**Formulation**	**Dosing Recommendations**[a]	**Use in Pregnancy**	**Last Reviewed**
		• LPV/r 520 mg/130 mg oral solution (6.5 mL) twice daily with food **Pregnancy** *PKs in Pregnancy:* • With twice-daily dosing, LPV exposure is reduced in pregnant women who receive 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. • When standard dosing is used, monitor virologic response and, if possible, LPV drug levels.		

Table 10. Antiretroviral Drug Use in Pregnant Women with HIV: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy

Generic Name (Abbreviation) *Trade Name*	**Formulation**	**Dosing Recommendations**[a]	**Use in Pregnancy**	**Last Reviewed**
Entry and Attachment Inhibitors Entry and attachment inhibitors block viral binding or fusion of HIV to host cells.				
Fostemsavir (FTR) *Rukobia*	Extended Release Tablet: 600 mg	**Standard Adult Doses** *(FTR) Rukobia:* • FTR 600 mg twice daily with or without food **Pregnancy** *PK in Pregnancy:* • No PK studies in human pregnancy. *Dosing in Pregnancy:* • Insufficient data to make dosing recommendation	No human data are available regarding placental passage. A study in rats demonstrates placental passage of temsavir or other metabolites. Insufficient data to assess for teratogenicity in humans. No evidence of teratogenicity in rats or rabbits.	December 29, 2020
Ibalizumab-uiyk (IBA) *Trogarzo*	**IBA (Trogarzo):** • Solution for IV infusion is available in single-dose vials	**Standard Adult Doses** IBA 2,000-mg loading dose, followed by IBA 800-mg maintenance doses administered every 2 weeks **Pregnancy** *PKs in Pregnancy:* • No PK studies in human pregnancy. *Dosing in Pregnancy:* • Insufficient data to make dosing recommendations.	No data available, but placental transfer of IBA, a monoclonal antibody, is possible. Insufficient data to assess for teratogenicity in humans.	December 29, 2020

Table 10. Antiretroviral Drug Use in Pregnant Women with HIV: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy

Generic Name (Abbreviation) *Trade Name*	**Formulation**	**Dosing Recommendations**[a]	**Use in Pregnancy**	**Last Reviewed**
Maraviroc (MVC) *Selzentry*	**MVC (Selzentry)** *Tablets:* • 150 mg • 300 mg	**Standard Adult Doses** • MVC 300 mg twice daily with or without food. • MVC should be used only for patients with CCR5-tropic virus (and no X4-tropic virus). *Dose Adjustments:* • Increase to MVC 600 mg twice daily when used with the potent CYP3A inducers EFV, ETR, and rifampin. • Decrease to MVC 150 mg twice daily when used with CYP3A inhibitors, which includes all PIs except TPV/r and itraconazole. **Pregnancy** *PKs in Pregnancy:* • A PK study in human pregnancy demonstrated a 20 to 30% overall decrease in MVC AUC, but C_{trough} exceeded the recommended minimum concentration of 50 ng/mL. *Dosing in Pregnancy:* • Adjusting the standard adult MVC dose for concomitant use with ARV drugs seems appropriate.	Moderate placental transfer to fetus.[b] No evidence of teratogenicity in rats or rabbits; insufficient data to assess for teratogenicity in humans.	December 29, 2020

Table 10. Antiretroviral Drug Use in Pregnant Women with HIV: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations[a]	Use in Pregnancy	Last Reviewed
INSTIs INSTIs, the viral enzyme that catalyzes the two-step process that inserts HIV DNA into the genome of the host cell.				
Bictegravir/ Emtricitabine/ Tenofovir Alafenamide (BIC/FTC/TAF) *Biktarvy* **Note:** BIC is only available as part of an FDC tablet.	**BIC/FTC/TAF (Biktarvy):** • BIC 50 mg/FTC 200 mg/TAF 25 mg tablet	**Standard Adult Doses** • One tablet once daily with or without food **Pregnancy** *PK in Pregnancy:* • No PK studies in human pregnancy. *Dosing in Pregnancy:* • Insufficient data to make dosing recommendations. 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. BIC can be taken with food at the same time as any preparation containing iron or calcium, including prenatal vitamins but should not be administered within 2 hours of these preparations when taken on an empty stomach. BIC can be taken at least 2 hours before or 6 hours after antacids containing aluminum or magnesium.	December 29, 2020
Dolutegravir (DTG) *Tivicay* *Tivicay PD* (DTG/3TC) *Dovato* (DTG/RPV) *Juluca*	**DTG (Tivicay):** • DTG 10 mg, 25 mg, and 50 mg film coated tablets **DTG (Tivicay PD):** • DTG 5 mg dispersible tablet for oral suspension	**Standard Adult Doses** *In ARV-Naive or ARV Experienced (but INSTI-Naive) Patients* DTG (Tivicay): • One 50 mg tablet once daily, without regard to food DTG (Tivicay PD): • Six 5 mg tablets (30 mg) dissolved in water once daily, without regard to food DTG/3TC (Dovato): • One tablet once daily, without regard to food	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.	December 29, 2020

Table 10. Antiretroviral Drug Use in Pregnant Women with HIV: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy

Generic Name (Abbreviation) *Trade Name*	**Formulation**	**Dosing Recommendations**[a]	**Use in Pregnancy**	**Last Reviewed**
(DTG/ABC/3TC) *Triumeq*	**DTG film-coated tablets and DTG dispersible tablets are not bioequivalent and are not interchangeable.** **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	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 50 mg tablet twice daily, without regard to food DTG (Tivicay PD): • Six 5 mg tablets (30 mg) dissolved in water 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).	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 such minerals as iron or calcium, including prenatal vitamins.	

Table 10. Antiretroviral Drug Use in Pregnant Women with HIV: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy

Generic Name (Abbreviation) *Trade Name*	**Formulation**	**Dosing Recommendations**[a]	**Use in Pregnancy**	**Last Reviewed**
Elvitegravir (EVG) **Note:** As of October 2017, the single-drug formulation of EVG (Vitekta) is no longer available. (EVG/c/FTC/TAF) *Genvoya* (EVG/c/FTC/TDF) *Stribild*	**EVG/c/FTC/TAF (Genvoya):** • EVG 150 mg/ COBI 150 mg/ FTC 200 mg/ TAF 10 mg tablet **EVG/c/FTC/TDF (Stribild):** • EVG 150 mg/ COBI 150 mg/ FTC 200 mg/ TDF 300 mg tablet	**Standard Adult Doses** *Genvoya and Stribild:* • One tablet once daily with food **Pregnancy** *PKs in Pregnancy:* • PK studies in women who received EVG/c demonstrated significant reduction in EVG plasma exposure during pregnancy. *Dosing in Pregnancy:* • EVG plasma concentrations are reduced with use of standard adult doses during pregnancy; however, higher-than-standard doses of EVG have not been studied. Insufficient data are available to recommend a dose for use in pregnancy. For guidance about use of combination products in pregnancy, please see the specific sections on other components (i.e., COBI, FTC, TAF).	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/c **is not recommended** for use in pregnancy. For women who become pregnant while taking EVG/c, consider frequent viral load monitoring or switching to a more effective, recommended regimen. If a woman continues taking a regimen that contains EVG/c, doses should be administered with a meal and should not be administered within 2 hours of ingesting any preparation that contains such minerals as iron or calcium, including prenatal vitamins.	December 29, 2020

Table 10. Antiretroviral Drug Use in Pregnant Women with HIV: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy

Generic Name (Abbreviation) *Trade Name*	**Formulation**	**Dosing Recommendations**[a]	**Use in Pregnancy**	**Last Reviewed**
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** *In Patients Who Are Not Receiving Rifampin:* • RAL 400 mg, film-coated tablets twice daily without regard to food • Two RAL 600 mg, film-coated tablets (1,200 mg) once daily without regard to food for ARV-naive patients or patients who are already virologically suppressed on an initial regimen of RAL 400 mg twice daily • Chewable tablets and oral suspension doses **are not interchangeable** with either film-coated tablets or each other. *In Patients Who Are Receiving Rifampin:* • Two RAL 400 mg, film-coated tablets (800 mg) twice daily without regard to food **Pregnancy** *PK in Pregnancy:* • Decreased drug concentrations in the third trimester are 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). There is a 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. RAL 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 29, 2020

Table 10. Antiretroviral Drug Use in Pregnant Women with HIV: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations[a]	Use in Pregnancy	Last Reviewed
Pharmacoenhancers Pharmacoenhancers reduce the metabolism of antiretroviral drugs and prolong their presence in plasma, allowing for more convenient dosing regimens.				
Cobicistat (COBI) *Tybost* (ATV/c) *Evotaz* (EVG/c/FTC/TAF) *Genvoya* (DRV/c) *Prezcobix* (EVG/c/FTC/TDF) *Stribild* (DRV/c/FTC/TAF) *Symtuza*	**COBI (Tybost)** *Tablet:* • COBI 150 mg **ATV/c (Evotaz):** • ATV 300 mg/ COBI 50 mg tablet **EVG/c/FTC/TAF (Genvoya):** • EVG 150 mg/ COBI 150 mg FTC 200 mg/ TAF 10 mg tablet **DRV/c (Prezcobix):** • DRV 800 mg/ COBI 150 mg tablet **EVG/c/FTC/TDF (Stribild):** • EVG 150 mg/ COBI 150 mg/ FTC 200 mg/ TDF 300 mg tablet **DRV/c/FTC/TAF (Symtuza):** • DRV 800 mg/	**Standard Adult Doses** *COBI (Tybost):* • When used as an alternative PK booster with ATV or DRV, the dose is one tablet once daily with food *ATV/c (Evotaz):* • One tablet once daily with food *EVG/c/FTC/TAF (Genvoya):* • One tablet once daily with food *DRV/c (Prezcobix):* • One tablet once daily with food *EVG/c/FTC/TDF (Stribild):* • One tablet once daily with food *DRV/c/FTC/TAF* (Symtuza): • One tablet once daily with food **Pregnancy** *PKs in Pregnancy:* • Based on limited data, COBI exposure and its pharmacoenhancing effect on ATV, DRV, and EVG are markedly reduced in pregnancy. • When coadministered with COBI, TAF exposure is not significantly different between pregnancy and the postpartum period.	Low placental transfer to fetus.[b] No evidence of human teratogenicity (can rule out twofold increase in overall birth defects). Use of COBI-boosted ATV, DRV, or EVG **is not recommended** in pregnancy.	December 29, 2020

Table 10. Antiretroviral Drug Use in Pregnant Women with HIV: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations[a]	Use in Pregnancy	Last Reviewed
	COBI 150 mg/ FTC 200 mg/ TAF 10 mg tablet	*Dosing in Pregnancy:* • Although COBI exposure is markedly reduced during pregnancy, higher-than-standard doses have not been studied. The Panel recommends RTV as the preferred pharmacoenhancer 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).		
Ritonavir (RTV) *Norvir* (LPV/r) *Kaletra*	**RTV (Norvir)** *Capsules:* • RTV 100 mg *Tablets:* • RTV 100 mg *Oral Solution:* • RTV 80 mg/mL *Powder:* • RTV 100 mg/sachet **LPV/r (Kaletra)** *Tablets:* • LPV/r 200 mg/50 mg • LPV/r 100 mg/25 mg	**Standard Adult Dose of RTV (Norvir) When Used as PK Booster for Other PIs:** • RTV 100–400 mg per day in one or two divided doses (refer to other PI sections for specific dosing recommendations) *Tablet:* • Take with food *Capsule or Oral Solution:* • To improve tolerability, take with food, if possible. **Standard Adult Doses of LPV/r (Kaletra):** • LPV/r 400 mg/100 mg twice daily, *or* • LPV/r 800 mg/200 mg once daily *Tablets:* • Take without regard to food.	Low placental transfer to fetus.[b] No evidence of increased risk of human teratogenicity (can rule out 1.5-fold increase in overall birth defects). RTV should only be used as low-dose booster for other PIs. RTV oral solution contains 43% alcohol and, therefore, **is not recommended** for use during pregnancy because no safe level of alcohol exposure during pregnancy is known. LPV/r oral solution contains 42% alcohol and 15% propylene glycol and **is not recommended** for use in pregnancy.	December 29, 2020

Table 10. Antiretroviral Drug Use in Pregnant Women with HIV: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy

Generic Name (Abbreviation) *Trade Name*	**Formulation**	**Dosing Recommendations**[a]	**Use in Pregnancy**	**Last Reviewed**
	Oral Solution: • Each 5 mL contains LPV/r 400 mg/ 100 mg	*Oral Solution:* • Take with food. *With EFV or NVP in PI-Naive or PI-Experienced Patients:* • LPV/r 500 mg/125 mg tablets twice daily without regard to meals (use a combination of two LPV/r 200 mg/50 mg tablets and one LPV/r 100 mg/25 mg tablet), *or* • LPV/r 520 mg/130 mg oral solution (6.5 mL) twice daily with food **Pregnancy** *PKs in Pregnancy:* • Lower RTV levels are seen during pregnancy than during postpartum, which may reduce the pharmaco-enhancing effect of RTV in pregnancy *RTV Dosing in Pregnancy:* • No dose adjustment is necessary when RTV is used as booster. *LPV/r 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	Once-daily LPV/r dosing **is not recommended** during pregnancy.	

Table 10. Antiretroviral Drug Use in Pregnant Women with HIV: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations[a]	Use in Pregnancy	Last Reviewed
		and in women who start treatment during pregnancy with a baseline viral load >50 copies/mL. • When standard dosing is used, monitor virologic response and, if possible, LPV drug levels. For guidance about use of combination products in pregnancy, please see the specific sections on other components (i.e., LPV/r).		

[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
[c] Only indicated for use in chronic HBV virus infection in adults.
[d] Generic product available

Key: 3TC = lamivudine; ABC = abacavir; 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; COBI = cobicistat; CYP = cytochrome P; DOR = doravirine; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FDA = Food and Drug Administration; FDC = fixed-dose combination; FTC = emtricitabine; FTR = fostemsavir; HBV = hepatitis b virus; HSR = hypersensitivity reaction; IBA =ibalizumab; INSTI = integrase strand transfer inhibitor; IV = intravenous; LPV = lopinavir; LPV/r = lopinavir/ritonavir; MVC = maraviroc; 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; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TPV = tipranavir; TPV/r = tipranavir/ritonavir; WHO = World Health Organization; ZDV = zidovudine

Supplement: Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy

Nucleoside and Nucleotide Analogue Reverse Transcriptase Inhibitors

Nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs) interfere with HIV reverse transcriptase by competitive inhibition. Nucleoside analogue drugs require three intracellular phosphorylation steps to form the triphosphate nucleoside, which is the active drug moiety. The nucleotide analogue tenofovir contains a monophosphate component attached to the adenine base and requires only two phosphorylation steps to form the active moiety.

For information regarding the nucleoside analogue drug class and potential mitochondrial toxicity in pregnant women and infants, see Recommendations for Use of Antiretroviral Drugs During Pregnancy and Long-Term Follow-Up of Infants Exposed to Antiretroviral Drugs.

Abacavir (Ziagen, ABC)
Emtricitabine (Emtriva, FTC)
Lamivudine (Epivir, 3TC)
Tenofovir Alfenamide (Vemlidy, TAF)
Tenofovir Disoproxil Fumarate (Viread, TDF)
Zidovudine (Retrovir, AZT, ZDV)

Didanosine and stavudine are no longer recommended for use in pregnant women. Zalcitabine is not available in the United States. Information on these drugs can be found in the Archived Drugs section.

Non-Nucleoside Reverse Transcriptase Inhibitors

Non-nucleoside reverse transcriptase inhibitors (NNRTIs) interfere with HIV reverse transcriptase by binding directly to the enzyme.

Doravirine (Pifeltro, DOR)
Efavirenz (Sustiva, EFV)
Etravirine (Intelence, ETR)
Nevirapine (Viramune, NVP)
Rilpivirine (Edurant, RPV)

Delavirdine is no longer available in the United States. Information on this drug can be found in the Archived Drugs section.

Protease Inhibitors

Protease inhibitors (PIs) block the activity of the protease enzyme, which is required to assemble new HIV viral particles that are capable of infecting new cells.

Using PIs during pregnancy may increase the risk of adverse maternal and neonatal outcomes; see Combination Antiretroviral Drug Regimens and Maternal and Neonatal Outcomes for more information.

Atazanavir (Reyataz, ATV)
Darunavir (Prezista, DRV)
Lopinavir/Ritonavir (Kaletra, LPV/r)

Fosamprenavir, indinavir, nelfinavir, saquinavir, and tipranavir are no longer recommended for use in pregnant women. Amprenavir is no longer available in the United States. Information on these drugs can be found in the Archived Drugs section.

Entry and Attachment Inhibitors

Entry and attachment inhibitors block viral binding or fusion of HIV to host cells.

Fostemsavir (Rukobia, FTR)
Ibalizumab-uiyk (Trogarzo, IBA)
Maraviroc (Selzentry, MVC)

Enfuvirtide is not recommended for use in pregnant women. Information on this drug can be found in the Archived Drugs section.

Integrase Inhibitors

Integrase inhibitors block integrase, the viral enzyme that catalyzes the two-step process that inserts HIV DNA into the genome of the host cell.

Bictegravir (BIC)
Dolutegravir (Tivicay, DTG)
Elvitegravir (EVG)
Raltegravir (Isentress, RAL)

For information regarding the possible increased risk of neural tube defects in infants born to women who were receiving dolutegravir at the time of conception, see Teratogenicity and Recommendations for Use of Antiretroviral Drugs During Pregnancy.

Pharmacoenhancers

Pharmacoenhancers reduce the metabolism of antiretroviral drugs and prolong their presence in plasma, allowing for more convenient dosing regimens.

Cobicistat (Tybost, COBI)
Ritonavir (Norvir, RTV)

Abacavir (Ziagen, ABC)

(Last updated December 29, 2020; last reviewed December 29, 2020)

Animal Studies

Carcinogenicity

Abacavir (ABC) has been found to be 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 exposures that were 6 to 32 times those observed in humans who received the recommended dose.[1]

Reproduction/Fertility

No effect of ABC on reproduction or fertility in male and female rodents has been seen at doses of up to 500 mg/kg per day. These doses produced exposures in rodents that were about eight times the exposures observed in humans who received the recommended dose. Exposures in this study were based on body surface area.

Teratogenicity/Adverse Pregnancy Outcomes

Rats treated with a dose of ABC 1,000 mg/kg during organogenesis showed signs of developmental toxicity (i.e., decreased fetal body weight and reduced crown-rump length) and had an increased incidence of fetal anasarca and skeletal malformations. This dose produced exposures in rats that were about 35 times those seen in humans who received the recommended dose; exposure was based on area under the curve. An increased number of resorptions and an increased incidence of stillbirths occurred among pregnant rats that received ABC 500 mg/kg once daily, beginning at embryo implantation and ending when the pups were weaned. Decreased fetal body weights also were observed, and the offspring had persistently low body weights throughout their lives. However, in rabbits, no evidence of drug-related developmental toxicity and no increase in fetal malformations were observed at doses of ABC up to 700 mg/kg. These doses produced exposures in rabbits that were about 8.5 times the exposures seen in humans who received the recommended dose.[1]

Placental and Breast Milk Passage

ABC 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 ABC 300 mg twice daily[2] and ABC 600 mg once daily[3] showed that the PKs during pregnancy are equivalent to the PKs observed during the postpartum period. A population PK study (analyzing 266 plasma samples from 150 pregnant women) found no effect of any covariate (including age, body weight, pregnancy, or gestational age) on ABC PKs.[4] Thus, no dose adjustment for ABC is needed during pregnancy.

Placental and Breast Milk Passage

Placental transfer of ABC is high, with ratios of ABC concentration in cord blood to ABC concentration in maternal plasma at delivery of approximately 1.0.[2,5] In the Mma Bana study,[6] the median breast milk-to-plasma ratio for ABC 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 ABC.

Teratogenicity/Adverse Pregnancy Outcomes

The Antiretroviral Pregnancy Registry has monitored sufficient numbers of first-trimester exposures to ABC to detect at least a 1.5-fold increase in the risk of overall birth defects and at least a twofold increase in the risk of cardiovascular and genitourinary defects (which are the more common classes of birth defects in the general

population). No such increase in the risk of birth defects has been observed with ABC. Among the cases of first-trimester ABC exposure that have been reported to the Antiretroviral Pregnancy Registry, the prevalence of birth defects was 3.2% (42 infants out of 1,320 live births; 95% confidence interval, 2.3% to 4.3%) compared with a 2.7% total prevalence in the U.S. population, based on Centers for Disease Control and Prevention surveillance.[7] First-trimester exposure to ABC 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 Cohort (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]

Pregnancy outcomes were similar between pregnant women who received an ABC/lamivudine (3TC) backbone (n = 252) and women who received a tenofovir disoproxil fumarate/emtricitabine backbone (n = 661) in the Italian National Program on Surveillance on Antiretroviral Treatment in Pregnancy. However, total cholesterol levels were higher in the group that received ABC.[11]

Ten percent of participants (711 pregnancies) received ABC plus 3TC in the EPPICC Study Group. The proportions of preterm deliveries and small-for-gestational-age infants that occurred among women who received ABC were similar to those seen among women who received other antiretroviral drugs.[12]

Other Safety Information

Serious hypersensitivity reactions (HSRs) have been associated with ABC 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. ABC **should not be restarted** following an HSR, 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 HSRs and should not receive ABC; HLA-B*5701 screening should be done before initiating ABC. Two meta-analyses have confirmed the association between this genotype and the HSR.[13,14]

After adjusting for birth cohort and other factors, the PHACS/SMARTT study (which followed participants for a median of 2.4 years) reported no increases in the likelihood of metabolic, cardiac, neurological, growth and development, or neurodevelopmental adverse events among infants whose mothers took ABC during pregnancy.[15]

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**
Abacavir (ABC) *Ziagen* (ABC/3TC) *Epzicom* (ABC/DTG/3TC) *Triumeq* (ABC/3TC/ZDV) *Trizivir* **Note:** Generic products are available for some formulations.	**ABC (Ziagen):**[d] *Tablet:* • 300 mg *Oral Solution:* • 20 mg/mL **ABC/3TC (Epzicom):**[d] • ABC 600 mg/3TC 300 mg tablet **ABC/DTG/3TC (Triumeq):** • ABC 600 mg/DTG 50 mg/3TC 300 mg tablet **ABC/3TC/ZDV (Trizivir):**[d] • ABC 300 mg/3TC 150 mg/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):* • One tablet once daily without regard to food *ABC/DTG/3TC (Triumeq):* • One tablet once daily without regard to food *ABC/3TC/ZDV (Trizivir):* • One tablet twice daily without regard to food **Pregnancy** *PKs in Pregnancy:* • PKs 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., 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 a patient's status **should be documented as negative** before initiating ABC. Patients should be educated regarding symptoms of HSR.

[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

[d] Generic product available

Key: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; DTG = dolutegravir; FDC = fixed-dose combination; HSR = hypersensitivity reaction; PK = pharmacokinetic; ZDV = zidovudine

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Emtricitabine (Emtriva, FTC)

(Last updated December 29, 2020; last reviewed December 29, 2020)

Animal Studies

Carcinogenicity

Emtricitabine (FTC) was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests. In long-term carcinogenicity studies of oral FTC, no drug-related increases in tumor incidence were found at doses up to 26 times (in mice) or 31 times (in rats) the exposures seen in humans who received the therapeutic dose.[1]

Reproduction/Fertility

FTC had no observable effect on reproduction or fertility at 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 following maternal FTC doses that produced systemic drug exposures that were 60-fold higher (in mice) or 120-fold higher (in rabbits) than those observed in humans who received the recommended dose.[1]

Placental and Breast Milk Passage

FTC has been shown to cross the placenta in mice and rabbits; the average fetal/maternal drug concentration ratio was 0.4 in mice and 0.5 in rabbits.[2]

Human Studies in Pregnancy

Pharmacokinetics

In the IMPAACT P1026s study, FTC exposure was modestly lower during the third trimester (geometric mean 8.0 mcg•h/mL; 90% confidence interval [CI], 7.1–8.9 mcg•h/mL) than during the postpartum period (9.7 mcg•/mL; 90% CI, 8.6–10.9 mcg•h/mL). Fifty-eight percent of pregnant women (15 of 26 women) met the AUC target (≤30% reduction from typical exposure for nonpregnant historical controls) compared to 95% of postpartum women (21 of 22 women). Trough FTC levels also were lower during pregnancy (C_{24h} geometric mean concentration [GMC] 58 ng/mL; 90% CI, 37–63 ng/mL) than during the postpartum period (C_{24h} GMC 85 ng/mL; 90% CI, 70–100 ng/mL).[3] Similar differences in pharmacokinetic parameters of FTC 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 FTC 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 a dose adjustment during pregnancy.

