Recommendations for the Use of Antiretroviral Drugs During Pregnancy and Interventions to Reduce Perinatal HIV Transmission in the United States

Developed by the HHS Panel on Treatment of
HIV During Pregnancy and Prevention of Perinatal Transmission—
A Working Group of the NIH Office of AIDS Research Advisory Council (OARAC)

How to Cite the Perinatal Guidelines:

Panel on Treatment of HIV During Pregnancy and Prevention of Perinatal Transmission. Recommendations for the Use of Antiretroviral Drugs During Pregnancy and Interventions to Reduce Perinatal HIV Transmission in the United States. Department of Health and Human Services. Available at https://clinicalinfo.hiv.gov/en/guidelines/perinatal. Accessed (insert date) [include page numbers, table number, etc., if applicable].

It is emphasized that concepts relevant to HIV management evolve rapidly. The Panels have a mechanism to update recommendations on a regular basis, and the most recent information is available on the Clinicalinfo website (https://clinicalinfo.hiv.gov/).

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What's New in the Guidelines

January 31, 2024

The Panel on Treatment of HIV During Pregnancy and Prevention of Perinatal Transmission (the Panel) has updated text and references throughout the guidelines to include new data and publications where relevant and to incorporate gender-inclusive language. These changes are highlighted in yellow in the PDF version of the guidelines. The shared sections with the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV—Diagnosis of HIV Infection in Infants and Children, Infant Feeding for Individuals with HIV in the United States, and Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection—are still being revised; it is anticipated that these sections will be published in April 2024.

- Throughout the guidelines, minor changes were made to the HIV RNA threshold for resistance testing to be consistent with the Drug-Resistance Testing section in the Adult and Adolescent Antiretroviral Guidelines.
- Review of Clinical Trials of Antiretroviral Interventions to Prevent Perinatal HIV Transmission, the former Appendix A that provided information about the historical context of perinatal HIV prevention, has been archived; see Perinatal Archived Guidelines.

Introduction

- This section has been revised to clarify terms and present recent data about perinatal HIV transmission (i.e., during pregnancy and labor and delivery) and postnatal HIV transmission (i.e., through breastfeeding).

Pregnancy and Postpartum HIV Testing and Identification of Perinatal and Postnatal HIV Exposure

- Revisions have been made to the section title and bulleted recommendations and throughout the text to provide added detail, new data, and clarification.
- The Panel recommends that when acute HIV infection is suspected during pregnancy, the intrapartum period, or while breastfeeding, a plasma HIV RNA assay should be performed in conjunction with an antigen/antibody immunoassay.

Pre-Exposure Prophylaxis (PrEP) to Prevent HIV During Periconception, Antepartum, and Postpartum Periods

- Given the lack of data, episodic or non-daily PrEP is not recommended for protection against vaginal exposure to HIV.
- For people planning to discontinue daily oral PrEP, ongoing use for 7 to 28 days after last HIV exposure is recommended. This timeframe aligns with recommendations for post-exposure prophylaxis.

- For people who become pregnant while receiving PrEP, including drugs not yet approved for PrEP during pregnancy (e.g., long-acting injectable cabotegravir [CAB-LA], tenofovir alafenamide [TAF]), clinicians are strongly encouraged to register them with the Antiretroviral Pregnancy Registry as early in pregnancy as possible.
- Efficacy studies evaluating TAF/emtricitabine (FTC) as PrEP in people with vaginal exposure have not been completed. Therefore, the Panel does not recommend TAF/FTC as PrEP for this population, including during pregnancy and postpartum. Additionally, TDF/FTC pharmacokinetic data cannot be readily extrapolated to TAF/FTC.

Reproductive Options When One or Both Partners Have HIV

- Rescreening for genital tract infections while attempting to conceive may be considered based on individual risk and duration of the preconception period.
- To prevent HIV acquisition, the Panel recommends that health care providers discuss PrEP with all sexually active people without HIV, including individuals who are trying to conceive. PrEP should be offered to those who desire PrEP or have specific indications for PrEP.

Initial Evaluation and Continued Monitoring of HIV During Pregnancy

- Revisions have been made to clarify recommendations for CD4 T lymphocyte cell count monitoring that align with guidance in the Adult and Adolescent Antiretroviral Guidelines.