Placental and Breast Milk Passage

FTC has been shown to have high placental transfer in pregnant women. In a study of 15 women who received FTC during pregnancy, the mean cord blood-to-maternal-plasma ratio was 1.2 (90% CI, 1.0–1.5).[3] In eight women who were given a single dose of FTC 600 mg with tenofovir disoproxil fumarate (TDF) 900 mg, the median cord blood FTC concentration was 717 ng/mL (range, 21–1,072 ng/mL), and the median cord blood-to-maternal-plasma ratio was 0.85 (range, 0.46–1.07).[4]

FTC is excreted into human milk. Among women in Uganda and Nigeria who were taking first-line antiretroviral therapy that contained FTC 200 mg, FTC concentrations in breast milk peaked later than they did in maternal plasma (at 4–8 hours compared with 2–4 hours) and were threefold higher than maternal plasma concentrations. FTC 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 FTC 400 mg, TDF 600 mg, and nevirapine

200 mg at onset of labor, followed by FTC 200 mg and TDF 300 mg once daily for 7 days postpartum. The median minimal and maximal concentrations of FTC 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 FTC 50% inhibitory concentration (IC_{50}) for HIV-1.[8] In a study of 50 women without HIV who received daily oral FTC 200 mg and TDF 300 mg as pre-exposure prophylaxis (PrEP), median peak and trough breast milk concentrations of FTC were 212.5 ng/mL (IQR 140.0–405.0 ng/mL) and 183.0 ng/mL (IQR 113.0–250.0 ng/mL), respectively. FTC was detectable in 47 of 49 infants at a median concentration of 13.2 ng/mL (IQR 9.3–16.7 ng/mL), corresponding to estimated daily infant ingestion of a 31.9-mcg/kg dose (IQR 21.0–60.8 mcg/kg) of FTC, 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 FTC. No increase in the incidence of congenital anomalies was observed in the TDF plus FTC arm.[10] There was no overall difference between the rate of pregnancy loss in the TDF plus FTC arm and the rate of pregnancy loss in the TDF arm of this PrEP study.

In the U.S. PHACS/SMARTT cohort study, FTC exposure was not associated with an increase in specific or overall birth defect risk.[11] In a large French cohort, FTC exposure in the first trimester was associated with lower risk of birth defects.[12] The Antiretroviral Pregnancy Registry has monitored sufficient numbers of first-trimester exposures to FTC to detect at least a 1.5-fold increased risk of overall birth defects and at least a twofold increase in 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 FTC. Among the cases of first-trimester FTC exposure that have been reported to the Antiretroviral Pregnancy Registry, the prevalence of birth defects was 2.6% (94 of 3,601 live births; 95% CI, 2.1% to 3.2%) compared with a total prevalence of 2.7% 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 FTC led to no increase in the likelihood of adverse metabolic, growth and development, cardiac, neurological, or neurodevelopmental outcomes.[14]

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**
Emtricitabine (FTC) *Emtriva* (FTC/EFV/TDF) *Atripla* (FTC/BIC/TAF) *Biktarvy* (FTC/RPV/TDF) *Complera* (FTC/TAF) *Descovy* (FTC/EVG/c/TAF) *Genvoya* (FTC/RPV/TAF) *Odefsey* (FTC/EVG/c/TDF) *Stribild* (FTC/DRV/c/TAF) *Symtuza* (FTC/TDF) *Truvada* **Note:** Generic products are available for some formulations.	**FTC (Emtriva)** *Capsule*:[d] • 200 mg *Oral Solution:* • 10 mg/mL **FTC/EFV/TDF (Atripla):**[d] • FTC 200 mg/EFV 600 mg/TDF 300-mg tablet **FTC/BIC/TAF (Biktarvy):** • FTC 200 mg/BIC 50 mg/TAF 25-mg tablet **FTC/RPV/TDF (Complera):** • FTC 200 mg/RPV 25 mg/TDF 300-mg tablet **FTC/TAF (Descovy):** • FTC 200 mg/TAF 25 mg tablet **FTC/EVG/c/TAF (Genvoya):** • FTC 200 mg/EVG 150 mg/COBI 150 mg/TAF 10-mg tablet **FTC/RPV/TAF (Odefsey):** • FTC 200 mg/RPV 25 mg/TAF 25 mg tablet	**Standard Adult Doses** *FTC (Emtriva)* Capsule: • FTC 200 mg once daily without regard to food Oral Solution: • FTC 240 mg (24 mL) once daily without regard to food *FTC/EFV/TDF (Atripla):* • One tablet once daily at or before bedtime • Take on an empty stomach to reduce or mitigate side effects. *FTC/BIC/TAF (Biktarvy):* • One tablet once daily with or without food • *FTC/RPV/TDF (Complera):* • One tablet once daily with food *FTC/TAF (Descovy):* • One tablet once daily with or without food *FTC/EVG/c/TAF (Genvoya):* • One tablet once daily with food *FTC/RPV/TAF (Odefsey):* • One tablet once daily with food *FTC/EVG/c/TDF (Stribild):* • One tablet once daily with food	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 HBV/HIV coinfection, it is possible that a HBV flare may occur if the drug is stopped; see Hepatitis B Virus/HIV Coinfection.

Generic Name (Abbreviation) *Trade Name*	**Formulation**	**Dosing Recommendations**[a]	**Use in Pregnancy**
	FTC/EVG/c/TDF (Stribild): • FTC 200 mg/EVG 150 mg/COBI 150 mg/TDF 300-mg tablet **FTC/DRV/c/TAF (Symtuza):** • FTC 200 mg/DRV 800 mg/COBI 150 mg/TAF 10-mg tablet **FTC/TDF (Truvada):**[d] • FTC 200 mg/TDF 300-mg tablet	*FTC/DRV/c/TAF (Symtuza):* • One tablet once daily with food *FTC/TDF (Truvada):* • One tablet once daily without regard to food **Pregnancy** *PKs in Pregnancy:* • PKs of FTC are not significantly altered in pregnancy. *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., TDF, TAF, EFV, RPV, DRV, EVG, BIC, COBI).	

[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

[d] Generic product available

Key: BIC = bictegravir; COBI = cobicistat; DRV/c = darunavir/cobicistat; EFV = efavirenz; EVG/c = elvitegravir/cobicistat; FDC = fixed-dose combination; FTC = emtricitabine; HBV = hepatitis B virus; PK = pharmacokinetic; RPV = rilpivirine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

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Lamivudine (Epivir, 3TC)

(Last updated December 29, 2020; last reviewed December 29, 2020)

Animal Studies

Carcinogenicity

Lamivudine (3TC) was found to have weak mutagenic activity in one *in vitro* assay, but no evidence of *in vivo* genotoxicity was found in rats at 35 to 45 times the exposure observed in humans who received the standard dose. Long-term animal studies have shown no evidence of carcinogenicity at exposures that were 10 times (in mice) and 58 times (in rats) the exposure seen in humans who received the standard dose.[1]

Reproduction/Fertility

In rats that received 3TC in doses up to 4,000 mg/kg per day, which produced plasma levels 47 to 70 times those seen in humans who received the standard dose, no evidence was found of impaired fertility and no effects on the offspring's survival, growth, or development up to the time of weaning.[1]

Teratogenicity/Adverse Pregnancy Outcomes

No evidence exists of 3TC-induced teratogenicity in rats and rabbits at plasma concentrations of 3TC that are 35 times those seen in human plasma. 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 3TC exposures that were 35 times the exposure observed in humans who received the standard dose.[1]

Placental and Breast Milk Passage

In studies of pregnant rats, 3TC was transferred to the fetus through the placenta.[1]

Human Studies in Pregnancy

Pharmacokinetics

In an analysis of specimens obtained from 228 pregnant women in the antepartum (114), intrapartum (123) and postpartum (47) periods in which all participants received standard once-daily or twice-daily 3TC doses,[2] women had a 22% higher apparent clearance rate during pregnancy than in the postpartum period, but the resulting lower 3TC exposure in pregnant women was not subtherapeutic and was relatively close to exposure reported previously for nonpregnant adults.[2] Thus, no dose adjustment is necessary for 3TC during pregnancy.

Placental and Breast Milk Passage

3TC readily crosses the placenta in humans, achieving cord blood concentrations comparable to maternal plasma concentrations.[3] In a study of 123 mother–infant pairs, the placental transfer, expressed as the fetal-to-maternal area under the curve (AUC) ratio, was 0.86. The 3TC amniotic fluid accumulation, expressed as the amniotic fluid-to-fetal AUC ratio, was 2.9.[2] Urinary excretion of 3TC by the fetus can cause 3TC to accumulate in the amniotic fluid.[4]

3TC is excreted into human breast milk. In a study in Kenya of 67 nursing mothers who received a combination regimen of zidovudine, 3TC, and nevirapine, the median breast milk 3TC concentration was 1,214 ng/mL and the median ratio of 3TC concentration in breast milk to the concentration in plasma was 2.56.[5] In infants who were exposed to 3TC only via breast milk, the median plasma 3TC concentration was 23 ng/mL (inhibitory concentration 50% [IC_{50}] of 3TC against wild-type HIV = 0.6–21 ng/mL). In a separate study of breastfeeding women in Malawi who were receiving 3TC in combination with tenofovir disoproxil fumarate and efavirenz, concentrations of 3TC 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 3TC 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] Lower 3TC exposure in these older infants is attributable to increased renal clearance with age.

Teratogenicity/Adverse Pregnancy Outcomes

Based on prospective reports to the Antiretroviral Pregnancy Registry (APR), the FDA has concluded that no difference exists between the overall risk of birth defects for lamivudine compared with the background birth defect rate in the United States.[1]

In a large French cohort, 3TC exposure during the first trimester was associated with an increased risk of overall birth defects (adjusted odds ratio = 1.37; 95% confidence interval [CI], 1.06–1.73), but not of a defect in any specific organ system or of a specific birth defect.[7] However, the Antiretroviral Pregnancy Registry has monitored sufficient numbers of first-trimester exposures to 3TC to detect at least a 1.5-fold increase in the risk of overall birth defects and at least a twofold increase in the risk of cardiovascular and genitourinary defects (the more common classes of birth defects in the general population). No such increase in the risk of birth defects has been observed with 3TC. Among the cases of first-trimester 3TC exposure that have been reported to the APR, the prevalence of birth defects was 3.1% (167 of 5,353 live births; 95% CI, 2.7% to 3.6%) 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 than with use of antiretroviral regimens that do not include lamivudine.[9]

Other Safety Information

In a large U.S. cohort study of infants without HIV born to women with HIV, 3TC 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

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**
Lamivudine (3TC) *Epivir* (3TC/TDF) *Cimduo* (3TC/ZDV) *Combivir* (3TC/DOR/TDF) *Delstrigo* (3TC/DTG) *Dovato* (3TC/ABC) *Epzicom* (3TC/EFV/TDF) (3TC/EFV/TDF) (3TC/TDF) *Temixys* (3TC/ABC/DTG) *Triumeq* (3TC/ABC/ZDV) *Trizivir* **Note:** Generic products are available for some formulations.	**3TC (Epivir)**[d] *Tablets:* • 150 mg • 300 mg *Oral Solution:* • 10 mg/mL **3TC/TDF (Cimduo):** • 3TC 300 mg/TDF 300 mg tablet **3TC/ZDV (Combivir):**[d] • 3TC 150 mg/ZDV 300 mg tablet **3TC/DOR/TDF (Delstrigo):** • 3TC 300 mg/DOR 100 mg/TDF 300 mg tablet **3TC/DTG (Dovato):** • 3TC 300 mg/DTG 50 mg tablet **3TC/ABC (Epzicom):**[d] • 3TC 300 mg/ABC 600 mg tablet **3TC/EFV/TDF (Symfi):** • 3TC 300 mg/EFV 600 mg plus TDF 300 mg tablet **3TC/EFV/TDF (Symfi Lo):** • 3TC 300 mg/EFV 400 mg/TDF 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):* • One tablet once daily without regard to food *3TC/ZDV (Combivir):* • One tablet twice daily without regard to food *3TC/DOR/TDF (Delstrigo):* • One tablet once daily without regard to food *3TC/DTG (Dovato):* • One tablet once daily without regard to food *3TC/ABC (Epzicom):* • One tablet once daily without regard to food *Lo):* • One tablet once daily on an empty stomach and preferably at bedtime *3TC/TDF (Temixys):* • One tablet once daily without regard to food *3TC/ABC/DTG (Triumeq):* • One 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). If patient has HBV/HIV coinfection, it is possible that an HBV flare may occur if the drug is stopped; see Hepatitis B Virus/HIV Coinfection. 3TC products that were developed specifically for treatment of HBV (e.g., Epivir-HBV) contain a lower dose of 3TC that **is not appropriate** for treatment of HIV.

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations[a]	Use in Pregnancy
	3TC/TDF (Temixys): • 3TC 300 mg/TDF 300 mg tablet **3TC/ABC/DTG (Triumeq):** • 3TC 300 mg/ABC 600 mg/DTG 50 mg tablet **3TC/ABC/ZDV (Trizivir):**[d] • 3TC 150 mg/ABC 300 mg/ZDV 300 mg tablet	*3TC/ABC/ZDV (Trizivir):* • One tablet twice daily without regard to food **Pregnancy** *PKs in Pregnancy:* • PKs not significantly altered in pregnancy. *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, DOR, DTG, EFV, TDF, ZDV)	

[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

[d] Generic product available

Key: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; DOR = doravirine; DTG = dolutegravir; EFV = efavirenz; FDC = fixed-dose combination; HBV = hepatitis B virus; PK = pharmacokinetic; TDF = tenofovir disoproxil fumarate; ZDV = zidovudine

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Tenofovir Alafenamide (Vemlidy, TAF)

(Last updated December 29, 2020; last reviewed December 29, 2020)

Tenofovir alafenamide (TAF) is an orally bioavailable form of tenofovir (TFV). For information about tenofovir disoproxil fumarate (TDF), see the TDF section.

Animal Studies

Carcinogenicity

Tenofovir alafenamide (TAF) and tenofovir disoproxil fumarate (TDF) are both prodrugs of tenofovir (TFV). TAF is converted rapidly to TFV, and TFV exposure in rats and mice is lower after TAF administration than TDF administration. Carcinogenicity studies for TFV were performed with TDF, but given the lower TFV exposure with TAF, the associated carcinogenicity is assumed to be commensurate or lower. Long-term oral carcinogenicity studies of TFV in mice and rats were carried out at TFV exposures that were 167 times (in mice) and 55 times (in rats) the TFV exposures observed in humans who received the recommended doses of TAF. In female mice, liver adenomas were increased.[1,2]

Reproduction/Fertility

Reproduction studies have been performed at TAF exposures that in rats were similar to and in rabbits were 53 times higher than the exposure seen in humans who received the recommended dose. These studies revealed no evidence of impaired fertility or mating performance associated with TAF administration.[1,2]

Teratogenicity/Adverse Pregnancy Outcomes

No effects on early embryonic development were seen when TAF was administered to male or female rats at doses that produced exposures that were 62 times the exposure seen in humans who received the therapeutic dose.[1,2]

Placental and Breast Milk Passage

Rat studies demonstrated secretion of TFV in breast milk after administration of TDF, but whether TAF is present in animal milk is not known.[1]

Human Studies in Pregnancy

Pharmacokinetics

The pharmacokinetics (PK) of TAF were evaluated in 31 women who were taking TAF 25 mg without a PK enhancer and in 27 women who were taking TAF 10 mg boosted with cobicistat (COBI)[3] 150 mg. This study evaluated plasma TAF exposures with and without boosting in pregnant and postpartum women relative to nonpregnant adults and did not find significant differences in the PK between pregnant and postpartum women who were taking TAF 10 mg boosted with COBI. The study did find, however, that although pregnant women who were taking unboosted TAF had plasma TAF exposures similar to those observed in nonpregnant adults, the TAF exposures in these women increased significantly during the postpartum period. Another report described TAF PK in 17 women who were taking TAF 25 mg boosted with either COBI or ritonavir; plasma exposures for TAF during pregnancy were similar to those seen postpartum.[4]

Placental and Breast Milk Passage

Very limited data exist on the TAF levels in placental and breast milk. One study found that TAF was below the assay limit of quantification (<3.9 ng/mL) in 15 of 15 cord blood samples tested; intracellular TFV diphosphate was not measured in the cord blood or the samples of maternal plasma at delivery, and maternal plasma TAF concentrations at delivery were measurable in only 2 of the 15 paired samples.[3] No data are available on the breast milk passage of TAF in humans.

Teratogenicity/Adverse Pregnancy Outcomes

The data from the International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) 2010, a randomized trial of dolutegravir (DTG) containing ART regimens in pregnancy, found lower composite adverse outcomes in the group receiving DTG+FTC/TAF (TAF with emtricitabine and dolutegravir) than in the group receiving DTG+FTC/TDF (TDF with emtricitabine and dolutegravir) or EFV+FTC/TDF (TDF with efavirenz and emtricitabine), although it is noteworthy that the DTG+FTC/TAF arm of the trial had higher maternal weight gain than the other two arms and an increased risk of stillbirth compared with the arm receiving EFV+FTC/TDF (3.7% vs. 1.9%).[5]

The Antiretroviral Pregnancy Registry has monitored sufficient numbers of first-trimester exposures to TAF to detect at least a twofold increase in the risk of overall birth defects. However, no such increase in the risk of birth defects has been observed with TAF. Among the cases of first-trimester TAF exposure that have been reported to the Antiretroviral Pregnancy Registry, the prevalence of birth defects was 4.9% (17 of 349 live births; 95% confidence interval, 2.9% to 7.7%) compared with a 2.7% total prevalence in the U.S. population, according to the Centers for Disease Control and Prevention birth defects surveillance system MACDP (Metropolitan Atlanta Congenital Defects Program). The data reflect a modest but statistically significant increase in the rate of overall defects for TAF compared with MACDP, but this increase was not observed in comparison with the 4.17% prevalence of overall defects reported in the Texas Birth Defects Registry. No pattern was found in the reported birth defects, and the clinical significance of these findings has not been determined.[6]

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**
Tenofovir Alafenamide (TAF) *Vemlidy* (TAF/BIC/FTC) *Biktarvy* (TAF/FTC) *Descovy* (TAF/EVG/c/FTC) *Genvoya* (TAF/FTC/RPV) *Odefsey* (TAF/DRV/c/FTC) *Symtuza*	**TAF (Vemlidy)** *Tablet:* • 25 mg **TAF/BIC/FTC (Biktarvy):** • TAF 25 mg/BIC 50 mg/FTC 200 mg tablet **TAF/FTC (Descovy):** • TAF 25 mg/FTC 200 mg tablet **TAF/EVG/c/FTC (Genvoya):** • TAF 10 mg/EVG 150 mg/COBI 150 mg/FTC 200 mg tablet	**Standard Adult Doses** *TAF (Vemlidy)*: • One tablet once daily with food *TAF/BIC/FTC (Biktarvy)*: • One tablet once daily with or without food *TAF/FTC (Descovy):* • One tablet once daily with or without food • Same dose (TAF 25 mg) can be used with or without PK enhancers. *TAF/EVG/c/FTC (Genvoya)*: • One tablet once daily with food *TAF/FTC/RPV (Odefsey)*: • One tablet once daily with food	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 the potential for renal toxicity.

	TAF/FTC/RPV (Odefsey): • TAF 25 mg/FTC 200 mg/RPV 25 mg tablet **TAF/DRV/c/FTC (Symtuza):** • TAF 10 mg/DRV 800 mg/COBI 150 mg/FTC 200 mg tablet	*TAF/DRV/c/FTC (Symtuza)*: • One tablet once daily with food **Pregnancy** *PKs in Pregnancy:* • Plasma PKs not significantly altered in pregnancy. *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., BIC, COBI, DRV, EVG, FTC, RPV).	

[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: ARV = antiretroviral; BIC = bictegravir; COBI = cobicistat; DRV/c = darunavir/cobicistat; EVG/c = elvitegravir/cobicistat; FDC = fixed-dose combination; FTC = emtricitabine; PK = pharmacokinetic; RPV = rilpivirine; TAF = tenofovir alafenamide

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Tenofovir Disoproxil Fumarate (Viread, TDF)

(Last updated December 29, 2020; last reviewed December 29, 2020)

Tenofovir disoproxil fumarate (TDF) is an orally bioavailable form of tenofovir (TFV). For information about tenofovir alafenamide (TAF), see the TAF section.

Animal Studies

Carcinogenicity

TFV was mutagenic in one of two *in vitro* assays and has shown no evidence of clastogenic activity. Long-term oral carcinogenicity studies of TFV were carried out at 16 times (in mice) and 5 times (in rats) the exposure seen in humans who received the standard dose. In female mice, the incidence of liver adenomas was increased at exposures that were 16 times those observed in humans who received therapeutic doses. In rats, there was no evidence of carcinogenicity at exposures up to five times those observed in humans who received the therapeutic dose.[1]

Reproduction/Fertility

Reproduction studies have been performed using doses of TFV up to 14 times (in rats) and 19 times (in rabbits) the human dose, based on body surface area comparisons. The use of TFV was not associated with impaired fertility or harm to the fetus in these studies. There were also no effects on fertility, mating performance, or early embryonic development when TFV was administered (at a dose of 600 mg/kg per day; equivalent to 10 times the human dose based on body surface area) to male rats for 28 days before mating, and to female rats from 15 days before mating through Day 7 of gestation. However, an alteration of the estrous cycle in female rats was observed.[1]

Teratogenicity/Adverse Pregnancy Outcomes

Fetal monkeys with chronic, high-level exposure to TFV that was 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 than TFV-unexposed fetal monkeys. A slight reduction in fetal bone porosity also was observed in TFV-exposed fetal monkeys. These effects were observed within 2 months of maternal treatment.[1]

Placental and Breast Milk Passage

Intravenous administration of TFV to pregnant cynomolgus monkeys resulted in a fetal/maternal plasma ratio of 0.17, demonstrating that TFV crosses the placenta.[2]

Human Studies in Pregnancy

Pharmacokinetics

In a retrospective population pharmacokinetic (PK) 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 TFV than nonpregnant women. Apparent clearance decreased slightly but significantly with increasing age.[3] In the P1026s study (a Phase IV, PK study of selected antiretroviral [ARV] drugs already in use by pregnant women with HIV during pregnancy and postpartum) of 37 women who received TDF-based combination therapy during pregnancy and postpartum, the percentage of women with TFV AUC that exceeded the target of 1.99 µg•hour/mL (the 10th percentile in nonpregnant adults) was lower at 30 to 36 weeks gestation (73%, 27 of 37 women) than at 6 to 12 weeks postpartum (84%, 27 of 32 women). TFV trough levels and AUC 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 (FTC) in the third trimester and postpartum, TFV AUC, peak concentration, and trough concentration 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] In pregnant women who had hepatitis B virus (HBV) infection but did not have HIV infection, the estimated geometric mean TFV $AUC_{0\text{-}24h}$ was 20% lower during pregnancy (95% confidence interval [CI], 19% to 21%) than during the postpartum period. There were no cases of perinatal HBV transmission in this study.[7]

Thus, in light of only modestly lower TFV exposure during pregnancy without evidence of adverse impact on virologic efficacy, standard dosing of TDF during pregnancy continues to be recommended.

Placental and Breast Milk Passage

In studies of pregnant women who were receiving chronic TDF, the cord blood-to-maternal-plasma ratio of TFV ranged from 0.60 to 1.03, indicating high placental transfer.[4,5,8] Intracellular TFV 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 FTC 400 mg, but intracellular TFV-DP was detectable in only 2 of 36 infants (5.5%).[9]

In a study of 50 breastfeeding women without HIV who received TDF/FTC (under directly observed therapy for 10 days) as PrEP, median peak and trough time-averaged TFV 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 TFV concentration was unquantifiable (<0.31 ng/mL) in 46 of 49 infants (94%); in the three infants with detectable TFV concentrations, the level was 0.9 ng/mL in two and 17.4 ng/mL in one. Based on this study's results, the median TFV dose ingested through breast milk was estimated to be 0.47 mcg/kg, or <0.01% of the proposed daily pediatric dose of TDF 6 mg/kg.[10] In a study of 59 breastfeeding women with HIV who received TDF/lamivudine (3TC)/efavirenz (EFV) in Uganda and Nigeria, no infant had detectable TFV in plasma after observed dosing.[11]

Reproduction/Fertility

In a retrospective analysis of 7,275 women who were receiving antiretroviral therapy (ART) (1,199 of whom were receiving regimens that contained TDF), women who used TDF had a slightly lower pregnancy rate than women who did not use TDF.[12] In contrast, in a trial in Kenya and Uganda in which participants who did not have HIV but whose sexual partners had HIV (serodiscordant heterosexual couples) were randomized to receive daily TDF, TDF/FTC, or placebo for PrEP, pregnancy incidence was not significantly different among the arms: pregnancy incidence per 100 patient-years was 10.0 among women assigned to receive placebo, 11.9 among those assigned to receive TDF ($P = 0.22$ vs. placebo), and 8.8 among those assigned to receive TDF/FTC ($P = 0.39$ vs. placebo).[13]

Teratogenicity

In a study of 431 pregnancies that occurred during an HIV PrEP trial in which women who did not have HIV were randomized to receive placebo, TDF, or TDF plus FTC, there was no difference in risk of congenital anomalies between the TDF-containing arms and placebo arms.[13] 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: Pediatric AIDS Clinical Trials Group (PACTG) 219/219C (n = 2,202, with 214 first-trimester TDF exposures), the P1025 protocol (n = 1,112, with 138 first-trimester TDF exposures),[14,15] and Pediatric HIV/AIDS Cohort Study (PHACS) (n = 2,580, with 431 first-trimester TDF exposures).[16] In the French Perinatal Cohort, no association was found between birth defects and the use of TDF, with a power of 70% for an odds ratio of 1.5 (n = 13,124, with 823 first-trimester TDF exposures).[17]

Finally, the Antiretroviral Pregnancy Registry has monitored sufficient numbers of first-trimester exposures to TDF to detect at least a 1.5-fold increased risk of overall birth defects and to detect at least a twofold increase in the risk of birth defects in the cardiovascular and genitourinary systems (the more common classes of birth defects in the general population). No such increase in the risk of birth defects has been observed with TDF. Among the cases of first-trimester TDF exposure that have been reported to the Antiretroviral Pregnancy Registry, the prevalence of birth defects was 2.4% (101 of 4,256 live 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.[18]

In summary, no evidence exists that the use of TDF increases the risk of birth defects.

Adverse Pregnancy Outcomes

Overall Adverse Pregnancy Outcomes

In an 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 (i.e., stillbirth, neonatal death, preterm delivery or very preterm delivery, small for gestational age [SGA] or very small for gestational age) was lower in women who received TDF/FTC/EFV than in women who received any other regimen (TDF/FTC plus nevirapine [NVP], adjusted relative risk [ARR] 1.15; TDF/FTC plus lopinavir/ritonavir [LPV/r], ARR 1.31; zidovudine [ZDV]/3TC plus NVP, ARR 1.30; ZDV/3TC plus LPV/r, ARR 1.21). Furthermore, among infants who were exposed to ART from conception, TDF/FTC/EFV was associated with lower risk for adverse birth outcomes than other antiretroviral (ARV) regimens.[19]

Fetal Growth Effects

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 birth weight (LBW) and SGA and similar newborn length-for-age and head circumference-for-age z-scores (LAZ and HCAZ, respectively).[20] In the P1025 study (a different U.S. cohort study), maternal TDF use was similarly not associated with differences in body size parameters at birth.[21] In a combined analysis of data from 4,646 births that occurred during the PHACS and P1025 studies, there were no differences in the risks of LBW infants (<2,500 g) and very LBW infants (<1,500 g) for women who received TDF/3TC plus LPV/r and those who received ZDV/3TC plus LPV/r during pregnancy.[22] In the European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC) cohort study, the use of TDF was similarly not associated with SGA infants.[23] However, in a Dutch study of 74 HIV-exposed infants (including 9 with *in utero* TDF exposure), maternal TDF use was linked to an increased risk of LBW (<2,500 g).[24]

In the largely Africa-based Promoting Maternal and Infant Survival Everywhere (PROMISE) trial, pregnant women with HIV but without advanced disease or immunosuppression (defined as CD4 T lymphocyte counts ≥350 cells/mm3) were randomized at ≥14 weeks gestation (with a median of 26 weeks gestation) to receive ZDV alone, ZDV/3TC plus LPV/r (ZDV-based ART), or TDF/FTC plus LPV/r (TDF-based ART). The TDF-based ART arm and ZDV-based ART arms showed no significant differences in the incidence of LBW infants (<2,500 g; 16.9% vs. 20.4%, P = 0.3).[25] In the large observational study in Botswana, the use of TDF/FTC/EFV was associated with a lower risk of SGA infants than all other regimens.[19] A fetal ultrasound study in South Africa demonstrated no association between duration of maternal TDF use and long-bone (femur and humerus) growth in the infant.[26] This same research group also demonstrated that the duration of *in utero* TFV exposure was not related to infant length at birth.[27]

Additionally, a placebo-controlled trial of TDF 300 mg that was initiated at 28 weeks gestation in Thai women with HBV (but not HIV) 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 2 twin pairs and 1 stillbirth in the TDF arm). No difference was observed in birth weights between infants born to women who received TDF and those who received placebo: median birth weight was 3,028 g in the TDF arm and 3,061 g in the placebo arm.[28]

In summary, the available evidence does not indicate a link between maternal TDF use and LBW or SGA.

Preterm Delivery

In the PROMISE trial, there were no significant differences between the TFV-based ART arm and the ZDV-based ART arms in the incidence of preterm delivery (delivery at <37 weeks; 18.5% vs. 19.7%, $P = 0.77$). However, TFV-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 ZDV based ART.[25] The greater number of early infant deaths was likely attributable to poor outcomes for very preterm infants in the settings where the trial took place, but the higher rate of very preterm delivery in the TFV-based ART arm remains unexplained. Subsequent analyses demonstrated persistence of this association even after adjustment for multiple well-established clinical, demographic, and obstetrical risk factors.[29] Potential explanations include a lower than expected very preterm delivery rate in the ZDV based ART arm or increased TFV exposure due to coadministration with LPV/r (LPV/r doses were increased in late pregnancy). However, investigators were unable to demonstrate a relationship between maternal TFV-DP levels and very preterm delivery/early neonatal death.[30]

In contrast to the PROMISE trial results, the use of ZDV/3TC plus LPV/r was associated with a higher risk of preterm birth, very preterm birth, and neonatal death than TDF/FTC/EFV in the large observational study in Botswana.[31] There was a higher risk of preterm delivery, however, for women who started treatment with TDF/FTC/EFV in the year prior to conception compared to women who started the same regimen late in the second trimester (adjusted risk ratio 1.33; 95% CI, 1.04–1.7).[19]

In a combined analysis of data from 4,646 births that occurred during the PHACS and P1025 studies, women who received TDF/3TC plus LPV/r and those who received ZDV/3TC plus LPV/r during pregnancy had no significant differences in the risks of preterm delivery overall (defined as a gestational age of <37 weeks) or very preterm delivery (<34 weeks).[22] Among women with HIV who became pregnant and started ART while enrolled in serodiscordant couple PrEP studies, preterm birth (defined as live birth at <37 weeks gestation) occurred less frequently among women who received TDF (adjusted prevalence rate ratio [aPRR] 0.34; $P = 0.02$), and there was no difference in the rates of neonatal death (aPRR 0.68; $P = 0.6$).[32]

Additionally, in the trial of TDF 300 mg in Thai women with HBV (but not HIV), no difference was observed in the frequency of preterm delivery between the TDF and placebo arms: Preterm delivery occurred for 8 of 162 infants (5%) in the TDF arm (with none at <35 weeks), and 13 of 160 infants [8%] experienced preterm delivery in the placebo arm, including 3 infants (2%) who were delivered between 32 and 34 weeks gestation.[28]

However, 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 higher rate of preterm delivery was not associated with whether the regimen also included a protease inhibitor, non-nucleoside reverse transcriptase inhibitor, or integrase strand transfer inhibitor.[33]

In all, some concern remains regarding a link between maternal TDF use and preterm birth, but the evidence is mixed; the role of concomitant medications and other cofactors and/or confounders requires further investigation.

Other Safety Data

Maternal Safety Outcomes

In a United Kingdom cohort of 71 pregnant women who were 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).[34]

In the Thai trial in which pregnant women received TDF or placebo from a gestational age of 28 weeks to 2 months postpartum to prevent HBV transmission, there was no significant effect of maternal TDF use on maternal bone mineral density (BMD) 1 year after delivery.[35]

Infant Safety Outcomes

In the U.S. PHACS/Surveillance Monitoring for ART Toxicities (SMARTT) cohort study, after adjusting for birth cohort and other factors, maternal use of TDF led to no increase in the likelihood of adverse infant metabolic, growth/development, cardiac, neurological, or neurodevelopmental outcomes.[36]

In the Development of Antiretroviral Therapy in Africa (DART) trial in Uganda and Zimbabwe, there were no differences in infant mortality between infants born to mothers who received TDF during pregnancy and those born to mothers who received other ARV drugs.[37]

Infant Growth Effects

In the U.S. PHACS study, there were no differences at birth in rates of LBW, SGA, or newborn LAZ and HCAZ between infants who were exposed to combination drug regimens that contained versus 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, $P = 0.02$). There was no difference in weight-for-age z-score (WAZ). There were also 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 at age 1 year are of uncertain significance.[20] 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 who were followed for 6 months, TDF exposure after the first trimester was associated with being underweight (WAZ <5%) at age 6 months (odds ratio [OR] 2.06; 95% CI, 1.01–3.95; $P = 0.04$) when compared to no exposure.[21]

A Kenyan cohort study also found an association between maternal TDF use (compared to ART without TDF) and lower infant 6-week WAZ despite no difference in infant weight at birth; however, TDF exposure was not associated with infant WAZ differences at age 9 months, and no associations were found with any other infant anthropometric measures at the 6-week or 9-month time points.[38] 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 birth weight and prematurity.[24]

On the other hand, results from a South African study demonstrated that the duration of *in utero* TFV exposure was not related to infant length at birth or to linear growth through the first 48 weeks of life.[27] In the DART trial, there were also no differences in infant growth rates between infants born to mothers who received TDF during pregnancy and those born to mothers who received other ARV drugs.[37]

Finally, in the placebo-controlled trial that involved Thai women with HBV (but not HIV) who initiated TDF at 28 weeks gestation, there was no difference in growth outcomes at age 6 months between infants in the maternal TDF arm and infants in the placebo arm.[28]

The evidence is inconsistent regarding the association between maternal TDF use during pregnancy and transient, small growth delays during the first year of life. These delays are of uncertain clinical significance.[39]

Infant Bone Effects

In a cross-sectional study of 68 children aged 1 to 6 years who were exposed to HIV (but who were not infected) and who had *in utero* exposure to combination regimens that contained TDF (n = 3) or that did not contain TDF (n = 35), quantitative bone ultrasound measures and bone metabolism marker levels were similar for both groups.[40] Another study evaluated whole body dual-energy X-ray absorptiometry 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 (-6.5 g; $P = 0.004$), as was the whole-body-less-head BMC (-2.6 g; $P = 0.056$).[41] In a small, randomized trial that enrolled pregnant women in China with HBV/HIV coinfection, BMD and BMC at age 6 months were non-significantly lower in 14 TDF-exposed infants than in 13 infants who were not exposed to TDF.[42]

On the other hand, in the randomized PROMISE trial, there was no difference in BMC between infants whose mothers received LPV/r-based ART with TDF and those whose mothers received LPV/r-based ART with ZDV.[43] In addition, in the Thai trial in which women with HBV (but not HIV) received TDF or placebo from a gestational age of 28 weeks to 2 months postpartum to prevent HBV transmission, there was no significant effect of maternal TDF use on infant BMD at age 1 year.[35]

A study of 136 infants in Malawi whose mothers received TDF/FTC/EFV 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.[44]

The impact of maternal TDF use on infant bone mineral status remains uncertain and requires further longitudinal evaluation.

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 the individual drug components of the FDC tablet during pregnancy.

Generic Name (Abbreviation) *Trade Name*	**Formulation**	**Dosing Recommendations**[a]	**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/c/FTC) *Stribild* (TDF/EFV/3TC) (TDF/EFV/3TC) (TDF/3TC) *Temixys* (TDF/FTC) *Truvada* **Note:** Generic products are available for some formulations.	**TDF (Viread)** *Tablet:*[d] • 300 mg *Powder:* • 40 mg/1 g oral powder **TDF/EFV/FTC (Atripla):** • TDF 300 mg/ EFV 600 mg/ FTC 200 mg tablet **TDF/3TC (Cimduo):** • TDF 300 mg/ 3TC 300 mg tablet **TDF/FTC/RPV (Complera):** • TDF 300 mg/ FTC 200 mg/ RPV 25 mg tablet **TDF/DOR/3TC (Delstrigo):** • TDF 300 mg/ DOR 100 mg/ 3TC 300 mg tablet **TDF/EVG/c/FTC (Stribild):** • TDF 300 mg/ EVG 150 mg/ COBI 150 mg/ FTC 200 mg tablet **TDF/EFV/3TC (Symfi):** • TDF 300 mg/ EFV 600 mg/ 3TC 300 mg tablet	**Standard Adult Doses** *TDF (Viread)* Tablet: • TDF 300 mg once daily without regard to food Powder: • TDF 8 mg/kg daily (up to a maximum of TDF 300 mg). Take with food. *TDF/EFV/FTC (Atripla):* • One tablet once daily at or before bedtime. Take on an empty stomach to reduce side effects. *TDF/3TC (Cimduo):* • One tablet once daily without regard to food *TDF/FTC/RPV (Complera):* • One tablet once daily with food *TDF/DOR/3TC (Delstrigo):* • One tablet once daily without regard to food *TDF/EVG/c/FTC (Stribild):* • One tablet once daily with food • One tablet once daily on an empty stomach and preferably at bedtime	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 twofold 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 has HBV/HIV coinfection, it is possible that an HBV flare may occur if TDF is stopped; see Hepatitis B Virus/HIV Coinfection. Renal function should be monitored because of potential for renal toxicity.

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations[a]	Use in Pregnancy
	TDF/EFV/3TC (Symfi Lo): • TDF 300 mg/EFV 400 mg/3TC 300 mg tablet **TDF/3TC (Temixys):** • TDF 300 mg/3TC 300 mg tablet **TDF/FTC (Truvada):** • TDF 300 mg/FTC 200 mg tablet	*TDF/3TC (Temixys):* • One tablet once daily without regard to food *TDF/FTC (Truvada):* • One tablet once daily without regard to food **Pregnancy** *PKs in Pregnancy:* • AUC is lower in third trimester than postpartum, but trough levels are adequate. *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., 3TC, COBI, DOR, EFV, EVG, FTC, RPV)	

[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

[d] Generic product available

Key: 3TC = lamivudine; ARV = antiretroviral; AUC = area under the curve; COBI = cobicistat; DOR = doravirine; EFV = efavirenz; EVG/c = elvitegravir/cobicistat; FDC = fixed-dose combination; FTC = emtricitabine; HBV = hepatitis B virus; PK = pharmacokinetic; RPV = rilpivirine; TDF = tenofovir disoproxil fumarate

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Zidovudine (Retrovir, ZDV)

(Last updated December 29, 2020; last reviewed December 29, 2020)

Animal Studies

Carcinogenicity

Zidovudine (ZDV) 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 of ZDV have been performed in mice and rats.[1] 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 in animals given 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 (in mice) and 24 times (in rats) the estimated human exposure at the recommended therapeutic dose of ZDV 100 mg every 4 hours. The predictive value of rodent carcinogenicity studies for adverse effects in humans is unknown.[2]

Two trans-placental carcinogenicity studies were conducted in mice.[3,4] In one study, ZDV was administered at doses of 20 mg/kg per day or 40 mg/kg per 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 ZDV exposures approximately three times the estimated exposure for humans who receive the recommended dose. After 24 months, an increase in the incidence of vaginal tumors was noted, with no increase in the incidence of tumors in the liver, 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, ZDV was administered at the maximum tolerated doses of 12.5 mg per day or 25 mg per day (approximately 1,000 mg/kg of nonpregnant body weight or approximately 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 ZDV.

Reproduction/Fertility

ZDV had no effect on fertility when it was administered to male and female rats at doses up to seven times the usual adult dose based on body surface area; in this instance, fertility was judged by rates of conception. ZDV 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 observed at ZDV concentrations similar to levels achieved with human therapeutic doses.[5]

Teratogenicity/Adverse Pregnancy Outcomes

In animal reproduction studies, administration of oral ZDV to female rats prior to mating and throughout gestation resulted in embryotoxicity at doses that produced systemic exposures (expressed as AUC) approximately 33 times higher than the exposures observed in humans who received the recommended clinical dose. However, no embryotoxicity was observed in pregnant rats during organogenesis at exposures that were approximately 117 times higher than clinical exposures. Embryotoxicity occurred in pregnant rabbits that received oral ZDV during organogenesis at doses that produced exposures approximately 108 times higher than the exposure observed in humans who received the recommended dose. No embryotoxicity was observed at doses that produced exposures approximately 23 times higher than the exposures observed in humans who received the recommended dose of ZDV.[2]

In an additional teratology study in rats, a dose of ZDV 3,000 mg/kg per day (which was very near the median lethal oral dose in rats of 3,683 mg/kg) caused marked maternal toxicity and an increase in the incidence of fetal malformations. This dose resulted in peak ZDV plasma concentrations that were 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 per day). No evidence of teratogenicity was seen in this experiment at doses of ZDV 600 mg/kg per day or less.

Human Studies in Pregnancy

Pharmacokinetics

ZDV pharmacokinetics (PKs) are not significantly altered by pregnancy, and standard adult doses are recommended during pregnancy.[6,7] A population PK analysis that evaluated oral and intravenous (IV) ZDV doses during pregnancy and labor found high fetal exposure to ZDV with current IV intrapartum dosing regimens. Simulations suggested that reduced intrapartum ZDV dosing regimens might provide lower, but still adequate, fetal ZDV exposures.[8] However, standard dosing of IV ZDV during labor continues to be recommended for women with unknown or elevated viral loads. In pregnant women, as with nonpregnant adults, intracellular ZDV triphosphate concentrations do not vary with plasma concentrations, over a wide range of plasma ZDV concentrations.[9]

Placental and Breast Milk Passage

ZDV rapidly crosses the human placenta, achieving cord blood-to-maternal-plasma ratios of about 0.80. The ratio of ZDV in amniotic fluid to ZDV in maternal plasma is 1.5.[10] ZDV is excreted into human breast milk, with breast milk-to-maternal-plasma ZDV concentration ratios ranging from 0.44 to 1.35. No ZDV was detectable in the plasma of nursing infants who were only exposed to ZDV 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 ZDV or placebo, and no specific patterns of defects were seen.[6,14] Similarly, no increase in the incidence of 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 increase in the risk of hypospadias among infants who were exposed to ZDV, 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 ZDV and congenital anomalies.[19]

In the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposures to ZDV have been monitored to be able to detect at least a 1.5-fold increase in risk of overall birth defects and a two fold increase in risk of defects in the more common classes, including the cardiovascular and genitourinary systems. No such increase in the risk of birth defects has been observed in infants who were exposed to ZDV. With first-trimester ZDV exposure, the prevalence of birth defects was 3.2% (134 of 4,196 births; 95% confidence interval [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 the incidence of birth defects among infants with first-trimester ZDV 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 ZDV exposure during the first trimester and most congenital malformations.[22]

The French Perinatal Cohort reported that first-trimester ZDV 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 ZDV-exposed infants in the Antiretroviral Pregnancy Registry (n= 13,073) reported no difference in the prevalence of ventricular septal defect and congenital heart defects among infants exposed to ZDV-containing regimens (nine 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 regimens that did not contain ZDV (two of 1,839 infants exposed during the first trimester, rate 0.11; three 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 ZDV plus lamivudine plus lopinavir/ritonavir (LPV/r) or LPV/r alone. 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 who had not been exposed to HIV, infants born to mothers who received ZDV were more likely to have thicker myocardial walls and smaller left ventricular cavities than other infants, regardless of HIV exposure. Maternal ZDV treatment was the only factor significantly associated with fetal cardiac changes.[25] Another study by the same authors reported the presence of hypertrophic myocardium and signs of increased mitochondrial content in the cord blood of infants who had been exposed to HIV. In this study, both conditions were associated with maternal use of ZDV during pregnancy.[26]

Cancer has been observed no more frequently among ZDV-exposed infants than among other HIV-exposed or HIV-unexposed infants in a long-term follow-up study for the original PACTG 076 study,[27] in prospective cohort studies,[28] and in matches between HIV surveillance and cancer registries.[29,30]

Other Safety Information

In the placebo-controlled perinatal trial PACTG 076, no difference in disease progression was seen between women who received ZDV and those who received a placebo during 4 years of follow-up postpartum.[31]

No differences in immunologic, neurologic, or growth parameters were seen between PACTG 076 infants with *in utero* ZDV exposure and those who received a placebo during nearly 6 years of follow-up.[14,27]

Mitochondrial dysfunction in mothers and infants who were 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 is a recognized possibility; however, this risk does not outweigh the clear benefit of these drugs in preventing perinatal HIV transmission.[2]

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, ZDV use was associated with an increased risk of meeting the study's definition of a metabolic case (adjusted relative risk 1.69; 95% CI, 1.08–2.64).[32,33]

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**
Zidovudine (ZDV) *Retrovir* (ZDV/3TC) *Combivir* (ZDV/ABC/3TC) *Trizivir* **Note:** Generic products are available for all formulations.	**ZDV (Retrovir)** *Capsule:* • 100 mg *Tablet:* • 300 mg *Oral Solution:* • 10 mg/mL *IV Solution:* • 10 mg/mL **ZDV/3TC (Combivir):** • ZDV 300 mg/3TC 150 mg tablet **ZDV/ABC/3TC (Trizivir):** • ZDV 300 mg/ ABC 300 mg/3TC 150 mg tablet	**Standard Adult Doses** *ZDV (Retrovir):* • ZDV 300 mg twice daily or ZDV 200 mg three times a day without regard to food • Patients in active labor should receive ZDV 2 mg/kg IV as a loading dose, followed by ZDV 1 mg/kg/hour continuous infusion from beginning of active labor until delivery. *ZDV/3TC (Combivir):* • One tablet twice daily without regard to food *ZDV/ABC/3TC (Trizivir):* • One tablet twice daily without regard to food **Pregnancy** *PKs in Pregnancy:* • PKs not significantly altered in pregnancy. *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).	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 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; FDC = fixed-dose combination; IV = intravenous; PK = pharmacokinetic; ZDV = zidovudine

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Doravirine (Pifeltro, DOR)

(Last updated December 29, 2020; last reviewed December 29, 2020)

Animal Studies

Carcinogenicity

Doravirine (DOR) was not carcinogenic in long-term oral carcinogenicity studies in mice and rats at exposures up to six times and seven 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 that received the high dose (which produced the sevenfold increase in exposure) of DOR; however, the incidence was similar to the incidence observed among historical controls that did not receive DOR. DOR was not genotoxic in a battery of *in vitro* or *in vivo* mutagenicity assays.[1]

Reproduction/Fertility

In rats, DOR did not affect fertility, reproductive performance, or early embryonic development at exposures (based on area under the curve [AUC]) that were approximately seven 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 DOR exposures (based on AUC) that were approximately nine times (in rats) and eight 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 DOR exposures that were approximately nine 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 DOR. Fetal plasma concentrations observed on gestation Day 20 were up to 40% (in rabbits) and 52% (in rats) of maternal concentrations. DOR was excreted into the milk of lactating rats at concentrations that were 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 DOR in pregnant women have been reported.