Antiretroviral Therapy for People with HIV Who Are Trying to Conceive

- Data are not available about the efficacy and safety of injectable cabotegravir (CAB) and rilpivirine (RPV) during pregnancy. For those who are considering switching regimens prior to conception to prevent fetal exposure, it is important to recognize that CAB and RPV injections must be stopped at least 1 year before conception to ensure that these long-acting drugs are fully eliminated.
- Among those on long-acting injectable antiretroviral therapy (ART) who have a history of poor adherence to oral medications, switching from long-acting injectable CAB and RPV to oral ART to prepare for conception may be associated with increased risk of viral rebound and non-nucleoside reverse transcriptase inhibitor resistance. Shared decision-making should be used when making decisions about changing to an oral regimen.

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

- The following dolutegravir (DTG)-based regimens are *Preferred* as initial ART for pregnant people who have never received antiretroviral (ARV) drugs:
  - DTG plus (tenofovir disoproxil fumarate [TDF] or TAF) plus (FTC or lamivudine [3TC]) *or*
  - DTG plus abacavir (ABC) plus 3TC—only for individuals who are HLA-B*5701 negative and without chronic hepatitis B virus (HBV) coinfection

- However, in people with a history of CAB exposure for PrEP, the following ritonavir-boosted darunavir (DRV/r)–based regimens are *Preferred* for initial ART due to concerns about integrase strand transfer inhibitor (INSTI) resistance mutations:
  - DRV/r plus (TDF or TAF) plus (FTC or 3TC) *or*
  - DRV/r plus ABC plus 3TC—only for individuals who are HLA-B*5701 negative and without HBV coinfection
- In other situations, DRV/r is now recommended as an *Alternative* rather than a *Preferred* ARV for use in pregnancy; see Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs in Pregnant People and Nonpregnant People Who Are Trying to Conceive.
- Table 6. What to Start: Initial Antiretroviral Regimens During Pregnancy for People Who Are Antiretroviral-Naive has been revised to reflect updated Panel recommendations for persons who are ARV naive and list the advantages and disadvantages of ARV combinations and regimens.

Pregnant People Who Have Not Achieved Viral Suppression on Antiretroviral Therapy

- Revisions were made to update bulleted recommendations and text on the definition, evaluation, and management of lack of viral suppression and virologic failure.
- The Panel does not recommend adding a single ARV drug to a virologically failing regimen. The Adult and Adolescent Antiretroviral Guidelines discuss specific regimen modifications for situations in which viral suppression has not been achieved or where there has been a rebound of viral load (see Virologic Failure) that can be considered in conjunction with Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs in Pregnant People and Nonpregnant People Who Are Trying to Conceive.

Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs in Pregnant People and Nonpregnant People Who Are Trying to Conceive

- Based on new data about pharmacokinetics in pregnancy and updated information in the Antiretroviral Pregnancy Registry, bictegravir (BIC) is now recommended as an *Alternative* ARV for use in pregnancy and for people who are trying to conceive; it was previously categorized as *Insufficient Data to Recommend* use in pregnancy. Data are still limited, but no safety concerns have been observed.
- DRV/r is now recommended as an *Alternative* rather than a *Preferred* ARV for use in pregnancy and for people who are trying to conceive. However, in pregnant people with a history of CAB exposure for PrEP, DRV/r is a *Preferred* ARV for initial ART regimens due to concerns about INSTI resistance mutations.
- DRV/r, rather than ritonavir-boosted atazanavir (ATV/r), is recommended as an option for initial ART in nonpregnant adults. However, DRV/r requires twice-daily dosing in pregnancy, and dosing frequency affects ARV adherence. For this reason, when a protease inhibitor–based regimen is indicated in pregnancy, some Panel members would use ATV/r rather than DRV/r.
- Panel recommendations for fostemsavir and ibalizumab (IBA) have been revised from *Not Recommended* to *Not Recommended Except in Special Circumstances* since they may be needed for some pregnant people with extensive treatment experience.

- Appendix C. Antiretroviral Counseling Guide for Health Care Providers has been updated to incorporate changes in the tables and text sections that address recommendations regarding the use of specific ARV drugs in pregnancy.

HIV-2 Infection and Pregnancy

- BIC was added to the ARV drugs that are recommended for treating HIV-2 infection during pregnancy and for people who are trying to conceive.
    - For patients with multidrug-resistant virus, IBA and lenacapavir (LEN) demonstrate *in vitro* potency against HIV-2 and may be considered; these drugs are *Not Recommended Except in Special Circumstances* for use in pregnancy.

Early (Acute and Recent) HIV Infection

- Based on changes to Panel recommendations on the use of BIC in pregnancy, BIC plus TAF plus FTC is now recommended as an *Alternative* ART regimen for pregnant people with early infection and without a history of prior use of CAB-LA as PrEP.