Placental and Breast Milk Passage

No data are available on placental or breast milk passage of DOR in humans.

Teratogenicity/Adverse Pregnancy Outcomes

No data are currently available on the risk of birth defects in infants born to women who received DOR during pregnancy.

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 the individual drug components of the FDC tablet during pregnancy.

Generic Name (Abbreviation) *Trade Name*	**Formulation**	**Dosing Recommendations**[a]	**Use in Pregnancy**
Doravirine (DOR) *Pifeltro* (DOR/3TC/TDF) *Delstrigo*	**DOR (Pifeltro):** • 100 mg tablet **DOR/3TC/TDF (Delstrigo):** • DOR 100 mg/3TC 300 mg/TDF 300 mg tablet	**Standard Adult Doses** *DOR* (*Pifeltro*): • DOR 100 mg once daily with or without food *DOR/3TC/TDF* (*Delstrigo*): • One tablet once daily with or without food **Pregnancy** *PKs in Pregnancy:* • No PK studies in human pregnancy *Dosing in Pregnancy:* • Insufficient data to make dosing recommendations For guidance about use of combination products in pregnancy, please see the specific sections on other components (i.e., 3TC, TDF).	No data are available on the placental transfer of DOR in humans, 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 Antiretroviral Guidelines, Appendix B, Table 10).

Key: 3TC = lamivudine; ARV = antiretroviral; DOR = doravirine; FDC = fixed-dose combination; PK = pharmacokinetic; TDF = tenofovir disoproxil fumarate

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Efavirenz (Sustiva, EFV)

(Last updated December 29, 2020; last reviewed December 29, 2020)

Animal Studies

Carcinogenicity

Efavirenz (EFV) was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests. A study that evaluated the genotoxicity of EFV 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.[1] Long-term animal carcinogenicity studies with EFV have been completed in mice and rats. No increase in tumor incidence above background was observed in male mice at systemic drug exposures that were approximately 1.7-fold higher than the exposures seen in humans who received standard therapeutic doses. In female mice, an increase in tumor incidence above background was seen for 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 EFV exposures that were lower than those seen in humans who received therapeutic doses.[2]

Reproduction/Fertility

EFV has had no observable effects on reproduction or fertility in rodents.[2]

Teratogenicity/Adverse Pregnancy Outcomes

An increase in fetal resorption was observed in female rats at EFV doses that produced peak plasma concentrations and area under the curve (AUC) values less than or equal to those in humans who received the recommended dose of EFV 600 mg once daily. EFV produced no reproductive toxicities when given to pregnant rabbits at doses that produced peak plasma concentrations similar to those achieved in humans who received EFV 600 mg once daily. AUC values in these rabbits were approximately half of the values seen in humans who received EFV 600 mg once daily.[2]

Central nervous system malformations and cleft palate were observed in 3 of 20 infant monkeys born to pregnant cynomolgus monkeys that received EFV between gestational day 20 and gestational day 150 at a dose of EFV 60 mg/kg per 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.[2]

A study in pregnant and lactating rats exposed to EFV found that perinatal exposure to EFV provoked cell death, significant changes in cytoarchitecture, and disturbances in serotonergic and dopaminergic innervation in the medial prefrontal cortex of adult offspring.[4]

Placental and Breast Milk Passage

EFV readily crosses the placenta in rats, rabbits, and primates, producing cord blood concentrations that are similar to the concentrations observed in maternal plasma. Maternal and fetal blood concentrations in pregnant rabbits and cynomolgus monkeys are equivalent, while fetal concentrations in rats exceeded maternal concentrations.[2]

Human Studies in Pregnancy

Pharmacokinetics/Pharmacogenomics

In an intensive sampling pharmacokinetic (PK) study of 25 pregnant women who received EFV during the third trimester, EFV clearance was slightly increased and trough levels were decreased compared with levels measured postpartum.[5] These differences are not of sufficient magnitude to warrant dose adjustment during

pregnancy. A review of this study and four others that measured EFV concentrations in pregnant women found that EFV concentrations were not significantly affected by pregnancy and that high rates of HIV RNA suppression at delivery were achieved with EFV-based regimens.[6]

In a PK study of 42 pregnant women who received EFV 600 mg once daily, EFV exposure was similar during pregnancy and postpartum. EFV PK data were available for 15 women during their second trimester, 42 women during their third trimester, and 40 women postpartum. EFV AUC during the third trimester (60 mcg•h/mL) was similar to the AUC observed in nonpregnant adults (58 mcg•h/mL). EFV drug levels in the second trimester were lower than postpartum values, but they remained within 80% to 125% of postpartum values. Viral loads at delivery were <400 copies/mL and <50 copies/mL for 96.7% and 86.7% of women, respectively.[7]

In an open-label, two-center study in the United Kingdom and Uganda, 25 pregnant women with HIV who were virally suppressed (defined as a viral load <50 copies/mL) on a regimen that included EFV 600 mg once daily had their dose reduced to EFV 400 mg in the third trimester. PK parameters, AUC, and plasma concentrations at 24 hours postdose were slightly lower in the third trimester than during the postpartum period but generally remained within the therapeutic range; all participants maintained viral suppression.[8]

A PK modeling study was conducted using pooled data from seven studies of women who were taking regimens that included EFV. The study included an analysis of 1,968 PK samples, 774 of which were collected during pregnancy. This analysis predicted that the reduced EFV dose of 400 mg would generate median EFV AUC_{24h} and C_{12h} during the third trimester that were 91% and 87%, respectively, of the values observed among nonpregnant women.[9] A more recent physiologically based pharmacokinetic (PBPK) modeling study evaluated EFV exposure in the third trimester in women with extensive, intermediate, and poor cytochrome P450 2B6 (CYP2B6) metabolism. The model predicted about a twofold increase in drug clearance in the third trimester when compared with clearance prior to pregnancy—resulting in subtherapeutic concentrations of EFV in the third trimester in 57% of extensive metabolizers. These results suggest that the recommended reduction in EFV dose from 600 mg to 400 mg may not provide therapeutic drug levels in extensive metabolizers during the third trimester and that clinical trials to evaluate the effectiveness of a 400 mg dose of EFV in the third trimester, especially in extensive metabolizers, are indicated prior to a dose adjustment in pregnancy.[10]

In a pharmacogenomics study, nonpregnant individuals with the CYP2B6 516 TT genotype had greater than threefold increases in both short-term and long-term EFV exposure, as measured by drug levels in plasma and hair. This suggests that drug levels could vary significantly with CYP2B6 polymorphisms.[11,12] The frequency of this allele varies among different ethnic populations, with a prevalence of 3.4% in white people, 6.7% in Hispanic people, and 20% in African Americans.[5]

Placental and Breast Milk Passage

In a PK study of 42 pregnant women who received EFV 600 mg once daily, EFV readily crossed the placenta, and infant elimination half-life was more than twice that of maternal participants. The cord blood-to-maternal-plasma concentration ratio was 0.67 (range 0.36–0.95). Among 23 infants for whom washout data were available, median elimination half-life was 65.6 hours (interquartile range, 40.6–129 hours). Viral loads at delivery were <400 copies/mL and <50 copies/mL for 96.7% and 86.7% of women, respectively.[7]

In a study of 25 mother–infant pairs, the median EFV cord blood-to-maternal-blood concentration ratio was 0.49 (range 0.37–0.74).[5] In a study of 13 women in Rwanda, EFV was given during the third trimester and for 6 months after delivery.[13] EFV concentrations were measured in maternal plasma, breast milk, and infant plasma. EFV concentration was significantly higher in maternal plasma than in skim breast milk (with a mean breast milk-to-maternal-plasma concentration ratio of 0.54) and higher in skim breast milk than in infant plasma (with a mean skim breast-milk-to-newborn-plasma concentration ratio of 4.08). The mean infant plasma EFV

concentration was 860 ng/mL, 13.1% of mean maternal plasma concentrations. All infants had detectable plasma concentrations of EFV, and 8 of 13 newborns had plasma EFV concentrations that were below the minimum therapeutic concentration of 1,000 ng/mL that is recommended for treatment of adults with HIV.

In a study of 51 women in Nigeria who received EFV 600 mg once daily, the median milk-to-maternal-plasma concentration ratio was 0.82 (range 0.51–1.1) and the median infant EFV concentration was 178 ng/mL (range 88–340 ng/mL).[14] In a study of 56 mother–infant pairs in which the mothers received EFV-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 EFV during pregnancy and breastfeeding, with approximately one-third of transfer occurring postpartum (40% cumulative transfer, with 15% of transfer occurring during breastfeeding).[15] All mothers and infants had detectable EFV plasma levels at 0, 8, and 12 weeks, and mean infant-to-maternal-hair concentration at 12 weeks postpartum was 0.40 for EFV. No data are currently available about the safety and PK of EFV in neonates.

Teratogenicity/Adverse Pregnancy Outcomes

In pregnancies with prospectively reported exposure to EFV-based regimens in the Antiretroviral Pregnancy Registry through January 2020, birth defects were observed in 27 of 1,142 live births with first-trimester exposure (2.4%; 95% confidence interval [CI], 1.6% to 3.4%).[16] 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 and a twofold increase in cardiovascular and genitourinary defects, the low incidence of neural tube defects (NTDs) 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 EFV exposure have documented one NTD case (0.9%), which is consistent with the expected background prevalence.[16]

In a meta-analysis of 23 studies that was designed to update the 2013 World Health Organization (WHO) guidelines for antiretroviral therapy (ART) in low- and middle-income countries, there were 44 infants with birth defects among 2,026 live births to women who received EFV during the first trimester. The pooled proportion of overall birth defects was 1.63% (95% CI, 0.78% to 2.48%).[17] The rate of overall birth defects was similar among women who received EFV-containing regimens and women who received regimens that did not contain EFV during the first trimester (pooled relative risk [RR] 0.78; 95% CI, 0.56–1.08). Across all births, one NTD (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 EFV exposures was insufficient to rule out a significant increase in low-incidence birth defects, such as NTDs. The incidence of NTDs in the general U.S. population is 0.06% to 0.07%.[18]

A French study of 13,124 live births between 1994 and 2010 included an analysis of 372 infants born after first-trimester exposure to EFV.[19] In the primary analysis, which used the European Surveillance of Congenital Anomalies and Twins (EUROCAT) classification system, no increase in the incidence of birth defects was detected among infants with first-trimester EFV exposure compared to those without exposure to EFV during pregnancy (adjusted odds ratio 1.16; 95% CI, 0.73–1.85). A secondary analysis that used the modified Metropolitan Atlanta Congenital Defect Program classification (used by the Antiretroviral Pregnancy Registry), found an association between first-trimester EFV exposure and neurologic defects, but none of the four defects that were reported during this study (ventricular dilatation with anomalies of the white substance, partial agenesis of the corpus callosum, subependymal cyst, and pachygyria) were NTDs, and none had similar embryologic origins.[20]

Recently, Zash et al. reported on the outcomes of a large birth surveillance study in Botswana. Among 7,959 deliveries to women who were taking EFV around the time of conception, there were three NTDs

(0.04%; 95% CI, 0.01% to 0.11%), which is similar to the rate of NTDs that was observed among infants born to 89,372 women without HIV (0.08%; 95% CI, 0.06% to 0.10%).[21] This study adds to available data on first-trimester EFV exposures, providing strong evidence against an elevated risk of NTDs in infants who were exposed to EFV. The South African Pregnancy Exposure Registry similarly found no association between first-trimester use of EFV-based ART regimens and congenital malformations.[22]

The Food and Drug Administration continues to advise women to avoid becoming pregnant while taking EFV and to advise health care providers to avoid administering EFV during the first trimester, because fetal harm may occur. However, the data on more than 7,900 periconception exposures to EFV from Botswana are sufficient to rule out a threefold or greater increased risk of NTDs with the use of EFV. As a result, the Perinatal Guidelines do not restrict the use of EFV during pregnancy or in women who are planning to conceive; this is consistent with the British HIV Association guidelines and WHO guidelines for use of antiretroviral (ARV) drugs in pregnancy, both of which note that EFV can be used throughout pregnancy.[23–25] EFV should be continued in pregnant women who are receiving 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 HIV transmission.[26]

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* EFV exposure. The relative risk of microcephaly in infants with *in utero* EFV exposure was 2.56 (95% 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.[27] 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 and lamivudine than among those who had been exposed to EFV plus tenofovir disoproxil fumarate and emtricitabine. 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 (see the Teratogenicity section).

A study of Botswana HIV-exposed but uninfected children evaluated the association between neurodevelopmental deficits and the timing of initial *in utero* EFV exposure. Adjusted mean scores for the 126 children in the EFV-exposed group were lower than for the 367 children in the EFV-unexposed group on Bayley Scales of Infant and Toddler Development, Third Edition (BSID III) Receptive Language (21.5 vs. 22.5; $P = 0.05$); DMC Locomotor (30.7 vs. 32.0; $P < 0.01$) and Fine Motor scales (17.8 vs. 19.2; $P < 0.01$); and Profile of Social Emotional Development (PSED) (11.7 vs. 9.9; $P = 0.02$); however, scores for the first group were higher on the DMC Language scale (17.6 vs. 16.5; $P = 0.01$). Earlier (vs. later) EFV exposure was associated with lower scores on the BSID III Receptive Language scale (20.7 vs. 22.2; $P = 0.02$). Consistent with findings from other trials, HIV-exposed but uninfected children exposed *in utero* to EFV-based ART may be at higher risk for neurodevelopmental and social-emotional deficits than HIV-exposed but uninfected children exposed to non-EFV-based ART.[28] An additional prospective study of a cohort of 3,747 HIV-exposed but uninfected children found that children exposed to EFV at any time during pregnancy had a higher risk of neurodevelopmental abnormalities (adjusted relative risks [aRR] 1.53; 95% CI, 0.94–2.51). This association was stronger when comparing EFV exposure at conception to no exposure during pregnancy (aRR 1.92; 95% CI, 1.09–3.36) and considering follow-up and case diagnosis only through age 2 (aRR 2.14; 95% CI, 1.11–4.12).[29]

Safety

The Promoting Maternal and Infant Survival Everywhere (PROMISE) trial randomized ART naive antepartum and postpartum women with HIV, CD4 >350, and ALT <2.5 ULN to different ART regimens. The study found

that 2.5% of the 2,435 women randomized to EFV-based regimens developed severe hepatotoxicity, and 3% of women with severe hepatotoxicity developed liver-related mortality.[30]

Drug–Drug Interactions

PK interactions between EFV and the progestin component of some hormonal contraceptives may decrease the efficacy of emergency contraception, combined oral contraceptive pills, progestin-only pills, and progestin implants and may increase the risk of contraceptive failure.[31–35] (see Preconception Counseling and Care for Women of Childbearing Age Living with HIV and Table 3).

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**
Efavirenz (EFV) *Sustiva* (EFV/FTC/TDF) *Atripla* (EFV/3TC/TDF) (EFV/3TC/TDF) **Note:** Generic products are available for some formulations.	**EFV (Sustiva)**[d] *Capsules:* • *50 mg* • *200 mg* *Tablet:* • *600 mg* **EFV/FTC/TDF (Atripla):** • EFV 600 mg/FTC 200 mg/TDF 300 mg tablet **EFV/3TC/TDF (Symfi):** • EFV 600 mg/3TC 300 mg/TDF 300 mg tablet **EFV/3TC/TDF (Symfi Lo):** • EFV 400 mg/3TC 300 mg/TDF 300 mg tablet	**Standard Adult Doses** *EFV (Sustiva):* • EFV 600 mg once daily at or before bedtime • Take on an empty stomach to reduce side effects. *EFV/FTC/TDF (Atripla)*: • One tablet once daily at or before bedtime • Take on an empty stomach to reduce side effects. • One tablet once daily on an empty stomach and preferably at bedtime **Pregnancy** *PKs 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. However, the data on more than 7,900 periconception EFV exposures from Botswana rule out a threefold or greater increased risk of NTDs. 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

		For guidance about the use of combination products in pregnancy, please see the specific sections on other components (i.e., 3TC, FTC, TDF).	in pregnant women who are on a virally 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).

[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
[d] Generic product available

Key: 3TC = lamivudine; ARV = antiretroviral; AUC = area under the curve; EFV = efavirenz; FDA = Food and Drug Administration; FDC = fixed-dose combination; FTC = emtricitabine; NTDs = neural tube defects; PK = pharmacokinetic; TDF = tenofovir disoproxil fumarate; WHO = World Health Organization

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Etravirine (Intelence, ETR)

(Last updated December 29, 2020; last reviewed December 29, 2020)

Animal Studies

Carcinogenicity

Etravirine (ETR) was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests.[1] ETR was evaluated for carcinogenic potential in mice and rats for up to approximately 104 weeks. Because of intolerance of the formulation, the areas under the curve (AUC) for ETR were 0.6-fold (in mice) and 0.2-fold to 0.7-fold (in rats), compared with 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 those of hepatocellular adenomas or carcinomas combined were observed. Whether these liver tumor findings in mice are relevant to humans is unclear.[1]

Reproduction/Fertility

ETR had no effect on fertility and early embryonic development when tested in pregnant rats at doses that produced systemic drug exposures equivalent to those observed in humans who received the recommended dose of ETR 400 mg per 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 ETR 400 mg per day.[1]

Human Studies in Pregnancy

Pharmacokinetics

ETR pharmacokinetics (PK) in pregnant women have been reported in two studies. Ramgopal et al. found approximately 1.1-fold to 1.4-fold increases in total ETR AUC, C_{min}, and C_{max} during the second (n = 13) and third trimesters (n = 10) compared with the levels in the same women postpartum (n = 10). The differences in unbound ETR 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 ETR AUC, C_{min}, and C_{max} during the third trimester (n = 13) compared with the levels in the same women postpartum (n = 8).[3] ETR was well tolerated in both of these studies. ETR is a substrate for cytochrome P450 (CYP) 2C19 metabolism, and the increase in ETR exposure during pregnancy is consistent with the previously observed decrease in CYP2C19 activity during pregnancy.[4]

Placental and Breast Milk Passage

In seven mother–infant pairs, the median ratio of ETR concentration in cord blood to ETR concentration in maternal plasma 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 ETR was described in a report on the use of ETR, darunavir/ritonavir, and enfuvirtide in a woman who gave birth to twins. Cord-blood ETR levels were 414 ng/mL in Twin 1 and 345 ng/mL in Twin 2 (maternal plasma ETR concentration at delivery was not reported).[5]

Plasma and breast milk concentrations were measured on postpartum Days 5 and 14 in eight women who began taking ETR on postpartum Day 1.[6] Plasma PK were similar between Days 5 and 14 and were similar to the published PK parameters of ETR in nonpregnant adults. ETR $AUC_{0–12h}$ in breast milk was higher in mature milk (collected on Day 14) than in colostrum and/or transitional milk (collected on Day 5): 12,954 ± 10,200 ng•h/mL versus 4,372 ± 3,016 ng•h/mL ($P = 0.046$). Median ETR concentrations in plasma and breast milk on Day 5 were 300 ng/mL and 241 ng/mL, respectively (within-subject breast milk concentration/plasma concentration

ratio was 109%). Median plasma and breast milk concentrations on Day 14 were 197 ng/mL and 798 ng/mL, respectively (within-subject breast milk concentration/plasma concentration ratio was 327%). The maximum ETR concentration in breast milk was significantly higher than the maximum concentration 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 having suppressed plasma viral loads. ETR concentrations in the plasma and breast milk of these women were similar to those observed in women with undetectable HIV RNA in breast milk. ETR penetrates well and may accumulate in breast milk.

Teratogenicity/Adverse Pregnancy Outcomes

In eight reported cases of ETR use in pregnancy, no maternal, fetal, or neonatal toxicities were noted.[5,7] 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.[5] Seventy-one live births of infants who were exposed to ETR during the first trimester have been reported to the Antiretroviral Pregnancy Registry; among these infants, only one birth defect has been reported. These data are insufficient to draw conclusions about the risk of birth defects among infants who were exposed to ETR.[8]

Excerpt from Table 10

Generic Name (Abbreviation) *Trade Name*	**Formulation**	**Dosing Recommendations**[a]	**Use in Pregnancy**
Etravirine (ETR) *Intelence*	**Tablets:** • 25 mg • 100 mg • 200 mg For patients who are unable to swallow tablets whole, the tablets may be dispersed in a glass of water.	**Standard Adult Doses** • 200 mg twice daily with food **Pregnancy** *PK in Pregnancy:* • PK data in pregnancy suggest 1.2-fold to 1.6-fold increases in ETR exposure during pregnancy. *Dosing in Pregnancy:* • No change in dose indicated.	Placental transfer varies; it is usually in the moderate-to-high categories, ranging 0.19–4.25.[b] 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 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: ARV = antiretroviral; ETR = etravirine; PK = pharmacokinetic

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Nevirapine (Viramune, NVP)

(Last updated December 29, 2020; last reviewed December 29, 2020)

Animal Studies

Carcinogenicity

Nevirapine (NVP) showed no evidence of mutagenic or clastogenic activity in a battery of *in vitro* and *in vivo* studies. Hepatocellular adenoma and carcinomas are increased at all doses of NVP in mice and rats; however, given the lack of genotoxic activity of NVP, it is unclear if this is relevant to humans.[1]

Reproduction/Fertility

Female rats showed impaired fertility at systemic NVP exposures comparable to human therapeutic exposures.[1]

Teratogenicity/Adverse Pregnancy Outcomes

In studies of rats and rabbits, no teratogenic effects of NVP have been observed other than a significant decrease in fetal weight in rats at systemic concentrations 50% higher than human therapeutic exposure.[1]

Human Studies in Pregnancy

Pharmacokinetics

The pharmacokinetics (PKs) studies of NVP in pregnant women who received NVP as part of antiretroviral therapy (ART) during pregnancy demonstrate varied results. A study of 26 women during their second and third trimesters did not find altered PK parameters compared to the postpartum period;[2] however, two other studies found up to 30% lower exposure in pregnancy.[3,4] No dose adjustment is currently recommended for NVP during pregnancy.

Placental and Breast Milk Passage

NVP demonstrates rapid and effective placental transfer, achieving near-equivalent concentrations in maternal and cord blood (cord blood-to-maternal-plasma ratio ranges from 0.60 to 1.02).[5,6]

NVP also has been shown to be excreted into human breast milk, with breast milk-to-maternal plasma ratios of 0.27 to 0.6 and detectable NVP concentrations in breastfeeding infants.[7–9]

Teratogenicity/Adverse Pregnancy Outcomes

The Antiretroviral Pregnancy Registry has monitored sufficient numbers of first-trimester exposures to NVP to detect at least a 1.5-fold increase in risk of overall birth defects and a twofold increase in risk of birth defects in the cardiovascular and genitourinary systems (the most common classes of birth defects in the general population). No such increase in the risk of birth defects has been observed with NVP. Among the cases of first-trimester NVP exposure that have been reported to the Antiretroviral Pregnancy Registry, the prevalence of birth defects was 3.0% (35 of 1,169 live births; 95% confidence interval [CI], 2.1% to 4.1%) compared with a total prevalence of 2.7% in the U.S. population, based on Centers for Disease Control and Prevention surveillance.[10] Similarly, the French Perinatal Cohort reported no association between exposure to NVP and birth defects, with 71% power to detect a 1.5-fold increase.[11] During 2013–2014, at one KwaZulu hospital, one-time nurse-performed exams found a significantly higher risk ratio of total congenital malformations in infants with first-trimester NVP exposure (relative risk [RR] = 9.28, 2.27–37.94); 2 out of 52 infants with NVP exposure vs. 29 out of 7,592 without NVP exposure.[12]

Other Safety Information

The risk of NVP-associated 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 ranges—from 0.04% to 0.40%.[1,13] 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 patients should be regularly monitored for signs of toxicity.