Initial Postnatal Management of the Neonate Exposed to HIV

- Information about recommended testing for viral coinfections in the infants with perinatal HIV exposure (e.g., congenital cytomegalovirus, hepatitis C virus, HBV) with links to resources about testing and care has been added.

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

- Table 14: Antiretroviral Drug Use in Pregnant People with HIV: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy and the individual drug sections have been reviewed and updated. A new drug section was added for LEN. Although limited data in animals have not identified reproductive safety concerns, no data in humans are available about the use of LEN in pregnancy.

Panel Roster

Updated: January 31, 2024
Reviewed: January 31, 2024

Members of the Panel on Treatment of HIV During Pregnancy and Prevention of Perinatal Transmission

Revisions to the January 31, 2024, *Recommendations for the Use of Antiretroviral Drugs During Pregnancy and Interventions to Reduce Perinatal HIV Transmission in the United States* have been made by the U.S. Department of Health and Human Services Panel on Treatment of HIV During Pregnancy and Prevention of Perinatal Transmission (a Working Group of the Office of AIDS Research Advisory Council).

Members of the Panel	
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
Kristina M. Brooks, PharmD	University of Colorado Anschutz Medical Campus, Aurora, CO
Danielle Campbell, MPH	Los Angeles Women's HIV/AIDS Task Force, Los Angeles, CA
Rana Chakraborty, MD, MS, PhD	Mayo Clinic College of Medicine, Rochester, MN
Susan E. Cohn, MD, MPH	Northwestern University Feinberg School of Medicine, Chicago, IL (Retiree) Palo Alto VA Medical Center
Susan Cu-Uvin, MD	Alpert School of Medicine, Brown University, Providence, RI
Jennifer Jao, MD, MPH	Northwestern University Feinberg School of Medicine, Chicago, IL
Susana Keeshin, MD	The 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	The 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
Heather O'Connor	Buena Vista, VA
Anna Powell, MD, MS[a]	The Johns Hopkins University School of Medicine, Baltimore, MD
Lisa Rahangdale, MD, MPH	The University of North Carolina School of Medicine, Chapel Hill, NC
Julia Rosebush, DO, FAAP	The University of Chicago, Chicago, IL

Members of the Panel on Treatment of HIV During Pregnancy and Prevention of Perinatal Transmission

Rachel K. Scott, MD, MPH	MedStar Washington Hospital Center, MedStar Health Research Institute, Washington, DC Georgetown University, Washington, DC
Jeanne Sheffield, MD	The Johns Hopkins University School of Medicine, Baltimore, MD
Anandi Sheth, MD, MSc	Emory University School of Medicine, Atlanta, GA
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
Lynn M. Yee, MD, MPH	Northwestern University Feinberg School of Medicine, Chicago, IL
Rebecca Zash, MD	Harvard Medical School, Boston, MA

[a] American Congress of Obstetricians and Gynecologists liaison

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

Panel Co-chairs	
Elaine J. Abrams, MD	Columbia University, New York, NY
Andrea Ciaranello, MD, MPH	Massachusetts General Hospital, Harvard Medical School, Boston, MA
Mark Mirochnick, MD	Boston University Chobanian and Avedisian School of Medicine, Boston, MA
Rodney L. Wright, MD, MSc	Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY

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 of the Panel on Treatment of HIV During Pregnancy and Prevention of Perinatal Transmission

Members from the U.S. Government	
Michelle Chevalier, MD, MPH	Bureau of Global Health Security and Diplomacy, U.S. Department of State, Washington, DC
Athena P. Kourtis, MD, PhD, MPH	Centers for Disease Control and Prevention, Atlanta, GA
Margaret Lampe, RN, MPH, CPH	Centers for Disease Control and Prevention, Atlanta, GA
Charu Mullick, MD	U.S. Food and Drug Administration, Silver Spring, MD
George K. Siberry, MD, MPH	United States Agency for International Development, Washington, DC
Prabha Viswanathan, MD	U.S. Food and Drug Administration, Silver Spring, MD
Ronald Wilcox, MD	Health Resources and Services Administration, Rockville, MD

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

Panel Coordinator	
Olusegun Adeyemi, MD, PhD, MPH	The Scientific Consulting Group, Gaithersburg, MD

Financial Disclosure

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Financial Disclosure List for Members of the U.S. Health and Human Services Panel on Treatment of HIV During Pregnancy and Prevention of Perinatal Transmission (Reporting Period: December 2022 to December 2023)