Incidence of severe NVP-associated skin rash has been reported to be 5.5 times to 7.3 times more common in women than men. In 17 clinical trials of NVP therapy, women with CD4 counts >250 cells/mm³ were 9.8 times more likely to experience symptomatic, often rash-associated, NVP related hepatotoxicity than women with lower CD4 counts.[13] Higher CD4 counts also have been associated with an increased risk of severe, NVP-associated skin rash.[14]

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 counts >250 cells/mm³. Some researchers have suggested that genetic variation in drug metabolism polymorphisms (e.g., CYP2B6 variants), tumor necrosis factor receptor–associated factor (TRAF) proteins, and immune human leukocyte antigen loci may be associated with a higher risk of NVP-associated adverse events and that the relationship between genetic variants and adverse events may vary by race.[15–18] Published literature reports rash and hyperbilirubinemia in infants exposed to NVP through breast milk.[1]

Data are conflicting regarding the increased risk of hepatotoxicity in pregnant women receiving NVP.[19] In a systematic review of 20 studies that included 3,582 pregnant women from 14 countries who initiated NVP while pregnant, the pooled proportion of women who experienced a severe hepatotoxic event was 3.6% (95% CI, 2.4% to 4.8%), and the proportion of women who experienced severe rash was 3.3% (95% CI, 2.1% to 4.5%); overall, 6.2% of women stopped taking NVP because of an adverse event (95% CI, 4.0% to 8.4%).[20] These results were comparable to published frequencies in the general adult population and comparable to frequencies in nonpregnant women within the same cohorts; publications by Ouyang and colleagues echo these results.[21,22] 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 who were taking efavirenz, maraviroc, or NVP had an increased risk of liver enzyme elevation.[23]

Two systematic reviews and a small case-control study additionally indicate that pregnancy appears to increase the risk of cutaneous events, such as Stevens-Johnson. The systematic review discussed above also reported nonsignificant trends toward increased risk of cutaneous events (odds ratio [OR] 1.1; 95% CI, 0.8–1.6) and severe cutaneous adverse events in pregnant women with CD4 counts ≥250 cell/mm³ (OR 1.4; 95% CI, 0.8–2.4).[20] Another systematic review reported a significant association between increased toxicity risk and the initiation of NVP-based therapy during pregnancy in women with CD4 counts ≥250 cells/mm³.[24] A case-control study (6 cases, 30 controls) in South Africa reported that pregnancy increased the risk of Stevens-Johnson syndrome (OR 14.28; $P = 0.006$; 95% CI, 1.54–131.82).[25] NVP (as a component of a combination regimen) should be initiated in pregnant women with CD4 counts ≥250 cells/mm^3 only if the benefit clearly outweighs the risk. Women with CD4 counts <250 cells/mm^3 can receive NVP-based regimens, and women who become pregnant while taking NVP and who are tolerating their regimens well can continue using those regimens, regardless of their CD4 counts.

Because pregnancy itself can mimic some of the early symptoms of hepatotoxicity (i.e., pregnancy-related nausea and vomiting), health care providers caring for pregnant women who are receiving NVP 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.[26] Transaminase levels should be checked in all women who develop a rash while receiving NVP. 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 taking NVP and not receive the drug in the future.

In a retrospective study at eight government hospitals in Botswana, women who received ART regimens that contained NVP were more likely to experience certain adverse events than women on ART regimens that did not contain NVP, including hypertension (30% vs. 16%), severe hypertension (3.3% vs. 1.2%), gestational hypertension (18% vs. 10%), and early gestational hypertension (12% vs. 7%).[27]

Excerpt from Table 10

Generic Name (Abbreviation) *Trade Name*	**Formulation**	**Dosing Recommendations**[a]	**Use in Pregnancy**
Nevirapine (NVP) *Viramune* *Viramune XR* **Note:** Generic products are available for some formulations.	**NVP (Viramune)** *Tablet:* • 200 mg[d] *Oral Suspension:* • 50 mg/5 mL[d] **Viramune XR** *Tablets:* • 100 mg • 400 mg[d]	**Standard Adult Doses** • NVP 200 mg once daily (using Viramune immediate release) for a 14-day lead-in period; thereafter, NVP 200 mg twice daily or 400 mg (using 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 the lead-in period, continue lead-in dosing until rash resolves, but administer for ≤28 days total. **Pregnancy** *PKs in Pregnancy:* • PKs of immediate-release tablets not significantly altered in pregnancy. • No data 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 twofold increase in cardiovascular and genitourinary defects). There is an increased risk of symptomatic liver toxicity when first initiating therapy in women with CD4 counts ≥250/mm^3. Liver toxicity is often associated with a rash and can be fatal. Pregnancy does not appear to increase this risk. NVP should be initiated in pregnant women with CD4 counts ≥250 cells/mm^3 only if benefit clearly outweighs risk. There is a potential increased risk of life-threatening hepatotoxicity in women with high CD4 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 taking those regimens, regardless of their CD4 counts.

[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
[d] Generic product available

Key: ARV = antiretroviral; CD4 = CD4 T lymphocyte; NVP = nevirapine; PK = pharmacokinetic; XR = extended release

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Rilpivirine (Edurant, RPV)

(Last updated December 29, 2020; last reviewed December 29, 2020)

Animal Studies

Carcinogenicity

Rilpivirine (RPV) was neither mutagenic nor clastogenic in a series of *in vitro* and *in vivo* screening tests. RPV was not carcinogenic in rats when administered at doses that resulted in drug exposures that were three times higher than those seen in humans who received the recommended 25-mg dose of RPV once daily. Hepatocellular neoplasms were observed in both male and female mice at doses that produced exposures 21 times higher than human therapeutic exposure; however, whether these hepatocellular findings in mice are relevant to humans is unclear.[1]

Reproduction/Fertility

No effect on fertility was observed when RPV was administered to rats at a dose of 400 mg/kg per day, which produced systemic drug exposure that was 40 times the exposure seen in humans who received the recommended dose.[1]

Teratogenicity/Adverse Pregnancy Outcomes

Rat and rabbit dams treated with RPV during pregnancy showed no evidence of embryonic or fetal toxicity, and reproductive function was unaffected. RPV exposures were 15 times higher (in rats) and 70 times higher (in rabbits) than the exposures observed in humans who received the recommended dose of RPV 25 mg once daily. When rats were administered RPV 400 mg/kg per day through lactation, no drug-related adverse effects were seen in the offspring.[1]

Placental and Breast Milk Passage

Studies in lactating rats and their offspring indicate that RPV is present in rat milk.[1]

Human Studies in Pregnancy

Pharmacokinetics

A study that presented pharmacokinetic (PK) and safety data from 32 pregnant women with HIV found that median RPV 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 RPV concentrations were significantly lower at 14 visits where the women had detectable HIV RNA (30 ng/mL) than at 62 visits where they had undetectable HIV RNA (63 ng/mL). Ninety percent of women had trough concentrations above the protein-adjusted EC_{90} for RPV. PK parameters between participants were 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] Schalkwijk et al. recommended the use of therapeutic drug monitoring during the third trimester.[3] Furthermore, they recommended that providers remind patients to take RPV doses with meals. A third study reported that total RPV exposure decreased by approximately 30%, and unbound RPV levels decreased by 22% to 25% during pregnancy in 15 women compared with the RPV exposures seen in the same women postpartum.[4] Cervicovaginal fluid RPV concentrations were described in a study of 24 women who took RPV daily during pregnancy and postpartum. RPV steady-state concentrations in the cervicovaginal fluid of these women were similar to the concentrations seen in their plasma. The RPV cervicovaginal fluid-to-plasma AUC ratio was higher during pregnancy than postpartum.[5] Although RPV plasma concentration is reduced during pregnancy, higher-than-standard doses of RPV have not been studied, and not enough data are available to recommend a dosing change during pregnancy. In the ANRS-EPF French Perinatal Cohort, 184 virologically suppressed women who switched to RPV-free regimens during pregnancy had a higher risk of viral rebound compared with 63 women who continued RPV during pregnancy (20% vs. 0%, $P = 0.046$). Delivery outcomes

were similar between groups.[6] For considerations regarding switching antiretroviral drugs during pregnancy, see Pregnant Women with HIV Who Are Currently Receiving Antiretroviral Therapy. Pregnant women who receive the standard dose of RPV should have their viral loads monitored more frequently than women who are not receiving RPV (see Monitoring of the Woman and Fetus During Pregnancy).

Placental and Breast Milk Passage

One of the PK and safety studies described above included data on RPV concentration at delivery for 21 mother–infant pairs, with a median cord blood RPV plasma concentration of 29.2 ng/mL (range <10.0 to 101.5 ng/mL), a median maternal delivery plasma RPV concentration of 55.2 ng/mL (range <10.0 to 233.8 ng/mL), and a median cord blood-to-maternal-plasma ratio of 0.55 (range 0.3–0.8).[2] Osiyemi et al. found that the median ratio of cord blood-to-maternal-plasma concentration of total RPV in eight women was 0.55 (range 0.43–0.98).[4] Similarly, Schalkwijk et al. found a median cord blood-to-maternal-plasma ratio of 0.5 (range 0.35–0.81) in five women.[3] An *ex vivo* human cotyledon perfusion model also showed that RPV crosses the placenta, with fetal transfer rates ranging from 17% to 37%.[7,8] No data exist on whether RPV is excreted in breast milk in humans.

Teratogenicity/Adverse Pregnancy Outcomes

The Antiretroviral Pregnancy Registry had monitored sufficient numbers of first-trimester exposures to RPV to detect at least a twofold increase in the risk of overall birth defects. No such increase in the risk of birth defects has been observed with RPV. Among the cases of first-trimester exposures to RPV that have been reported to the Antiretroviral Pregnancy Registry, the prevalence of birth defects was 1.4% (7 infants out of 495 live births; 95% confidence interval, 0.6% to 2.9%) compared with a 2.7% total prevalence in the U.S. population, according to Centers for Disease Control and Prevention surveillance.[9]

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 the individual drug components of the FDC tablet during pregnancy.

Generic Name (Abbreviation) *Trade Name*	**Formulation**	**Dosing Recommendations**[a]	**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/ FTC 200 mg/ TDF 300 mg tablet **RPV/DTG (Juluca):** • RPV 25 mg/ DTG 50 mg tablet **RPV/FTC/TAF (Odefsey):** • RPV 25 mg/ FTC 200 mg/ TAF 25 mg tablet	**Standard Adult Doses** *RPV (Edurant):* • RPV 25 mg once daily with a meal *RPV/FTC/TDF (Complera):* • One tablet once daily with a meal *RPV/DTG (Juluca):* • One tablet once daily with a meal *RPV/FTC/TAF (Odefsey):* • One tablet once daily with a meal **Pregnancy** *PKs in Pregnancy:* • RPV PKs are highly variable during pregnancy. RPV AUC and trough concentrations are 20% to 50% lower in pregnancy than postpartum. Although most pregnant women exceeded target exposure, those with detectable viral loads had lower RPV troughs. *Dosing in Pregnancy:* • Although RPV plasma concentration is reduced during pregnancy, higher-than-standard doses have not been studied, and not enough data are available to recommend a dosing change during pregnancy. Pregnant women receiving standard dosing should have their viral loads monitored more frequently than women who are not receiving RPV. For guidance about the 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 twofold increase in overall birth defects). Two-drug regimens (e.g., the RPV/DTG FDC) **are not recommended** for use 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 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: ARV = antiretroviral; AUC = area under the curve; DTG = dolutegravir; FDC = fixed-dose combination; FTC = emtricitabine; PK = pharmacokinetic; RPV = rilpivirine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

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Atazanavir (Reyataz, ATV)

(Last updated December 29, 2020; last reviewed December 29, 2020)

Animal Studies

Carcinogenicity

In *in vitro* and *in vivo* assays, atazanavir (ATV) shows evidence of clastogenicity but not mutagenicity. Two-year carcinogenicity studies in mice and rats were conducted with ATV. In female mice, the incidence of benign hepatocellular adenomas increased at systemic exposures that were 2.8-fold to 2.9-fold higher than those seen in humans who received the recommended therapeutic dose (ATV 300 mg boosted with ritonavir [RTV] 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 rats 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 ATV on reproduction or fertility in male and female rodents was observed at drug exposure levels (as measured by area under the curve [AUC]) 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 ATV exposure levels (as measured by AUC) that were 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 (through pregnancy and lactation) that produced systemic ATV exposure that was 1.3 times the human exposure resulted in reversible neonatal growth retardation. 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 separate study demonstrated an association between maternal protease inhibitor (PI) use (including the use of ATV) and lower progesterone levels, which correlated with lower birthweight in mice.[2, 3]

Placental and Breast Milk Passage

ATV maternal-to-fetal (transplacental) transfer is reduced, possibly because ATV is a substrate of the p-glycoprotein, which is an ATP-binding cassette transporter responsible for drug efflux across the placenta.[4]

ATV is excreted in the milk of lactating rats. Maternal ATV use in rats that produced systemic ATV exposure that was 1.3 times the human exposure 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.[5] Overall, most pregnant women achieved undetectable HIV RNA at the time of delivery in these studies.[1,6–10]

In studies that evaluated full PK profiles of daily ATV/r 300 mg/100 mg during pregnancy, the ATV AUC was lower during pregnancy than the ATV AUC reported in other studies of nonpregnant adults with HIV.[6,8,9,11] In one of the studies, there was no difference in the ATV AUC during pregnancy and postpartum, but the AUC at both times was lower than the AUC observed in nonpregnant historic controls with HIV.[8] In the other studies, the ATV AUC was lower during pregnancy than it was in the same patients postpartum and in nonpregnant control populations.[6,7,9,11] Intracellular ATV levels in women taking ATV/r 300 mg/100 mg appear stable

throughout pregnancy.[12] Genetic variants appear to partially explain the interpatient variability in third-trimester ATV exposure seen in pregnant women who receive ATV/r.[13]

ATV/r combined with tenofovir disoproxil fumarate (TDF) and emtricitabine provides a complete, once-daily antiretroviral therapy regimen for pregnant women. However, the ATV AUC of pregnant women in the third trimester who received concomitant TDF was 30% lower than the ATV AUC of women who were not receiving concomitant TDF, an effect similar to that seen in nonpregnant adults.[9,11] The magnitude of the increase in ATV AUC postpartum relative to ATV AUC in the third trimester in women taking concomitant TDF was similar to that in women not taking concomitant TDF.[9] On the other hand, a smaller PK study demonstrated that concomitant TDF did not result in a lower ATV AUC or a higher risk of ATV trough concentrations <0.15 mg/L (the target trough concentration for antiretroviral-naive patients) in pregnant women during their third trimester.[14] In a therapeutic drug monitoring (TDM) study of 103 women (most of whom were African) in Paris, the proportions of women with an ATV trough concentration of <0.15 mg/L were similar for women who did and women who did not take concomitant TDF.[10]

In studies that evaluated the use of once-daily ATV/r 400 mg/100 mg during pregnancy,[6,7] pregnant women who received this increased dose without TDF had an ATV AUC that was equivalent to the ATV AUC seen in historic nonpregnant controls with HIV who received the standard ATV 300 mg dose without TDF. Pregnant women who received the increased ATV 400 mg dose with TDF had an ATV AUC equivalent to that seen in nonpregnant patients with HIV who received the standard ATV 300 mg dose with TDF.[6,7] Although some experts recommend an increased dose of ATV for all women during the second and third trimesters, the package insert recommends the use of an increased dose of ATV during the second and third trimesters only for antiretroviral-experienced pregnant women who also are receiving either TDF or an H2-receptor antagonist. TDM of ATV 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 Antiretroviral Guidelines.

The pharmacoenhancing effect of cobicistat (COBI) on ATV is impacted during pregnancy. Pregnant women who received ATV boosted with COBI had trough ATV concentrations that were 80% and 85% lower during the second and third trimesters, respectively, than historical ATV trough concentrations in nonpregnant adults with HIV.[16] Concomitant use of ATV and COBI **is not recommended** during pregnancy because of these substantial reductions in drug exposures (see Cobicistat).[17]

Placental and Breast Milk Passage

In studies of women receiving ATV/r combination therapy during pregnancy, cord blood ATV concentration averaged 13% to 21% of maternal serum levels at delivery.[1,8,9]

In a study of three women, the median ratio of breast milk ATV concentration to plasma ATV concentration was 0.13.[18]

Teratogenicity/Adverse Pregnancy Outcomes

In a multicenter study that evaluated a U.S. cohort of children who were exposed to HIV but who did not contract HIV, first-trimester ATV 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 ATV 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 ATV in humans to be able to detect at least a 1.5-fold increase in the risk of overall birth defects and at least a twofold 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 ATV. Among the cases of first-trimester ATV exposure that have

been reported to the Antiretroviral Pregnancy Registry, the prevalence of birth defects was 2.2% (31 of 1,403 live births; 95% confidence interval [CI], 1.5% to 3.1%) 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 ATV-related inhibition of the hepatic uridine diphosphate glucuronosyltransferase (UGT) enzyme occurs frequently during treatment with ATV, 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 ATV during pregnancy.[1,6,8,9,23–25] In some studies, neonatal bilirubin elevations that require treatment with phototherapy occur more frequently after prenatal ATV 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 among patients within a study and across different studies.[23,24] Elevated neonatal bilirubin in neonates exposed to ATV is not associated with UGT-1 genotypes that have been linked to decreased UGT function.[25]

In an evaluation of neurodevelopmental outcomes in 374 infants aged 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 ATV than for infants who were exposed to other drugs.[26,27] In a study of language assessments among 792 children aged 1 to 2 years who were exposed to HIV but who did not contract HIV, children with ATV 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 ATV exposure, but this 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 was reported in 3 of 38 ATV-exposed infants who had 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 report of infant hypoglycemia is similar to a prior report in which 2 of 14 infants who were exposed to PIs (i.e., nelfinavir, saquinavir, or indinavir) developed hypoglycemia during the first day of life; both infants with hypoglycemia had been exposed to nelfinavir.[29]

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**
Atazanavir (ATV) *Reyataz* **Note:** Generic products are available for some formulations. **Note:** ATV must be combined with low-dose RTV boosting in pregnancy. **(ATV/c)** *Evotaz*	**ATV (Reyataz)** *Capsules:* • 100 mg (generic product only) • 150 mg[d] • 200 mg[d] • 300 mg[d] *Oral Powder:* • 50 mg packet **ATV/c (Evotaz):** • ATV 300 mg/ COBI 150-mg tablet	**Standard Adult Doses** *In 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. *In ARV-Naive Patients With RTV Boosting:* • ATV/r 300 mg/100 mg once daily with food • When combined with EFV in ARV-naive patients: ATV/r 400 mg/100 mg once daily with food *In ARV-Experienced Patients:* • ATV 300 mg plus RTV 100 mg once daily with food • **Do not use** with PPIs or EFV. *In ARV-Experienced Patients Who Are Receiving an H2-Receptor Antagonist:* • ATV/r 300/100 mg once daily with food *In ARV-Experienced Patients Who Are Receiving an H2-Receptor Antagonist and TDF:* • ATV/r 400 mg/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.	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 with RTV boosting in pregnancy. Effect of *in utero* ATV exposure on infant indirect bilirubin levels is unclear. Nonpathologic elevations of neonatal bilirubin 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. Use of ATV/c **is not recommended** during pregnancy. See Recommendations for Use of Antiretroviral Drugs During Pregnancy, Table 4 and Table 5 for discussions about avoiding the use of ATV/c during pregnancy.

Generic Name (Abbreviation) *Trade Name*	**Formulation**	**Dosing Recommendations**[a]	**Use in Pregnancy**
		ATV/c (Evotaz): • One tablet once daily with food **Pregnancy** *PKs in Pregnancy* *ATV (Reyataz):* • ATV concentrations are reduced during pregnancy, and they are further reduced when ATV is given concomitantly with TDF or an H2-receptor antagonist. *ATV/c (Evotaz):* • Use of ATV/c **is not recommended** during pregnancy, because ATV trough concentrations are 80% to 85% lower than the ATV concentrations seen in nonpregnant adults. *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 who are taking TDF and an H2-receptor antagonist. • Use of an increased dose (ATV/r 400 mg/100 mg once daily with food) during the second and third trimesters results in plasma ATV concentrations equivalent to those seen in nonpregnant adults receiving standard dosing. Although some experts recommend increased ATV dosing in all women during the second and third trimesters, the package insert recommends increased	

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations[a]	Use in Pregnancy
		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/c (Evotaz):* • Insufficient data to make dosing recommendation in pregnancy (see COBI). For guidance about the use of combination products in pregnancy, please see the specific sections on other components (i.e., COBI).	

[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
[d] Generic product available.

Key: ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; COBI = cobicistat; EFV = efavirenz; FDC = fixed-dose combination; PK = pharmacokinetic; PPI = proton pump inhibitor; RTV = ritonavir; TDF = tenofovir disoproxil fumarate

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Darunavir (Prezista, DRV)

(Last updated December 29, 2020; last reviewed December 29, 2020)

Animal Studies

Carcinogenicity

Darunavir (DRV) 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 was 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 DRV to rats caused hepatic microsomal enzyme induction and increased thyroid hormone elimination; this predisposes rats, but not humans, to thyroid neoplasms. At the highest tested doses, the systemic exposures to DRV (based on area under the curve [AUC]) were between 0.4-fold and 0.7-fold higher (in mice) and 0.7-fold and onefold higher (in rats) than the exposures observed in humans who received the recommended therapeutic doses of darunavir/ritonavir (DRV/r) 600 mg/100 mg twice daily or DRV/r 800 mg/100 mg once daily.[1]

Reproduction/Fertility

No effects on fertility or early embryonic development were seen in rats that received DRV.[1]

Teratogenicity/Adverse Pregnancy Outcomes

No embryotoxicity or teratogenicity was seen in rats that experienced DRV exposures (based on AUC) that were threefold higher than those seen in humans who received recommended DRV/r doses; likewise, no embryotoxicity or teratogenicity was seen in mice and rabbits that experienced DRV exposures that were less than onefold those seen in humans who received the recommended DRV/r doses. Administering DRV alone or with ritonavir to female rats during lactation resulted in a reduction in pup weight gain during a rat prenatal and postnatal development study. DRV/r **is not recommended** for pediatric patients aged <3 years due to the toxicity and mortality observed in juvenile rats dosed with DRV up to 23 to 26 days of age.[1]

Placental and Breast Milk Passage

No animal studies of placental passage of DRV have been reported. Passage of DRV into breast milk has been noted in rats.[1]

Human Studies in Pregnancy

Pharmacokinetics

Several studies of the pharmacokinetics (PKs) of DRV/r during pregnancy have been completed.[2–5] DRV plasma AUC during the third trimester, compared with postpartum, 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.[2–6] DRV trough concentration during the third trimester, compared with postpartum, 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.[3–5]

Three studies measured DRV protein binding during pregnancy. One study found no change in DRV protein binding during the third trimester. The other two studies reported decreased unbound DRV concentrations during pregnancy that were not considered clinically significant.[2,4,5] Because of the low DRV trough levels that occur with once-daily dosing, twice-daily dosing of DRV is recommended during pregnancy, especially for antiretroviral-experienced patients.[3,7] The Food and Drug Administration recommends the use of once-daily DRV/r 800 mg/100 mg dosing 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.[1] After reviewing the 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 DRV dose administered twice daily did not increase DRV exposure in pregnant women; use of this increased, twice-daily DRV dose during pregnancy **is not recommended.**[6]

Data are available from two studies describing the PK and safety of cobicistat (COBI) boosting of DRV during pregnancy. In both studies, darunavir/cobicistat (DRV/c) 800 mg/150 mg was administered during pregnancy.[8,9] In a study of seven pregnant women with HIV who were treated with DRV/c, no drug-related adverse events were observed. When PK parameters during the second and third trimesters were compared to postpartum PK parameters, total DRV AUC was reduced by 56% and 50%, and trough concentration was reduced by 92% and 89%, respectively. Unbound DRV concentrations decreased during the second and third trimesters of pregnancy compared to postpartum, with AUC 45% and 40% lower and trough concentration 92% and 88% lower, respectively. COBI exposures were lower during pregnancy, with reductions during the second and third trimesters of 63% and 49% for AUC and 83% and 83% for trough concentration, compared to postpartum. Six of seven participants remained virally suppressed during pregnancy. One woman who was not suppressed was found to be nonadherent to treatment, based on pill count. No infants born to study mothers contracted HIV.[9] On the basis of 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 DRV and COBI during pregnancy.[10] These findings are consistent with a larger study of 29 pregnant women who received the DRV/c combination. When PK parameters during the second and third trimesters were compared with postpartum PK parameters in these women, total DRV AUC was reduced by 33% and 48%, respectively, and DRV trough concentrations were reduced by 71% and 75%, respectively.[8]

Placental and Breast Milk Passage

In an *ex vivo* human cotyledon perfusion model, the mean fetal transfer rate of DRV was 15%.[11] In 5 studies that reported data from between 6 and 14 subjects each, the median ratio of DRV concentration in cord blood to DRV concentration in maternal delivery plasma ranged from 13% to 24%.[2–4,9,12] No data are available that describe the breast milk passage of DRV in humans.

Teratogenicity/Adverse Pregnancy Outcomes

The Antiretroviral Pregnancy Registry has monitored sufficient numbers of first-trimester exposures to DRV to allow detection of at least a twofold increase in the risk of overall birth defects. No such increase in the risk of birth defects has been observed with DRV. Among cases of first-trimester DRV exposure that have been reported to the Antiretroviral Pregnancy Registry, the prevalence of birth defects was 3.6% (22 of 604 live births; 95% confidence interval, 2.3% to 5.5%) compared with a 2.7% total prevalence in the U.S. population, based on Centers for Disease Control and Prevention surveillance.[13]

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**
Darunavir (DRV) *Prezista* **Note:** Must be combined with low-dose RTV or COBI boosting. (DRV/c) *Prezcobix* (DRV/c/FTC/TAF) *Symtuza*	**DRV (Prezista)** *Tablet:* • 75 mg • 150 mg • 600 mg • 800 mg *Oral Suspension:* • 100 mg/mL **DRV/c (Prezcobix):** • DRV/c 800 mg/ 150 mg tablet **DRV/c/FTC/TAF (Symtuza):** • DRV 800 mg/ COBI 150 mg/ FTC 200 mg/ TAF 10 mg tablet	**Standard Adult Doses** *ARV-Naive Patients:* • DRV/r 800 mg/ 100 mg once daily with food • DRV/c 800 mg/ 150 mg once daily with food *ARV-Experienced Patients* <u>If Patient Has No DRV Resistance Mutations:</u> • DRV/r 800 mg/ 100 mg once daily with food • DRV/c 800 mg/ 150 mg once daily with food <u>If Any DRV Resistance Mutations Are Present:</u> • DRV/r 600 mg/ 100 mg twice daily with food DRV/c *(Prezcobix)*: • One tablet once daily with food DRV/c/FTC/TAF *(Symtuza)*: • One tablet once daily with food **Pregnancy** *PKs in Pregnancy:* • Decreased exposure in pregnancy with use of DRV/r.	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 **<u>does not recommend</u>** once-daily dosing with DRV/r during pregnancy or the use of DRV/c during pregnancy. If a DRV/c regimen is continued during pregnancy, viral load should be monitored frequently.

Generic Name (Abbreviation) *Trade Name*	**Formulation**	**Dosing** • **Recommendations**[a]	**Use in Pregnancy**
		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/r 600 mg/100 mg with food) is recommended for all pregnant women. • Increased, twice-daily DRV dose (DRV/r 800 mg/100 mg with food) during pregnancy does not result in an increase in DRV exposure and **is not recommended.** For guidance about the use of combination products in pregnancy, please see the specific sections on other components (i.e., COBI, FTC, TAF).	

[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: 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

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Lopinavir/Ritonavir (Kaletra, LPV/r)

(Last updated December 29, 2020; last reviewed December 29, 2020)

Animal Studies

Carcinogenicity

Neither lopinavir (LPV) nor ritonavir (RTV) was found to be mutagenic or clastogenic in a battery of *in vitro* and *in vivo* assays. The lopinavir/ritonavir (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 an increased combined incidence of hepatocellular adenomas plus carcinoma in male and female mice and in male rats at doses that produced approximately 1.6 times to 2.2 times (in mice) and 0.5 times (in rats) the exposure seen in humans who received the recommended therapeutic dose of LPV/r 400 mg/100 mg (exposure was based on area under the curve [AUC]$_{0–24hr}$ measurement). Administration of LPV/r did not cause a statistically significant increase in the 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 LPV and RTV at a 2:1 ratio. These rats experienced exposures that were approximately 0.7-fold (for LPV) and 1.8-fold (for RTV) the exposures seen in humans who received the recommended therapeutic dose.[1]

Teratogenicity/Adverse Pregnancy Outcomes

No teratogenicity has been reported in studies where LPV/r was administered to pregnant rats and rabbits. In rats treated with a maternally toxic dosage (LPV/r 100 mg/kg and 50 mg/kg per day), embryonic and fetal developmental toxicities (i.e., 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 LPV) and 1.8-fold (for RTV) the exposures observed in humans who received 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/kg and 20 mg/kg per day or greater. In rabbits, no embryonic or fetal developmental toxicities were observed with a maternally toxic dose, when drug exposure was 0.6-fold (for LPV) and one-fold (for RTV) the exposures seen in humans who received the recommended therapeutic dose.[1] In a study of pregnant rats receiving chronic administration of zidovudine (ZDV), LPV, and RTV, maternal body weight gain was significantly reduced compared to weight gain in rats that received no antiretroviral (ARV) drugs, but no adverse effects were observed in fetuses.[2] In pregnant mice, the use of RTV, LPV, and atazanavir was 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 LPV in animals.[1]

Human Studies in Pregnancy

Pharmacokinetics

The original capsule formulation of LPV/r has been replaced by a heat-stable tablet formulation that 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) that used either the capsule or tablet formulations in pregnant women have demonstrated a reduction in LPV plasma concentrations during pregnancy of around 30% compared with those seen in nonpregnant adults.[6–8] A further 33% reduction in LPV exposure was demonstrated in food-insecure, malnourished pregnant women in Uganda compared to well-nourished, historical pregnant controls. The authors

attributed this reduction to decreased bioavailability of LPV.[9] Increasing the dose of LPV/r during pregnancy to 600 mg/150 mg using the tablet formulation results in LPV plasma concentrations that are equivalent to those seen in nonpregnant adults who received standard doses.[10,11]

Clinical experience suggests that most, but not all, pregnant women who receive standard LPV/r tablet dosing during pregnancy will have trough LPV concentrations that exceed 1.0 mcg/mL, the usual target for trough concentration in therapeutic drug monitoring programs for ARV-naive subjects. However, higher trough concentrations are recommended for protease inhibitor (PI)-experienced subjects, and some PI-experienced women who take the standard LPV/r dose during pregnancy will not achieve these concentrations.[4,7] A population PK study of LPV/r in 154 pregnant women demonstrated that body weight influences LPV clearance and volume of distribution; 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 the LPV concentrations observed in pregnant women who were taking the more bioavailable tablet formulation and those seen in nonpregnant adults taking the original capsule formulation.[13] In one study of 29 women, LPV 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 LPV concentration associated with pregnancy.[14] In a study of 12 women, total LPV exposure was significantly decreased throughout pregnancy, but the AUC and concentration at 12 hours post dose (C_{12h}) for unbound LPV did not differ throughout pregnancy, even with an increased dose of LPV/r 500 mg/125 mg. Modeling of these data showed that standard dosing should be effective during pregnancy in people with susceptible virus.[15,16] A population PK study found a 39% increase in total LPV clearance during pregnancy, but measured unbound LPV 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 during 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 possible, when standard doses of LPV/r are used during pregnancy, virologic response and LPV drug concentrations should be monitored. Instead of using 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 once-daily dosing produces adequate drug levels.

Placental and Breast Milk Passage

LPV crosses the human placenta; in the P1026s PK study (a Phase IV PK study of selected ARV drugs currently used in pregnant women with HIV), the average ratio of LPV concentration in cord blood to LPV concentration in maternal plasma at delivery was 0.20 ± 0.13. In contrast, in a study of 51 mother–infant pairs in Uganda in

which the mother received LPV/r during pregnancy and breastfeeding, infant LPV plasma levels at delivery and LPV hair levels at age 12 weeks suggested significant *in utero* transfer: 41% of infants had detectable plasma LPV concentrations at birth, and mean infant-to-maternal-hair concentrations at 12 weeks postpartum were 0.87 for LPV.[19] However, transfer during breastfeeding was not observed, and no infant had detectable plasma LPV levels at 12 weeks. LPV concentrations in human breast milk are very low to undetectable, and LPV concentrations in breastfeeding infants whose mothers received LPV are not clinically significant.[19-24]

Teratogenicity/Adverse Pregnancy Outcomes

The French Perinatal Cohort found no association between birth defects and LPV or RTV use with 85% power to detect a 1.5-fold increase.[25] The Pediatric HIV/AIDS Cohort Study found no association between LPV and congenital anomalies.[26] Surveillance data from the United Kingdom and Ireland during a 10-year period showed that among the infants born after 4,609 LPV-exposed pregnancies, 134 infants had an identified birth defect, resulting in an overall congenital abnormality rate of 2.9%. This rate is comparable to rates of congenital abnormalities observed in populations without HIV.[27] The Antiretroviral Pregnancy Registry has monitored sufficient numbers of first-trimester exposures to LPV/r to detect at least a 1.5-fold increase in risk of overall birth defects and at least a twofold increase in risk of birth defects in the cardiovascular and genitourinary systems (the more common classes of birth defects in the general population). No such increase in the risk of 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 infants out of 1,431 live births; 95% confidence interval, 1.4% to 3.0%) compared with a 2.7% total prevalence in the U.S. population based on the Centers for Disease Control and Prevention surveillance.[28]

In the Promoting Maternal and Infant Survival Everywhere (PROMISE) study, administering LPV/r with ZDV plus lamivudine (3TC) or with tenofovir disoproxil fumarate plus 3TC resulted in transmission rates that were lower than those seen with ZDV alone; however, the use of these LPV/r-containing regimens increased the incidence of low birth weight (<2,500 g).[29] Compared to ZDV alone, ZDV plus 3TC plus LPV/r was associated with increased rates of preterm delivery (<37 weeks). The Surveillance Monitoring for ART Toxicities (SMARTT) cohort of the Pediatric HIV/AIDS Cohort Study (PHACS) also found an increased rate of preterm birth among women who received PI-based ARV therapy, although not with specific individual drugs.[30] Similarly, a study in China found that women who received PI-based regimens had higher rates of preterm birth than those who received non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens.[31] 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; after adjusting for other factors, the use of LPV/r carried a greater risk of preterm delivery than the use of NNRTI-based regimens.[32] 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.

Other Safety Information

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 function and kidney excretory function in newborns can lead to accumulation of LPV and of alcohol and propylene glycol, resulting in adverse events (e.g., serious cardiac, renal, metabolic, or respiratory problems). For more information about LPV/r use in newborns, refer to Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection.[33,34]

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**
Lopinavir/ Ritonavir (LPV/r) *Kaletra*	**LPV/r (Kaletra)** *Tablets:* • LPV/r 200 mg/50 mg • LPV/r 100 mg/25 mg *Oral Solution:* • Each 5 mL contains LPV/r 400 mg/100 mg	**Standard Adult Doses** • 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 meal. *With EFV or NVP in PI-Naive or PI-Experienced Patients:* • LPV/r 500 mg/125 mg tablets twice daily without regard to meals (use a combination of two LPV/r 200 mg/50 mg tablets and one LPV/r 100 mg/25 mg tablet), *or* • LPV/r 520 mg/130 mg oral solution (6.5 mL) twice daily with food **Pregnancy** *PKs in Pregnancy:* • With twice-daily dosing, LPV exposure is reduced in pregnant women who receive 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.	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.

		• 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. • When standard dosing is used, monitor virologic response and, if possible, LPV drug levels.	

[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: EFV = efavirenz; FDC = fixed-dose combination; LPV = lopinavir; LPV/r = lopinavir/ritonavir; NVP = nevirapine; PI = protease inhibitor; PK = pharmacokinetic; RTV = ritonavir

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Fostemsavir (Rukobia, FTR)

(Last updated December 29, 2020; last reviewed December 29, 2020)

Fostemsavir (FTR) is a prodrug of the active drug temsavir, a gp120-directed attachment inhibitor.

Animal Studies

Carcinogenicity

Temsavir was not genotoxic or mutagenic *in vitro*.[1]

Reproduction/Fertility

FTR did not adversely affect the fertility of male or female rats at temsavir exposures approximately 10 times (males) and 186 times (females) higher than those achieved in humans at the recommended dose.[1]

Teratogenicity/Adverse Pregnancy Outcomes

No adverse embryo-fetal effects were observed in rats and rabbits at temsavir exposures of approximately 180 (rats) and 30 (rabbits) times the exposure in humans at the recommended dose. Maternal toxicity and increased embryonic death were observed in rabbits at temsavir exposures approximately 60 times those in humans. In a rat study conducted at drug exposures approximately 200 times those in humans, fetal abnormalities (cleft palate, open eyes, shortened snout, microstomia, misaligned mouth/jaw, and protruding tongue) and reductions in fetal body weights occurred in the presence of maternal toxicity.[1]

Placental and Breast Milk Passage

When FTR was administered to pregnant rats, FTR-related drug materials (e.g., temsavir or metabolites) crossed the placenta and were detectable in fetal tissue. Temsavir is excreted in rat milk and was present at concentrations similar to those measured in maternal plasma on day 11 postpartum.[1]

Human Studies in Pregnancy

Pharmacokinetics

No pharmacokinetic studies of FTR have been reported in pregnant women.

Placental and Breast Milk Passage

No data are available on placental or breast milk passage of FTR in humans.

Teratogenicity/Adverse Pregnancy Outcomes

No data are available to inform the risk for birth defects following exposure to FTR.

Excerpt from Table 8

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations[a]	Use in Pregnancy
Fostemsavir (FTR) *Rukobia*	Extended Release Tablet: 600 mg	**Standard Adult Doses** *(FTR) Rukobia:* • FTR 600 mg twice daily with or without food Pregnancy *PK in Pregnancy:* • No PK studies in human pregnancy. *Dosing in Pregnancy:* • Insufficient data to make dosing recommendation	No human data are available regarding placental passage. A study in rats demonstrates placental passage of temsavir or other metabolites. 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 Antiretroviral Guidelines, Appendix B, Table 10).

Key: ARV = antiretroviral; FTR = fostemsavir; PK = pharmacokinetic

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Ibalizumab-uiyk (Trogarzo, IBA)

(Last updated December 29, 2020; last reviewed December 29, 2020)

Animal Studies

Carcinogenicity

Carcinogenicity and mutagenicity studies of ibalizumab-uiyk (IBA) have not been conducted.[1]

Reproduction/Fertility

Reproductive toxicology studies of IBA have not been conducted.[1]

Teratogenicity/Adverse Pregnancy Outcomes

Early embryonic development and embryo-fetal development studies with IBA have not been conducted.

Placental and Breast Milk Passage

No data are available on placental or breast milk passage of IBA in animals.

Human Studies in Pregnancy

Pharmacokinetics

No pharmacokinetic studies of IBA in pregnant women have been reported.

Placental and Breast Milk Passage

No data are available on placental or breast milk passage of IBA in humans. However, because monoclonal antibodies are transported across the placenta during pregnancy, IBA has the potential to be transmitted from the mother to the developing fetus. Human immunoglobulin G also is 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 currently available on the risk of birth defects in infants born to women who received IBA during pregnancy.

Excerpt from Table 8

Generic Name (Abbreviation) *Trade Name*	**Formulation**	**Dosing Recommendations**[a]	**Use in Pregnancy**
Ibalizumab-uiyk (IBA) *Trogarzo*	**IBA (Trogarzo):** • Solution for IV infusion is available in single-dose vials	**Standard Adult Doses** • IBA 2,000-mg loading dose, followed by IBA 800-mg maintenance doses administered every 2 weeks **Pregnancy** *PKs in Pregnancy:* • No PK studies in human pregnancy. *Dosing in Pregnancy:* • Insufficient data to make dosing recommendations.	No data available, but placental transfer of IBA, a monoclonal antibody, is possible. Insufficient data to assess for teratogenicity in humans.

[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).

Key: ARV = antiretroviral; IBA = ibalizumab; IV = intravenous; PK = pharmacokinetic

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1. Ibalizumab (Trogarzo) [package insert]. Food and Drug Administration. 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761065s008lbl.pdf.

Maraviroc (Selzentry, MVC)

(Last updated December 29, 2020; last reviewed December 29, 2020)

Animal Studies

Carcinogenicity

Maraviroc (MVC) was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests. Long-term carcinogenicity studies of MVC in rats showed no drug-related increases in tumor incidence at exposures that were approximately 11 times those observed in humans who received the therapeutic dose.

Reproduction/Fertility

No adverse effects were observed on the fertility of male or female rats at doses of MVC that produced exposures (based on 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 in animals that received MVC. During organogenesis in the rat and rabbit, systemic exposures to MVC (based on AUC) were approximately 20 times (in rats) and five times (in rabbits) the exposure seen in humans given the recommended 300 mg, twice-daily dose. In a rat prenatal and postnatal development study, maternal MVC AUC was about 14 times the exposure observed 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 MVC had poor placental transfer and rapid clearance from infant monkeys' blood.[2] Studies in lactating rats indicate that MVC is secreted extensively into rat milk.[1]

Human Studies in Pregnancy

Pharmacokinetics

A U.S./European intensive pharmacokinetic (PK) study measured 12-hour PK profiles in the third trimester and at least 2 weeks postpartum included 18 women who were taking MVC as part of clinical care.[3] Sixty-seven percent of the women in the study were taking MVC 150 mg twice daily with a protease inhibitor; 11% took MVC 300 mg twice daily, and 22% took an alternative regimen. The geometric mean ratio for third-trimester AUC versus postpartum AUC was 0.72; the geometric mean ratio for maximum MVC concentration in the third trimester versus maximum MVC concentration postpartum was 0.70. Despite an overall 30% decrease in MVC AUC during pregnancy and a 15% decrease in trough concentration (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 the postpartum period. These data suggest that the standard adult dose adjusted for concomitant antiretroviral (ARV) drugs is appropriate in pregnancy. A review of interactions between ARV drugs and oral contraceptives found that it is safe to coadminister oral contraceptives with MVC.[4]

Placental and Breast Milk Passage

An *ex vivo* human placental cotyledon perfusion model demonstrated minimal placental passage of MVC.[5] In a study of six mother–infant pairs, the median ratio of MVC concentration in cord blood to MVC concentration in maternal plasma was 0.33 (with a range of 0.03–0.56).[3] Whether MVC is secreted into human milk is unknown.

Teratogenicity/Adverse Pregnancy Outcomes

In a prospective study, 30 cases of first-trimester exposure to MVC have been reported to the Antiretroviral Pregnancy Registry to date,[6] and other first-trimester exposure data are available.[7] Data are still insufficient, however, to determine the risk of birth defects for infants who were exposed to MVC.

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.[8] MVC, efavirenz, and nevirapine were associated with an increased risk of liver enzyme elevation during pregnancy; the adjusted hazard ratio for MVC was 4.19 (1.34–13.1, $P = 0.01$). In a model that used human placental BeWo cells, MVC inhibited transplacental passage of two fluorescent organic cations, suggesting that it might influence placental drug transfer and cause drug–drug interactions.[9]

Excerpt from Table 10

Generic Name (Abbreviation) *Trade Name*	**Formulation**	**Dosing Recommendations**[a]	**Use in Pregnancy**
Maraviroc (MVC) *Selzentry*	**MVC (Selzentry)** *Tablets:* • 150 mg • 300 mg	**Standard Adult Doses** • MVC 300 mg twice daily with or without food. • MVC should be used only for patients with CCR5-tropic virus (and no X4-tropic virus). *Dose Adjustments:* • Increase to MVC 600 mg twice daily when used with the potent CYP3A inducers EFV, ETR, and rifampin. • Decrease to MVC 150 mg twice daily when used with CYP3A inhibitors, which includes all PIs except TPV/r and itraconazole. **Pregnancy** *PKs in Pregnancy:* • A PK study in human pregnancy demonstrated a 20 to 30% overall decrease in MVC AUC, but C_{trough} exceeded the recommended minimum concentration of 50 ng/mL. *Dosing in Pregnancy:* • Adjusting the standard adult MVC dose for concomitant use with ARV drugs seems appropriate.	Moderate placental transfer to fetus.[b] No evidence of teratogenicity in rats or rabbits; insufficient data to assess for teratogenicity in humans.

[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: ARV = antiretroviral; AUC = area under the curve; CCR5 = C-C chemokine receptor type 5; C_{trough} = trough concentration; CYP = cytochrome P; EFV = efavirenz; ETR = etravirine; MVC = maraviroc; PI = protease inhibitor; PK = pharmacokinetics; TPV/r = tipranavir/ritonavir

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Bictegravir (BIC)

(Last updated December 29, 2020; last reviewed December 29, 2020)

Animal Studies

Carcinogenicity

Bictegravir (BIC) has not been shown to be genotoxic or mutagenic *in vitro*.[1]

Reproduction/Fertility

BIC did not affect fertility, reproductive performance, or embryonic viability in male and female rats at exposures (based on area under the curve [AUC]) that were 29 times higher than those observed in humans who received the recommended dose.[1]

Teratogenicity/Adverse Pregnancy Outcomes

No adverse embryo-fetal effects were observed in rats and rabbits at BIC exposures (based on AUC) of up to about 36 times (in rats) and 0.6 times (in rabbits) the exposures observed in humans who received the recommended dose. Spontaneous abortion, increased clinical signs (e.g., fecal changes, thin body, cold-to-touch), and decreased body weight were observed in rabbits at a maternally toxic dose (i.e., 1,000 mg/kg per day, which produced an exposure approximately 1.4 times higher than the exposure observed in humans who received the recommended dose).[1]

Placental and Breast Milk Passage

No data are available on placental passage of BIC. In a pre- and postnatal development study conducted in rats, BIC was detected in the plasma of nursing rat pups on postnatal Day 10, likely due to the presence of BIC in milk.[1]

Human Studies in Pregnancy

Pharmacokinetics

No pharmacokinetics studies of BIC in pregnant women have been reported.

Placental and Breast Milk Passage

No data are available on placental or breast milk passage of BIC in humans.

Teratogenicity/Adverse Pregnancy Outcomes

The Antiretroviral Pregnancy Registry has prospectively monitored 40 pregnancies in women treated with BIC during periconception or pregnancy, including 25 infants with periconception exposure, 3 infants with later first-trimester exposure, and 12 infants with exposure in the second or third trimester. No cases of birth defects have been reported to date, but these data are insufficient to make conclusions regarding the safety of BIC during pregnancy.[2]

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**
Bictegravir/ Emtricitabine/ Tenofovir Alafenamide (BIC/FTC/TAF) *Biktarvy* **Note:** BIC is only available as part of an FDC tablet.	**BIC/FTC/TAF (Biktarvy):** • BIC 50 mg/FTC 200 mg/TAF 25 mg tablet	**Standard Adult Doses** One tablet once daily with or without food **Pregnancy** *PK in Pregnancy:* • No PK studies in human pregnancy. *Dosing in Pregnancy:* • Insufficient data to make dosing recommendations. 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. BIC can be taken with food at the same time as any preparation containing iron or calcium, including prenatal vitamins but should not be administered within 2 hours of these preparations when taken on an empty stomach. BIC can be taken at least 2 hours before or 6 hours after antacids containing aluminum or magnesium.

[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).