Name	Panel Status	Company	Relationship
Abrams, Elaine J.	M	None	N/A
Badell, Martina L.	M	None	N/A
Best, Brookie M.	M	PPD	DSMB
		IQVIA	DSMB
		Syneos Health	DSMB
		Easthorn	DSMB
Boucoiran, Isabelle	ExOM	Moderna, Altona, Ferring	Research Support
Brooks, Kristina M.	M	ViiV Healthcare	Consultant
Campbell, Danielle	M	None	N/A
Chakhtoura, Nahida	ES	None	N/A
Chakraborty, Rana	M	None	N/A
Chevalier, Michelle	HHS	None	N/A
Ciaranello, Andrea	CC	None	N/A
Cohn, Susan E.	M	ViiV Healthcare	Scientific Advisory Board
Cu-Uvin, Susan	M	AIDS Malignancy Consortium	DSMB
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
Lampe, Margaret	HHS	None	N/A
Lazenby, Gweneth B.	M	None	N/A
Levison, Judy	M	None	N/A
Matthews, Lynn	M	Gilead	Research Support

Financial Disclosure List for Members of the U.S. Health and Human Services Panel on Treatment of HIV During Pregnancy and Prevention of Perinatal Transmission (Reporting Period: December 2022 to December 2023)

Name	Panel Status	Company	Relationship
Mirochnick, Mark	CC	ViiV Healthcare	Research Support
		Merck	Research Support
		Gilead	Research Support
		AstraZeneca	DSMB
Mofenson, Lynne M.	M	ViiV Healthcare	Research Support
Momplaisir, Florence	M	None	N/A
Mullick, Charu	HHS	None	N/A
O'Connor, Heather	M	None	N/A
Pollock, Lealah	ExOM	None	N/A
Prioleau, Fatima Y.	M	None	N/A
Powell, Anna	M	None	N/A
Rahangdale, Lisa	M	None	N/A
Rosebush, Julia	M	None	N/A
Scott, Rachel K.	M	ViiV Healthcare	Research Support
		GSK	Research Support
		Gilead	Research Support
Sheffield, Jeanne	M	None	N/A
Sheth, Anandi	M	None	N/A
Short, William R.	M	ViiV Healthcare	Consultant
		Janssen	Consultant
Siberry, George K.	M	None	N/A
Sissoho, Fatoumatta	M	None	N/A
Spector, Stephen A.	M	Johnson & Johnson	Stockholder
Storm, Deborah	C	Merck	Stockholder
		Eli Lilly and Company	Stockholder
		Roche	Stockholder
Viswanathan, Prabha	HHS	None	N/A
Wilcox, Ronald	HHS	None	N/A

Financial Disclosure List for Members of the U.S. Health and Human Services Panel on Treatment of HIV During Pregnancy and Prevention of Perinatal Transmission (Reporting Period: December 2022 to December 2023)

Name	Panel Status	Company	Relationship
Wright, Rodney L.	M	None	N/A
Yee, Lynn M.	M	None	N/A
Zash, Rebecca	M	None	N/A

Key: DSMB = Data and 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

Introduction

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Recommendations regarding HIV screening in pregnancy, the treatment of pregnant people with HIV, and the use of antiretroviral (ARV) drugs to prevent perinatal (vertical) HIV transmission (i.e., during pregnancy and labor and delivery) and postnatal HIV transmission (i.e., through breastfeeding) 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 people with HIV, scheduled cesarean delivery for people with plasma HIV RNA >1,000 copies/mL near delivery, appropriate infant ARV management, and infant feeding counseling have resulted in a dramatic decrease in the rate of perinatal transmission of HIV to 1% or less in the United States and Europe.[2-4] In the United States, the estimated number of annual live births to pregnant people with HIV decreased from 4,587 in 2010 to 3,525 in 2019, and the number of U.S.-born infants with perinatal HIV infection decreased from 74 in 2010 to 32 in 2019.[4]

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 a rate of <1% among infants exposed to HIV.[5] However, incomplete implementation of routine antenatal HIV testing and other recommended interventions remains a barrier to achieving this goal.[3,6] 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.[7-9] Testing coverage is also poorer in subgroups that are perceived by health care providers to be at low risk of HIV acquisition (e.g., married, White, non-Hispanic, or multiparous).[10,11] Additionally, despite recommendations for repeat HIV testing in the third trimester for people at high risk of acquiring HIV and rapid testing of the birthing parent in labor or newborn testing when HIV status of the birthing parent is not known, implementation is incomplete, and many states do not have laws in place to require testing in such circumstances.[12,13] To address such challenges, many states and the District of Columbia have developed additional strategies to advance progress toward eliminating perinatal HIV transmission.[14] To further support HIV prevention and the reduction of perinatal HIV transmission, the Panel on Treatment of HIV During Pregnancy and Prevention of Perinatal Transmission (the Panel) has now added guidance about the use of HIV pre-exposure prophylaxis in people at risk of HIV acquisition who are trying to conceive, pregnant, postpartum, or breastfeeding (see Pre-Exposure Prophylaxis (PrEP) to Prevent HIV During Periconception, Antepartum, and Postpartum Periods).

In addition to primary prevention of HIV infection in people who can become pregnant, the best way to prevent HIV acquisition in infants is to focus on appropriate overall medical care for cisgender women, transgender men, and gender-diverse individuals 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 pregnant person with HIV receives ART that sustainably suppresses viral replication to below the level of viral load assay detection as early as possible during pregnancy or, ideally, before conception.

Additionally, in the setting of maternal ART that achieves consistently undetectable plasma viral load throughout pregnancy and the postnatal period along with appropriate neonatal ARV prophylaxis, the risk of HIV transmission postnatally through breast milk may be up to 1%. In response to these data, this Panel—as well as guidelines in many high-resource countries such as Canada, Britain, and Switzerland—recommend that pregnant people receive patient-centered, evidence-based counseling on infant feeding options, including breastfeeding[15,16] (see Infant Feeding for Individuals with HIV in the United States).

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 people who are pregnant or are trying to conceive. The National Institutes of Health (NIH) 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 people who are pregnant (or who may become pregnant), the Panel generally uses data from efficacy studies performed in nonpregnant adults; however, because short-term tolerability and safety may be different in pregnancy and drug exposure can change during pregnancy, evidence from direct safety and pharmacokinetic (PK) studies in pregnant people is required.[17]

In addition to considering direct evidence about short-term safety in pregnant people, the Panel also must 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. Robust evidence about fetal safety is not available at the time of drug licensure and remains limited for most licensed drugs.[18]

When strong evidence of harm to the fetus (or birthing parent) 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 people 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 people who are pregnant or breastfeeding, or in those who are of reproductive potential.[19-23]

In the meantime, to ensure that pregnant people are not denied the best available ART—while acknowledging that some drugs have not yet been evaluated sufficiently for evidence of harm to the fetus or birthing parent—the Panel uses a graded approach to make recommendations for regimens to use during pregnancy. Selection of ARV drugs should be individualized according to the pregnant person's ARV history, results of drug-resistance testing, and presence of comorbidities. In general, people who are already on a fully suppressive regimen when pregnancy occurs should continue their regimens. The Panel classifies ARV drugs for use in people who are pregnant or trying to conceive as *Preferred*, *Alternative*, *Insufficient Data to Recommend*, *Not Recommended Except in Special Circumstances*, and *Not Recommended* (see Table 6. What to Start: Initial Antiretroviral Regimens During Pregnancy for People Who Are Antiretroviral-Naive and Table 7. Situation-Specific

Recommendations for Use of Antiretroviral Drugs in Pregnant People and Nonpregnant People Who Are Trying to Conceive):

- *Preferred:* ARV drugs that are designated as *Preferred* in pregnancy are those that have proven durable efficacy in clinical trials in adults. *Preferred* drugs 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 with other ARV options, incorporating outcomes for pregnant people, fetuses, or newborns. Some *Preferred* drugs may have minor toxicity or incompletely evaluated teratogenicity risks that are offset by other advantages for people with HIV who are pregnant or trying to conceive.
- *Alternative:* Preferred ARV drugs for nonpregnant adults that do not meet the above criteria can be considered as options for *Alternative* drugs in pregnant people when available data on the use of these drugs in pregnancy are generally favorable, but still limited. Most *Alternative* drugs or combinations 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. Some *Alternative* drugs or combinations may have known risks that are offset by other advantages for people 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 people. In some cases, it may be appropriate to continue using these drugs or drug combinations in patients who become pregnant on ART that has been fully suppressive and well tolerated, with consideration of additional virologic monitoring during pregnancy.
- *Not Recommended Except in Special Circumstances:* Although some drugs are not recommended for initial ART in ART-naive people because of specific safety concerns or very limited safety and efficacy data in pregnancy, there may be circumstances in which ART-experienced people need to initiate or continue using specific drugs to reach or maintain viral suppression.
- *Not Recommended:* Some drugs are designated as *Not Recommended* in pregnancy because they have inferior virologic efficacy (and thus are not recommended for adults in general), because PK data demonstrate low drug levels and a risk of viral rebound during pregnancy, or because there is evidence of serious safety concerns for the fetus or birthing parent.