Key: ARV = antiretroviral; BIC = bictegravir; FDC = fixed-dose combination; FTC = emtricitabine; PK = pharmacokinetics; TAF = tenofovir alafenamide

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Dolutegravir (Tivicay, Tivicay PD, DTG)

(Last updated December 29, 2020; last reviewed December 29, 2020)

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.[6] Similar reductions in DTG exposure were seen in a study of 15 European pregnant women, with DTG AUC reduced by 14% and minimum concentration (C_{min}) by 26% during pregnancy compared to postpartum. DTG was well tolerated, and all participants had viral load below 50 copies/mL during the third trimester.[8]

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 maximum concentration (C_{max}) and no differences in the 24-hour concentration (C_{24h}) and AUC from 0 to 24 hours ($AUC_{0\text{-}24h}$) 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.[7] 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.[6,7] 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.[7]

Teratogenicity/Adverse Pregnancy Outcomes

The Antiretroviral Pregnancy Registry has monitored sufficient numbers of first-trimester exposures to DTG to detect at least a twofold increase in the risk of overall birth defects. No such increase in the risk of birth defects has been observed with DTG. Among the cases of first-trimester DTG exposure that have been reported to the Antiretroviral Pregnancy Registry as of January 31, 2020, the prevalence of birth defects was 3.5% (16 of 455 live births; 95% confidence interval, 2.0–5.7).[10] Supplemental data from the Antiretroviral Pregnancy Registry on central nervous system (CNS) birth defect outcomes in 740 live births to women who were exposed to DTG during periconception or pregnancy reported 4 infants with central nervous system birth defects: 2 of 382 infants with periconception exposure, 1 of 73 infants with exposure in the later first trimester, and 1 of 285 infants with second- or third-trimester exposure. One of the CNS defects was a neural tube defect (NTD) in an infant with periconception exposure; no encephalocele defects were reported.[10]

In the U.S. PK study in pregnant women discussed above, birth abnormalities were reported in 7 of 29 infants: 3 with normal variants; 1 with total anomalous pulmonary venous return (DTG was initiated at 16 weeks gestation); 1 with a polycystic right kidney (DTG was initiated at 11 weeks gestation); 1 with an isolated left renal cyst (DTG was initiated at 12 weeks gestation); and 1 with jitteriness and chin tremors (DTG was initiated at 28 weeks gestation).[6] 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.[7] In two reviews of clinical experience with pregnant women who received DTG, birth defects were noted in 4 infants born to 81 European women, in 2 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] Expanded and ongoing surveillance of birth outcomes in Botswana among pregnant women receiving antiretrovirals between April 1, 2019, and April 30, 2020, revealed a rate of NTDs with DTG use of 0.19% and a decrease in the NTD prevalence difference between women receiving DTG and those receiving other antiretrovirals from 0.20% in the earlier report to 0.09%, a difference that is not statistically significant.[15] 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. 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 C: Antiretroviral Counseling Guide for Health Care Providers: Pregnant Women and Women who are Trying to Conceive). 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* *Tivicay PD* (DTG/3TC) *Dovato* (DTG/RPV) *Juluca* (DTG/ABC/3TC) *Triumeq*	**DTG (Tivicay):** • DTG 10 mg, 25 mg, and 50 mg film coated tablets **DTG (Tivicay PD):** • DTG 5 mg dispersible tablet for oral suspension **DTG film-coated tablets and DTG dispersible tablets are not bioequivalent and are not interchangeable.** **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 50 mg tablet once daily, without regard to food DTG (Tivicay PD): • Six 5 mg tablets (30 mg) dissolved in water 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 50 mg tablet twice daily, without regard to food DTG (Tivicay PD): • Six 5 mg tablets (30 mg) dissolved in water twice daily, without regard to food *In INSTI-Experienced Patients* DTG (Tivicay): • One tablet twice daily, without regard to food	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.

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations[a]	Use in Pregnancy
		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).	To maximize DTG absorption, doses should not be administered within 2 hours of ingesting any preparation that contains such minerals 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

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Elvitegravir (EVG)

(Last updated December 29, 2020; last reviewed December 29, 2020)

Animal Studies

Carcinogenicity

In long-term studies of elvitegravir (EVG), no carcinogenicity was detected at exposures that were 14 fold higher (in mice and rats) and 27-fold higher (in rats) than those achieved in humans during systemic exposure to the recommended doses.[1]

Reproduction/Fertility

EVG did not affect fertility in male and female rats at approximately 16-fold and 30-fold higher exposures than those seen in humans who received 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 EVG.[1]

Placental and Breast Milk Passage

No data are available on the placental transfer of EVG in nonhuman primates. Studies in rats have demonstrated that EVG is secreted in breast milk.[1]

Human Studies in Pregnancy

Pharmacokinetics

Pharmacokinetic (PK) and safety data from 30 pregnant U.S. women living with HIV who received a fixed-dose combination (FDC) of EVG, cobicistat (COBI), emtricitabine, and tenofovir disoproxil fumarate (TDF) have been published. EVG exposure (based on area under the curve [AUC]) was 24% lower during the second trimester and 44% lower during the third trimester than during the postpartum period. EVG trough concentration (C_{24h}) was 81% lower during the second trimester and 89% lower during the third trimester than during the postpartum period. COBI AUC was 54% to 57% lower and C_{24h} was 72% to 76% lower during the second and third trimesters, respectively, than during the postpartum period. EVG AUC failed to reach the exposure target of 23 mcg•h/mL (the 10th percentile for nonpregnant adults) in 50% of women during the second trimester and 55% of women during the third trimester; 12% of women reached the exposure target during the postpartum period. Plasma HIV RNA at delivery was <50 copies/mL in 19 of 25 women (76%) for whom data were available.[2] In a European study that evaluated the PK of EVG administered with COBI in 14 pregnant women, EVG AUC was reduced by 34% and trough concentration was reduced by 77% during the third trimester compared with the postpartum period. EVG trough concentration was below the EC_{90} (0.13 mg/L) in 85% of women in the third trimester and in none postpartum. Two women experienced virologic failure during the third trimester and were switched to alternative regimens.[3]

Two case reports of EVG and COBI PKs, safety, and efficacy in individual pregnant women found similar reductions in EVG and COBI exposure during pregnancy, although viral loads in both women remained undetectable throughout pregnancy.[4,5] One case report described unbound EVG concentrations and found that the unbound fraction was 0.3% during pregnancy and 0.5% at 6 months postpartum. Reductions in both total EVG concentration and unbound EVG concentration increase the risk of suboptimal exposure.[5]

Because studies have reported reduced EVG exposure when pregnant women receive FDC tablets that contain EVG and COBI, the prescribing information for these products has been changed to indicate that these formulations are not recommended for use in pregnancy and should not be initiated in pregnancy; frequent viral load monitoring or use of an alternative regimen is recommended for individuals who become pregnant while

receiving these formulations.[1,6] If these formulations are used in pregnancy, to maximize absorption, they should be administered with a meal and should not be administered within 2 hours of intake of preparations containing such minerals as iron or calcium, including prenatal vitamins.[6]

Placental and Breast Milk Passage

Placental passage of EVG has been evaluated in two studies. A U.S. study of EVG PK and safety observed that EVG crossed the placenta well, with a median cord-to-maternal-plasma ratio of 0.91 in 15 women. The median EVG elimination half-life in neonates was 7.6 hours, similar to that in nonpregnant adults. COBI concentrations were low in cord blood and were not detected in the plasma of any neonates.[2] A European study reported similar results, with a median cord blood-to-maternal delivery plasma ratio of 0.75 in seven women.[3] No data are available on human breast milk transfer of EVG.

Teratogenicity/Adverse Pregnancy Outcomes

The Antiretroviral Pregnancy Registry has monitored sufficient numbers of first-trimester exposures to EVG to allow the detection of at least a twofold increase in the risk of overall birth defects. No such increase in the risk of birth defects has been observed with EVG.[7] Among the cases of first-trimester EVG exposure, the prevalence of birth defects was 3.4% (11 of 323 live births; 95% confidence interval, 1.7% to 6.0%) compared with a 2.7% total prevalence in the U.S. population, according to Centers for Disease Control and Prevention surveillance.[7] The Antiretroviral Pregnancy Registry reported supplemental data for central nervous system birth defect outcomes among 391 live births with exposure to EVG during periconception (n = 298) or pregnancy (late first trimester, n = 25; second or third trimester, n = 71). The Registry reported one central nervous system birth defect with exposure to EVG during periconception that was not a neural tube or an encephalocele defect.[7]

In the largest prospective PK and safety study of EVG in pregnancy, which 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 retrospective report of 137 infants in the United States who were born to mothers who received EVG during pregnancy, two birth defects were noted: one case of hydronephrosis and one case of encephalocele. Two cases of intrauterine fetal demise among the 134 pregnancies also were included in this report.[8]

Excerpt from Table 10

Note: When using FDC tablets, refer to other sections in Appendix B and Table 8 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**
Elvitegravir (EVG) **Note:** As of October 2017, the single-drug formulation of EVG (Vitekta) is no longer available. (EVG/c/FTC/TAF) *Genvoya* (EVG/c/FTC/TDF) *Stribild*	**EVG/c/FTC/TAF (Genvoya):** • EVG 150 mg/ COBI 150 mg/ FTC 200 mg/ TAF 10 mg tablet **EVG/c/FTC/TDF (Stribild):** • EVG 150 mg/ COBI 150 mg/ FTC 200 mg/ TDF 300 mg tablet	**Standard Adult Doses** *Genvoya and Stribild:* • One tablet once daily with food **Pregnancy** *PKs in Pregnancy:* • PK studies in women who received EVG/c demonstrated significant reduction in EVG plasma exposure during pregnancy. *Dosing in Pregnancy:* • EVG plasma concentrations are reduced with use of standard adult doses during pregnancy; however, higher-than-standard doses of EVG have not been studied. Insufficient data are available to recommend a dose for use in pregnancy. For guidance about use of combination products in pregnancy, please see the specific sections on other components (i.e., COBI, FTC, TAF).	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/c **is not recommended** for use in pregnancy. For women who become pregnant while taking EVG/c, consider frequent viral load monitoring or switching to a more effective, recommended regimen. If a woman continues taking a regimen that contains EVG/c, doses should be administered with a meal and should not be administered within 2 hours of ingesting any preparation that contains such minerals 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: ARV = antiretroviral; COBI = cobicistat; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FDC = fixed-dose combination; FTC = emtricitabine; PK = pharmacokinetic; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

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Raltegravir (Isentress, RAL)

(Last updated December 29, 2020; last reviewed December 29, 2020)

Animal Studies

Carcinogenicity

Raltegravir (RAL) was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests. Long-term carcinogenicity studies of RAL in mice did not show any carcinogenic potential at systemic exposures that were 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 RAL 600 mg/kg per day for 104 weeks. This dose produced exposures that were threefold 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 of RAL.[1]

Reproduction/Fertility

RAL had no adverse effects on the fertility of male or female rats at doses up to 600 mg/kg per day, which produced exposures that were up to threefold higher than the exposures seen in humans who received the recommended adult dose.

Teratogenicity/Adverse Pregnancy Outcomes

No treatment-related effects on embryonic/fetal survival or fetal weights were observed in studies where RAL was administered to rats and rabbits at doses that produced systemic exposures approximately threefold to fourfold higher than the exposures seen in humans who received the recommended 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 RAL 600 mg/kg per day (which produced exposures that were threefold higher than the exposure seen in humans who received the recommended daily dose).[1]

Placental and Breast Milk Passage

Placental transfer of RAL was demonstrated in both rats and rabbits. In pregnant rats given a dose of RAL 600 mg/kg per 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 after a maternal dose of 1,000 mg/kg per day.[1]

RAL is secreted in the milk of lactating rats. At a maternal dose of RAL 600 mg/kg per day, the mean drug concentration in milk was about threefold higher than the mean drug concentration in maternal plasma. No effects in rat offspring were attributable to RAL exposure through breast milk.[1]

Human Studies in Pregnancy

Pharmacokinetics

RAL pharmacokinetics (PKs) were evaluated in 42 pregnant women in the International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) P1026s study, a Phase IV prospective PK study of selected antiretroviral (ARV) drugs during pregnancy and postpartum. RAL PKs in pregnant women showed extensive variability that was similar to the variability seen in nonpregnant women. Median RAL area under the curve (AUC) was reduced by approximately 50% during pregnancy. No significant difference was seen between third-trimester trough concentrations and postpartum trough concentrations. Plasma HIV RNA levels were <400 copies/mL in 92% of women at delivery. Given the high rates of virologic suppression and the lack of a clear

relationship between RAL 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, a network of European centers that collect PK data in pregnant women with HIV, the geometric mean ratios of third-trimester/postpartum values were 0.71 for AUC from 0 to 24 h ($AUC_{0–12h}$) (range 0.53–0.96), 0.82 for maximum concentration (C_{max}) (range 0.55–1.253), and 0.64 for concentration 12 hours after dose ($C_{12h)}$ (range 0.34–1.22). One patient was below the target C_{12h} 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 RAL as part of intensification of an ARV regimen or as part of a triple-ARV regimen, the RAL C_{12h} in the second and third trimester were similar to historical data in a nonpregnant population, and the cord blood-to-maternal-plasma RAL concentration ratio was 1.03.[4]

In the P1097 study of washout PKs in 21 neonates born to women who received RAL during pregnancy, RAL elimination was highly variable and extremely prolonged in some infants (median half-life [$t_{1/2}$] 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 RAL, the cord blood level of RAL was 145 ng/mL; the level at 2 days of age was 106 ng/mL, and the level at 1 month of age was 29 ng/mL, still above the inhibitor concentration required to achieve 95% inhibition (IC_{95}) of 15 ng/mL.[5] In a report on 14 infants who were exposed to RAL *in utero*, the infants experienced no adverse effects, and RAL levels were within therapeutic range.[6]

Caution is advised when RAL is co-administered with atazanavir, a uridine diphosphate glucuronosyltransferase A1 inhibitor, because this combination can result in elevated levels of RAL in nonpregnant adult women with no medical conditions.[7]

Placental and Breast Milk Passage

An *ex vivo* study of term placentas from normal pregnancies reported high bidirectional transfer of RAL across the placenta.[8]

In vivo human studies have confirmed that RAL readily crosses the placenta. In the IMPAACT P1026s study, the ratio of cord blood to maternal plasma RAL concentrations was 1.5.[2] In the P1097 study, the median ratio of cord blood to maternal delivery plasma RAL concentrations 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-to-maternal-blood drug level ratios of 1.00 to 1.06.[10–12] In three cases of preterm delivery at 29 to 33 weeks gestation (in two of these cases, RAL 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 RAL is secreted in human breast milk is unknown.

Teratogenicity/Adverse Pregnancy Outcomes

In a retrospective study of 497 women in the French Perinatal Cohort who received RAL during pregnancy, rates of birth defects among infants born to women who were on RAL during the first trimester were similar to those born to women who initiated RAL in the second or third trimester (5.7% vs. 3.5%, $P = 0.29$). No specific pattern of birth defects emerged during the study.[14] Merck reviewed data on 456 periconception exposures to RAL and found no instances of neural tube defects; this review included data from the Merck company database, the Antiretroviral Pregnancy Registry, and the U.K./Ireland and French pregnancy cohorts.[15]

The IMPAACT P1081 study randomized 408 antiretroviral therapy-naive women in Africa, South America,

Thailand, and the United States who presented late in pregnancy to receive RAL plus two nucleoside reverse transcriptase inhibitors (NRTIs) or efavirenz plus two NRTIs. Both regimens were well tolerated, with similar rates of stillbirth and preterm birth among women and similar rates of serious adverse events among women and infants; a significantly larger proportion of women on a RAL-containing regimen achieved a viral load less than 200 copies per mL at or near delivery.[16] In multiple case reports and case series that involved 4, 5, and 14 pregnant women who were treated with RAL in combination with two or three other ARV drugs because of persistent viremia or late presentation, RAL was well tolerated and led to rapid reduction in HIV RNA levels.[17-23]

The Antiretroviral Pregnancy Registry has monitored sufficient numbers of first-trimester exposures to RAL to detect at least a twofold increase in the risk of overall birth defects. No such increase in the risk of birth defects has been observed with RAL. Among the cases of first-trimester RAL exposure that have been reported to the Antiretroviral Pregnancy Registry, the prevalence of birth defects was 3.1% (13 of 422 live births; 95% confidence interval [CI], 1.7%–5.2%), compared with a 2.7% total prevalence in the U.S. population, based on Centers for Disease Control and Prevention surveillance.[14,24] Supplemental data from the Antiretroviral Pregnancy Registry about central nervous system birth defect outcomes among 824 live births with exposure to RAL during periconception (n = 327) or pregnancy (later first trimester n = 95; second or third trimester n = 399) reported one central nervous system birth defect with exposure to RAL in the late first trimester, but this was not a neural tube or encephalocele defect.[24]

Safety

In the P1026s study, the P1081 study, and the PANNA study, RAL was well tolerated, with no treatment-related serious adverse events observed in pregnant women.[2,3,16] However, in one case report, 10-fold to 23-fold increases in maternal liver transaminase levels were reported after initiation of RAL. Resolution occurred when RAL was discontinued.[25] Drug levels were not measured.

One case of drug reaction has been reported in a postpartum woman with eosinophilia and systemic symptoms syndrome with extensive pulmonary involvement. The drug reaction resolved with discontinuation of RAL. Such reactions have been reported in nonpregnant adults who were receiving RAL, and these reactions should be taken into consideration when making a differential diagnosis of fever in women on RAL during pregnancy or the postpartum period.[26] In a study of 155 nonpregnant adults with HIV (mean age 49.2 years) who initiated RAL-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.[27]

Because RAL is highly protein bound to albumin, concern exists about displacement of bilirubin from albumin in the neonate, which could potentially increase the risk of neonatal hyperbilirubinemia. In an *in vitro* study, RAL 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.[28] These data suggest that the effect of RAL on neonatal bilirubin binding is unlikely to be clinically significant at the typical peak concentrations that are reached in adults who receive the recommended dose (adult concentrations with standard RAL 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).[28] In the P1097 study, 1 of 19 infants (5.3%) received phototherapy for treatment of hyperbilirubinemia, but this was judged to be unrelated to maternal RAL use.[9] In a retrospective study of 31 pregnant women who received a standard dose of RAL as part of a standard ARV regimen or as part of an intensification regimen late in pregnancy (at a median gestational age of 34 weeks), mild elevation of transaminase levels was reported in 35% of neonates.[29]

Excerpt from Table 10

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations[a]	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** *In Patients Who Are Not Receiving Rifampin:* • RAL 400 mg, film-coated tablets twice daily without regard to food • Two RAL 600 mg, film-coated tablets (1,200 mg) once daily without regard to food for ARV-naive patients or patients who are already virologically suppressed on an initial regimen of RAL 400 mg twice daily • Chewable tablets and oral suspension doses **are not interchangeable** with either film-coated tablets or each other. *In Patients Who Are Receiving Rifampin:* • Two RAL 400 mg, film-coated tablets (800 mg) twice daily without regard to food **Pregnancy** *PK in Pregnancy:* • Decreased drug concentrations in the third trimester are 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). There is a 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. RAL 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.

[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: RV = antiretroviral; HD = high dose; HSR = hypersensitivity reaction; PK = pharmacokinetic; RAL = raltegravir

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Cobicistat (Tybost, COBI)

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Animal Studies

Carcinogenicity

No increases in tumor incidence were seen in male and female mice at cobicistat (COBI) exposures that were 7 and 16 times the exposure observed in humans who received the recommended dose. 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

COBI did not affect 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 rat COBI exposures that were 1.4 times higher than the recommended human exposure and rabbit COBI exposures that were 3.3 times higher than the recommended human exposure.[1]

Placental and Breast Milk Passage

No information is available on placental passage of COBI. Studies in rats have shown that COBI is secreted in breast milk.[2]

Human Studies in Pregnancy

Pharmacokinetics

COBI pharmacokinetics (PKs) have been described in pregnant and postpartum women who were taking concomitant elvitegravir (EVG), atazanavir (ATV), and darunavir (DRV). In a study of 30 pregnant women who were receiving elvitegravir/cobicistat (EVG/c), the area under the curve (AUC) for COBI was 44% lower in the second trimester and 59% lower in the third trimester than during the postpartum period. Trough COBI 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 COBI 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.[3] Two other studies have described decreases of similar magnitudes in COBI exposures when COBI is coadministered with DRV in pregnant women.[4,5] In one of these abstracts, COBI AUC was decreased by 63% in the second trimester and 49% in the third trimester compared to the AUC postpartum. Trough COBI concentrations decreased by 83% in both the second and third trimesters.

The pharmacoenhancing effect of COBI on EVG was impacted during pregnancy; EVG AUC was reduced by 44% and trough concentrations were reduced by 89% in the third trimester when compared to postpartum AUC and trough concentrations. EVG apparent oral clearance during pregnancy and postpartum was negatively associated with COBI AUC.[3]

The pharmacoenhancing effect of COBI on ATV and DRV was also impacted during pregnancy. For DRV, AUC based on total DRV concentrations was 56% (in the second trimester) and 50% (in the third trimester) lower than the AUC postpartum, and AUC based on unbound concentrations was 45% and 40% lower, respectively. The effect on DRV 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) when compared to postpartum trough concentrations. One of six women in this study experienced virologic failure during the third trimester, and virologic failure continued through the postpartum period.[5] For ATV, trough ATV concentrations were 80% and 85% lower in the second and third trimesters compared to historical

ATV trough concentrations in nonpregnant adults with HIV.[6] Because of these substantial reductions in drug exposures during pregnancy, use of COBI-boosted EVG, ATV, or DRV **is not recommended** for patients starting or changing regimens during pregnancy.[7-9]

A study reported in a conference abstract evaluated tenofovir alafenamide (TAF) exposure in pregnant women when TAF was administered as a daily 10-mg dose with COBI 150 mg. There were no differences between TAF exposure during pregnancy and TAF exposure postpartum in the same women. The authors concluded that no dose adjustment is needed during pregnancy for TAF when it is coadministered with COBI.[10] However, TAF 10 mg with COBI is only available in fixed-dose combination products that also include either DRV or EVG, which are not recommended for use during pregnancy. Another study described TAF exposure in pregnant women when administered as a 25-mg dose with a pharmacoenhancer (either RTV 100 mg or COBI 150 mg). TAF exposures during pregnancy and postpartum did not differ.[11]

Placental and Breast Milk Passage

A study in 10 pregnant women who received EVG/c found a median ratio of cord blood to maternal plasma COBI concentrations of 0.09. This study also found measurable concentrations of COBI in placental tissue and cord blood peripheral blood mononuclear cells (PBMC), with a cord-blood-to-maternal-PBMC ratio of 0.49.[12] In another study, 7 of 15 pregnant women who received EVG/c had quantifiable plasma COBI concentrations at delivery. The median cord blood-to-maternal-plasma ratio for COBI concentration was 0.09. In 27 neonates born to mothers who were receiving EVG/c, COBI was below the assay quantitation limit of 10 ng/mL in all washout PK samples taken between 2 hours and 9 days postdelivery.[3] No data are available on breast milk passage of COBI in humans.

Teratogenicity/Adverse Pregnancy Outcomes

The Antiretroviral Pregnancy Registry has monitored sufficient numbers of first-trimester exposures to COBI to detect at least a twofold increase in the risk of overall birth defects in the general population. However, no such increase in the risk of birth defects has been observed with COBI. Among cases of first-trimester exposure to COBI that have been reported to the Antiretroviral Pregnancy Registry, the prevalence of birth defects was 3.9% (16 of 410 live births; 95% confidence interval, 2.3% to 6.3%) compared with a 2.7% total prevalence in the U.S. population, based on Centers for Disease Control and Prevention surveillance.[2]

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**
Cobicistat (COBI) *Tybost* (ATV/c) *Evotaz* (EVG/c/FTC/TAF) *Genvoya* (DRV/c) *Prezcobix* (EVG/c/FTC/TDF) *Stribild* (DRV/c/FTC/TAF) *Symtuza*	**COBI (Tybost)** *Tablet:* • COBI 150 mg **ATV/c (Evotaz):** • ATV 300 mg/ COBI 50 mg tablet **EVG/c/FTC/TAF (Genvoya):** • EVG 150 mg/ COBI 150 mg FTC 200 mg/ TAF 10 mg tablet **DRV/c (Prezcobix):** • DRV 800 mg/ COBI 150 mg tablet **EVG/c/FTC/TDF (Stribild):** • EVG 150 mg/ COBI 150 mg/ FTC 200 mg/ TDF 300 mg tablet **DRV/c/FTC/TAF (Symtuza):** • DRV 800 mg/ COBI 150 mg/ FTC 200 mg/ TAF 10 mg tablet	**Standard Adult Doses** *COBI (Tybost):* • When used as an alternative PK booster with ATV or DRV, the dose is one tablet once daily with food *ATV/c (Evotaz):* • One tablet once daily with food *EVG/c/FTC/TAF (Genvoya):* • One tablet once daily with food *DRV/c (Prezcobix):* • One tablet once daily with food *EVG/c/FTC/TDF (Stribild):* • One tablet once daily with food *DRV/c/FTC/TAF* (Symtuza): • One tablet once daily with food **Pregnancy** *PKs in Pregnancy:* • Based on limited data, COBI exposure and its pharmacoenhancing effect on ATV, DRV, and EVG are markedly reduced in pregnancy. • When coadministered with COBI, TAF	Low placental transfer to fetus.[b] No evidence of human teratogenicity (can rule out twofold increase in overall birth defects). Use of COBI-boosted ATV, DRV, or EVG **is not recommended** in pregnancy.

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations[a]	Use in Pregnancy
		exposure is not significantly different between pregnancy and the postpartum period. *Dosing in Pregnancy:* • Although COBI exposure is markedly reduced during pregnancy, higher-than-standard doses have not been studied. The Panel recommends RTV as the preferred pharmacoenhancer 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).	

[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: ARV = antiretroviral; ATV/c = atazanavir/cobicistat; COBI = cobicistat; DRV/c = darunavir/cobicistat; EVG/c = elvitegravir/cobicistat; 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

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Ritonavir (Norvir, RTV)

(Last updated December 29, 2020; last reviewed December 29, 2020)

Animal Studies

Carcinogenicity

Ritonavir (RTV) was neither mutagenic nor clastogenic in a series of *in vitro* and *in vivo* screening tests. In male mice, a dose-dependent increase in adenomas of the liver and combined adenomas and carcinomas of the liver was observed at RTV doses of 50 mg/kg per day, 100 mg/kg per day, or 200 mg/kg per day; exposure (based on area under the curve) in male mice at the highest dose was approximately 0.3-fold the exposure observed in male humans who received the recommended therapeutic dose. No carcinogenic effects were observed in female mice at exposures that were 0.6-fold the exposures observed in women who received the recommended therapeutic dose. No carcinogenic effects were observed in rats at exposures up to 6% of the recommended therapeutic human exposure.[1]

Reproduction/Fertility

RTV has had no observed effect on reproductive performance or fertility in rats at drug exposures that were 40% (in males) and 60% (in females) of the exposures achieved with human therapeutic dosing; higher doses were not feasible because of hepatic toxicity in the rodents.[1]

Teratogenicity/Adverse Pregnancy Outcomes

No RTV-related teratogenicity has been observed in rats or rabbits. Developmental toxicity—including early resorptions, decreased body weight, ossification delays, and developmental variations (e.g., wavy ribs, enlarged fontanelles)—was observed in rats; however, these effects occurred only at maternally toxic dosages (with exposures equivalent to 30% of human therapeutic exposures). In addition, a slight increase in cryptorchidism was noted in rats at exposures equivalent to 22% of human therapeutic exposures. In rabbits, developmental toxicity (i.e., resorptions, decreased litter size, and decreased fetal weight) also was 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 RTV has been observed in rats with fetal tissue-to-maternal serum ratios >1.0 at 24 hours postdose in midgestational and late-gestational fetuses.

Human Studies in Pregnancy

Pharmacokinetics

RTV concentrations were lower during pregnancy than during the postpartum period when RTV was administered to pregnant women with HIV at doses sufficient for HIV suppression (500 mg or 600 mg twice daily), in combination with zidovudine and lamivudine.[2] RTV concentrations also are reduced during pregnancy compared with postpartum, when the drug is used at a low dose (100 mg) to boost the concentrations of other protease inhibitors, but RTV is an effective booster of the protease inhibitors lopinavir (LPV), atazanavir (ATV), and darunavir (DRV) in pregnant women.[3–5] In contrast, the newer booster, cobicistat, is not an effective booster of protease inhibitors in pregnant women, and its use is not recommended during pregnancy.[6]

Placental and Breast Milk Passage

In a human placental perfusion model, the clearance index of RTV was very low, with little accumulation in the fetal compartment and no accumulation in placental tissue.[7] In a Pediatric AIDS Clinical Trials Group (PACTG) trial 354 Phase 1 study of pregnant women and their infants, transplacental passage of RTV was minimal, with an average cord blood-to-maternal plasma concentration ratio of 5.3%.[2] In a study of cord-blood samples from six women who were treated with RTV during pregnancy, the cord-blood concentration was less than the assay limit of detection in five of the women and was only 0.38 µg/mL in the remaining woman.[8] In

contrast, in a study of hair and plasma RTV concentrations in 51 mother–infant pairs after lopinavir/ritonavir was administered to the mothers during pregnancy and postpartum, hair and plasma concentrations over time suggested moderate *in utero* transfer of lopinavir, but negligible transfer via breastfeeding.[9]

Teratogenicity/Adverse Pregnancy Outcomes

The Antiretroviral Pregnancy Registry has monitored sufficient numbers of first-trimester exposures to RTV to detect at least a 1.5-fold increase in the risk of overall birth defects and at least a twofold 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 RTV. Among the cases of first-trimester RTV exposure that have been reported to the Antiretroviral Pregnancy Registry, the prevalence of birth defects was 2.3% (78 of 3,378 live births; 95% confidence interval, 1.8% to 2.9%), compared with a total prevalence of 2.7% in the U.S. population, according to Centers for Disease Control and Prevention surveillance.[10]

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**
Ritonavir (RTV) *Norvir* (LPV/r) *Kaletra*	**RTV (Norvir)** *Capsules:* • RTV 100 mg *Tablets:* • RTV 100 mg *Oral Solution:* • RTV 80 mg/mL *Powder:* • RTV 100 mg/sachet **LPV/r (Kaletra)** *Tablets:* • LPV/r 200 mg/50 mg • LPV/r 100 mg/25 mg *Oral Solution:* • Each 5 mL contains LPV/r 400 mg/ 100 mg	**Standard Adult Dose of RTV (Norvir) When Used as PK Booster for Other PIs:** • RTV 100–400 mg per day in one or two divided doses (refer to other PI sections for specific dosing recommendations) *Tablet:* • Take with food *Capsule or Oral Solution:* • To improve tolerability, take with food, if possible. **Standard Adult Doses of LPV/r (Kaletra):** • 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 in PI-Naive or PI-Experienced Patients:* • LPV/r 500 mg/125 mg tablets twice daily without regard to meals (use a combination of two LPV/r 200 mg/50 mg tablets and one LPV/r 100 mg/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 increased risk of human teratogenicity (can rule out 1.5-fold increase in overall birth defects). RTV should only be used as low-dose booster for other PIs. RTV oral solution contains 43% alcohol and, therefore, **is not recommended** for use during pregnancy because no safe level of alcohol exposure during pregnancy is known. LPV/r 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.

Generic Name (Abbreviation) *Trade Name*	**Formulation**	**Dosing Recommendations**[a]	**Use in Pregnancy**
		Pregnancy *PKs in Pregnancy:* • Lower RTV levels are seen during pregnancy than during postpartum, which may reduce the pharmaco-enhancing effect of RTV in pregnancy *RTV Dosing in Pregnancy:* • No dose adjustment is necessary when RTV is used as booster. *LPV/r 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 in women who start treatment during pregnancy with a baseline viral load >50 copies/mL. • When standard dosing is used, monitor virologic response and, if possible, LPV drug levels. For guidance about use of combination products in pregnancy, please see the specific sections on other components (i.e., LPV/r).	

[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: ARV = antiretroviral; EFV = efavirenz; LPV/r = lopinavir/ritonavir; NVP = nevirapine; PI = protease inhibitor; PK = pharmacokinetic; RTV = ritonavir

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Archived Drugs

Overview

The Archived Drugs section provides access to the last updated versions of drug sections that are no longer being reviewed by the Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission (the Panel). Archived Drugs includes older antiretroviral drugs that are no longer available in the United States or that the Panel does not recommend for use in pregnant women. These drugs may have unacceptable toxicities, inferior virologic efficacy, or a high pill burden, or there may be pharmacologic concerns or a limited amount of data on the use of these drugs in pregnant women.

Amprenavir

Delavirdine

Didanosine

Enfuvirtide

Fosamprenavir

Indinavir

Nelfinavir

Saquinavir

Stavudine

Tipranavir

Zalcitabine

Amprenavir (Agenerase)

Last Updated: November 7, 2007; Last Reviewed: November 7, 2007

Amprenavir is classified as FDA pregnancy category C and is no longer available in the United States.

Animal Studies

Carcinogenicity

In vitro screening tests for carcinogenicity have been negative. An increase in benign hepatocellular adenomas and hepatocellular carcinomas was observed in male mice and rats at the highest doses evaluated, which produced systemic exposures in mice 2-fold and in rats 4-fold higher than systemic exposure in humans receiving therapeutic doses of amprenavir. Female mice and rats were not affected.

Reproduction/Fertility

No effect has been seen on reproductive performance, fertility, or embryo survival in rats at exposures about twice those of human therapeutic exposure.

Teratogenicity/Adverse Pregnancy Outcomes

In pregnant rabbits, administration of amprenavir resulting in systemic exposures about one-twentieth of that observed with human therapeutic exposure was associated with abortions and an increased incidence of minor skeletal variations resulting from deficient ossification of the femur, humerus trochlea, and humerus. In rat fetuses, thymic elongation and incomplete ossification of bones were also attributed to amprenavir at systemic exposures about one-half that associated with the recommended human dose. Reduced body weights of approximately 10% – 20% were observed in offspring of rodents administered amprenavir from Day 7 of gestation to Day 22 of lactation (exposures approximately twice that observed with the human therapeutic dose). However, the subsequent development of the offspring, including fertility and reproductive performance, was not affected by maternal administration of amprenavir.

Placental and Breast Milk Passage

Whether amprenavir crosses the placenta is unknown. Amprenavir is excreted in the milk of lactating rats; it is not known if it is excreted in human milk.

Human Studies in Pregnancy

There have been limited studies of amprenavir in pregnant women and no studies in neonates. Amprenavir oral solution contains high levels of excipient propylene glycol in the oral solution vehicle; this is not true for the capsular formulation. Propylene glycol is metabolized by the alcohol and aldehyde dehydrogenase enzyme pathway. Some patients, including infants and children below the age of 4 years, pregnant women, patients with hepatic or renal failure, and patients treated with disulfiram or metronidazole, are not able to adequately metabolize and eliminate propylene glycol, thereby leading to its accumulation and potential adverse events. Thus, while the capsule formulation of amprenavir may be used in pregnancy, amprenavir oral solution is contraindicated in pregnant women and infants and in children under the age of 4 years.

Delavirdine (Rescriptor)

Last Updated: November 7, 2007; Last Reviewed: November 7, 2007

Delavirdine is classified as FDA pregnancy category C and is no longer available in the United States.

Animal Studies

Carcinogenicity

In vitro screening tests for carcinogenicity have been negative. In rats, delavirdine was noncarcinogenic at all doses studied. In mice, delavirdine was associated with an increase in hepatocellular adenoma and carcinoma in both males and females and urinary bladder tumors in males at systemic exposures 0.5- to 3-fold higher than human exposure at therapeutic doses for female mice and at exposures 0.2- to 4-fold higher in male mice.

Reproduction/Fertility

Delavirdine does not impair fertility in rodents.

Teratogenicity/Adverse Pregnancy Outcomes

Delavirdine is teratogenic in rats; doses of 50 to 200 mg/kg/day during organogenesis caused ventricular septal defects.

Exposure of rats to doses approximately 5 times human therapeutic exposure resulted in marked maternal toxicity, embryotoxicity, fetal developmental delay, and reduced pup survival.

Abortions, embryotoxicity, and maternal toxicity were observed in rabbits at doses approximately 6 times human therapeutic exposure.

Placental and Breast Milk Passage

Whether delavirdine crosses the placenta is unknown. Delavirdine is excreted in the milk of lactating rats; however, it is unknown if the drug is excreted in human breast milk.

Human Studies in Pregnancy

Delavirdine has not been evaluated in HIV-infected pregnant women. In premarketing clinical studies, the outcomes of seven unplanned pregnancies were reported: three resulted in ectopic pregnancies, three resulted in healthy live births, and one infant was born prematurely with a small muscular ventricular septal defect to a patient who received approximately 6 weeks of treatment with delavirdine and zidovudine early in the course of pregnancy.

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 8[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 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 to Acronyms: ARV = antiretroviral; d4T = stavudine; ddI = didanosine; EC = enteric coated; FDC = fixed-dose combination; PK = pharmacokinetic; TDF = tenofovir disoproxil fumarate

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Enfuvirtide (Fuzeon, T-20)

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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 8[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 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 to Acronyms: ARV = antiretroviral; PK = pharmacokinetic; SQ = subcutaneous; T-20 = enfuvirtide

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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 8[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 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 to Acronyms: ARV = antiretroviral; AUC = area under the curve; EFV = efavirenz; FPV = fosamprenavir; PI = protease inhibitor; PK = pharmacokinetic; RTV = ritonavir

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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 8[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 10).

[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

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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]

A PK study 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. In a follow up study, use of an increased dose of 1875 mg twice daily after 30 weeks gestation resulted in nelfinavir exposures during the third trimester that were equivalent to those seen with 1250 mg twice daily postpartum.[6]

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.[7] 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.[8]

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.[9] 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.[10]

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.[11]

Excerpt from Table 8[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 antiretroviral 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 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 to Acronyms: NFV = nelfinavir; PK = pharmacokinetic

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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 8[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 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 to Acronyms: ECG = electrocardiogram; PK = pharmacokinetic; RTV = ritonavir; SQV = saquinavir

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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 8[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 10).

[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

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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 8[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 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 to Acronyms: PK = pharmacokinetic; RTV = ritonavir; TPV = tipranavir; TPV/r = tipranavir/ritonavir

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Zalcitabine (HIVID, ddC)

Last Updated: November 7, 2007; Last Reviewed: November 7, 2007

Zalcitabine is classified as FDA pregnancy category C and is no longer available in the United States.

Animal Studies

Carcinogenicity

High doses of zalcitabine (more than 1,000 times that of human therapeutic exposure) have been associated with the development of thymic lymphomas in rodents.

Reproduction/Fertility

No effect of zalcitabine on reproduction or fertility in rodents has been seen. However, there is a dose-related cytotoxic effect on preimplantation mouse embryos, with inhibition at a zalcitabine concentration of 100 μM; no inhibition of postblastocyst development was observed.[1]

Teratogenicity/Adverse Pregnancy Outcomes

Teratogenicity (hydrocephalus) occurred in rats given very high doses (more than 1,000 times the maximally recommended human exposure) of zalcitabine.

Developmental toxicity, consisting of decreased fetal weight and skeletal defects, has been seen in rodents at moderate to high zalcitabine doses. Cytotoxic effects were observed on rat fetal thymocytes at zalcitabine concentrations as low as 10 μM (approximately 100 times human therapeutic exposure).

Placental and Breast Milk Passage

In primate and placental perfusion studies, zalcitabine crosses the placenta (fetal-to-maternal drug ratio approximately 0.50 to 0.60).[2] In rodents, zalcitabine concentrates in the fetal kidney and a relatively small proportion (approximately 20%) reaches the fetal brain. It is unknown if zalcitabine is excreted in breast milk.

Human Studies in Pregnancy

No studies of zalcitabine have been conducted in pregnant women or neonates.

References

1. Toltzis P, Mourton T and Magnuson T. Comparative embryonic cytotoxicity of antiretroviral nucleosides. *J Infect Dis*, 1994. 169(5):1100-2.
2. 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 Metab Dispos*, 1995. 23(8):881-4.

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 C: Antiretroviral Counseling Guide for Health Care Providers

(Last updated, February 10 2021; last reviewed, February 10, 2021)

Decision-making about Antiretroviral Drugs for Pregnant Women and Women Who Are Trying to Conceive[a]

This counseling guide summarizes information, based on currently available data, to support the process of informed decision-making by health care providers and their patients about the use of antiretroviral (ARV) drugs and antiretroviral therapy (ART) options by women who are pregnant or are trying to conceive.

For pregnant women and women who are trying to conceive, effective ART with sustained viral suppression maximizes both women's health and the prevention of perinatal HIV transmission. The risk of perinatal HIV transmission is reduced to the lowest levels (<1%) in women with HIV who initiate ART prior to conception and who have sustained viral suppression to undetectable levels throughout pregnancy.

When making decisions about ART, it is important to weigh the available data on the risks and benefits of all *Preferred* and *Alternative* ARVs, gestational age, tolerance of and satisfaction with the current ARV regimen, and the potential loss of virologic control with regimen changes. Patients should receive the information needed to help them make informed decisions about ARV drugs and regimens.

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, and contraceptive options to prevent unintended 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 certain 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; rather, it means that we do not have all the information about all the possible effects when using these drugs during pregnancy (e.g., bictegravir).
- For some ARV drugs (e.g., cobicistat-boosted regimens), pharmacokinetic (PK) changes occur in pregnancy that decrease blood levels of those agents, potentially leading to a loss of virologic control and an increased risk of perinatal transmission or adverse effects on maternal HIV infection.
- For newer ARV drugs, PK data may not be available to guide dosing in pregnancy.

General Antiretroviral Counseling for Pregnant Women and Women Who Are Trying to Conceive

- It is important to help women consider the available information about the advantages, disadvantages, and potential risks associated with the use of ARV drugs, such as other birth defects or other adverse pregnancy outcomes (e.g., preterm delivery); see the section on Counseling Regarding the Risk of Neural Tube Defects (NTDs) below, and refer to Table 4, Teratogenicity, and Antiretroviral Drug Regimens and Maternal and Neonatal Outcomes for additional information.
- Changes in ART during pregnancy can lead to an increase in viral load, which increases the risk of perinatal HIV transmission; this viral rebound may affect choices for future ARV regimens due to the possible development of resistance.
- Women who are receiving ARVs that are not Preferred or Alternative options for pregnant women and women who are trying to conceive should receive counseling about the risks and benefits of continuing their current ART or switching to another ARV regimen. Panel recommendations about the **continuation** of specific ARV drugs are summarized in Table 5.
- When assessing the benefits and risks of switching a patient's ARV regimen, clinicians and patients should consider such factors as the feasibility of switching to another ARV drug, the tolerability of each drug, the

ability to maintain viral suppression, the risk of perinatal HIV transmission, and the risk of NTDs or other adverse outcomes, such as preterm birth.
- Women who are trying to conceive should receive information about the use of specific ARV regimens during pregnancy, which will enable them to make informed decisions before they become pregnant.
- All cases of ARV drug exposure during pregnancy should be reported to the Antiretroviral Pregnancy Registry.

Antiretroviral Drugs That Are Recommended for Use in Pregnancy

- *Preferred* ARV drug options for women who are initiating ART while pregnant or while trying to conceive include dolutegravir (DTG), raltegravir,[b] atazanavir/ritonavir, and darunavir/ritonavir. A moderate amount of data exists about pregnancy outcomes and birth defects with each of these drugs and drug combinations. Although these data are reassuring, it is important to note that a rigorous, systematic birth surveillance program that includes large numbers of women with periconceptional exposure, like the Botswana study, is available only for DTG and efavirenz (EFV).
- EFV and rilpivirine 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 PK, dosing, tolerability, drug interaction, or resistance concerns than those in the *Preferred* category, but they are acceptable for use in pregnancy.
- 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. Current updates include the following:
  - DTG is now a *Preferred* ARV for women who are trying to conceive, in addition to being a *Preferred* ARV for women who are pregnant, irrespective of trimester.[c]
  - Lopinavir/ritonavir, formerly categorized as an *Alternative* ARV, now is *Not Recommended Except in Special Circumstances.* This change is based on data on increased risks of preterm delivery and small-for-gestational-age infants—as well as on requirements for twice-daily dosing and potential nausea and vomiting; see Antiretroviral Drug Regimens and Maternal and Neonatal Outcomes.
  - With the availability of additional data, the Panel now recommends tenofovir alafenamide as an *Alternative* nucleoside reverse transcriptase inhibitor for ARV regimens.
- 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 with their patients whether to continue the regimen or switch to one that is recommended for use during pregnancy (see Table 5 and Pregnant Women 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 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 recommended for use in pregnancy (see Table 4 and Table 5), and viral load should be checked 2 to 4 weeks after the switch.

Counseling Regarding the Risk of NTDs in Pregnant Women and Women Who Are Trying to Conceive

In 2018, the preliminary data from a study in Botswana identified an increased risk of infant NTDs in women who were taking DTG around the time of conception. Subsequent data and findings from later, planned analyses found that the risk of infant NTDs was lower than previously reported in the preliminary data, but there was still a very small, potentially increased risk of infant NTDs among women who were taking DTG around the time of conception or in early pregnancy.

Because the updated data indicate that the increased risk of NTDs associated with DTG use is very 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 maternal health and the prevention of perinatal HIV transmission—**the Panel recommends DTG as a Preferred ARV drug for use throughout pregnancy and also recommends it as a Preferred ARV drug for women who are trying to conceive.** The Panel strongly recommends that the use of DTG and all ARV drugs be accompanied by appropriate counseling to allow patients and their health care providers to make informed decisions about treatment. Considerations that should be addressed in counseling are summarized below. For additional information, see Teratogenicity, Recommendations for Use of Antiretroviral Drugs During Pregnancy, Table 4, Table 5, and Pregnant Women with HIV Who Are Currently Receiving Antiretroviral Therapy.

- Because of mandatory food folate fortification, the overall risk of NTDs in the United States is low in the general population. A background risk of NTDs exists, regardless of the ARV regimen used or a woman's HIV status. In the United States, the background risk of NTDs in the general population is 0.07%, or 7 infants with NTDs 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. Most NTDs occur before the neural tube closes at 4 weeks postconception (approximately 6 weeks after the 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.
- The most recent data from Botswana indicate that there is still a very small statistically significant increase in the risk of infant NTDs with DTG compared to EFV exposure at the time of conception. The prevalence of infant NTDs was slightly higher in women who were taking DTG around the time of conception (0.19%, or 19 infants with NTDs per 10,000 deliveries) than in women who were taking EFV or in women without HIV infection (0.07%, 7 infants with NTDs per 10,000 deliveries in both groups). However, the risk of NTDs in infants exposed to DTG around the time of conception was no longer significantly elevated when compared with infants exposed to any non-DTG ARV regimen around the time of conception in this setting.
- Data available studies have not shown an increase in the risk of NTDs in infants born to women who initiated DTG during pregnancy.
- Currently, insufficient DTG periconceptional exposures have been reported to the Antiretroviral Pregnancy Registry to determine whether an increased risk of NTDs exists in the United States.
- Folic acid is known to lower the risk of NTDs in the general population. The U.S. 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 in Botswana, food in the United States is fortified routinely with folate. However, no established link exists between the use of DTG and impaired folate metabolism, nor does any evidence show that folate supplementation prevents NTDs associated with the periconceptional 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 the risks of NTDs associated with other ARV drugs recommended for use in pregnancy. With the exception of EFV, not enough data are available to determine the risk of NTDs that may be associated with periconceptional use of any of the other currently recommended *Preferred* and *Alternative* ARV drugs in the United States. With data from Botswana, we now can rule out a threefold (or greater) increase in the risk of NTDs in infants who were exposed to EFV, which the Panel recommends as an *Alternative* ARV drug for pregnant women and women who are trying to conceive (see Table 4, Table 5, and Efavirenz).

Footnotes

[a]Guidance on the care of pregnant women and women who are trying to conceive also applies to transgender and nonbinary people of childbearing potential.
[b]Raltegravir requires twice-daily dosing during pregnancy and has a lower barrier to resistance than DTG.
[c]The first trimester is less than 14 weeks (up to 13 6/7 weeks) gestational age by last menstrual period

Appendix D: 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