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 January 2023 *Recommendations for the Use of Antiretroviral Drugs During Pregnancy and Interventions to Reduce Perinatal HIV Transmission in the United States*. The Panel, a working group of the 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., Pregnancy and Postpartum HIV Testing and Identification of Perinatal and Postnatal HIV Exposure, Diagnosis of HIV Infection in Infants and Children, Antiretroviral Management of Infants with Perinatal HIV Exposure or HIV Infection), as well as to ensure general harmony between the guidelines. Health care providers should discuss the information in these guidelines with pregnant people with HIV in

order to make collaborative, informed decisions regarding the use of ARV drugs during pregnancy, the use of scheduled cesarean delivery to reduce the risk of perinatal transmission of HIV, the use of ARV drugs in infants who have been exposed to HIV, and the method of infant feeding.

The guidelines are structured to address the care of all pregnant individuals with HIV, 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 gender-diverse people who are pregnant or are trying to conceive often are not available. The Panel continues to advocate for greater inclusion of transgender and gender-diverse people in research. When making recommendations, the Panel will strive for clarity about the appropriateness of extrapolating information from study populations of cisgender women to all people assigned female sex at birth. The Panel has begun to make changes in language throughout the guidelines to be inclusive of transgender and gender-diverse individuals assigned female sex at birth. Gender-inclusive language is now used for recommendations and general content (e.g., using "pregnant people" or "pregnant patients" vs. "pregnant women" when appropriate). The Guidelines will continue to refer to cisgender women as "women" and will refer to transgender and gender-diverse individuals where indicated for specific content. When reviewing data, results will be presented using the same terms used in the studies and publications being described (e.g., women, pregnant women, transgender men). The Panel is committed to updating and maintaining gender-inclusive language throughout the guidelines and has developed a new section to provide additional content (see Perinatal HIV Prevention for Transgender and Gender-Diverse People Assigned Female at Birth), in addition to content available in the Adult and Adolescent Antiretroviral Guidelines (see Transgender People with HIV). The Panel recognizes the importance of the countless contributions to date of the many cisgender women who have shaped our current scientific knowledge base for perinatal HIV treatment, care, and prevention through their participation in research studies in the United States and internationally. Without them, this work and these guidelines would not be possible. At the same time, changes to incorporate gender-inclusive language highlight the importance of providing care that addresses the needs of transgender and gender-diverse populations and begins to close a gap in providing gender-affirming pregnancy-related care and perinatal HIV prevention services.

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 people are evolving rapidly, 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 patients with HIV or at risk for HIV and their children, and it serves as a resource for obtaining expert consultation on individual cases.

The Panel's recommendations are designed to ensure that cisgender women, transgender men, and gender-diverse individuals who can become pregnant receive the full benefit of ART for their own health and to prevent perinatal transmission. However, the Panel recognizes that people have the right to make informed choices about treatment during pregnancy, even when their choices differ from their health care providers' recommendations.

The current guidelines have been structured to reflect the management of an individual birthing parent–infant pair and are organized into a brief discussion of prepregnancy care followed by principles for managing the care of pregnant people and their infants 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, including updated considerations around infant feeding in the United States. Alternative antiretroviral drug recommendations 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 people with HIV, prevent HIV acquisition during pregnancy, and prevent perinatal HIV transmission in infants exposed to HIV.
Panel Members	The Panel is composed of approximately 41 voting members who have expertise in managing the care of pregnant people 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 people and interventions for the prevention of perinatal transmission. The U.S. government representatives, appointed by their agencies, include at least one representative from each of the following U.S. Department of Health and Human Services agencies: Centers for Disease Control and Prevention (CDC), U.S. Food and Drug Administration (FDA), Health Resources and Services Administration (HRSA), and 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 people with HIV and infants who have been exposed to HIV
Developer	The Panel on Treatment of HIV During Pregnancy 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 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 substantive comments or votes against approval are made, 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 people 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 people; 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 people of reproductive potential is discussed briefly 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 Clinicalinfo website until the guidelines can be updated with the 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 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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Pregnancy and Postpartum HIV Testing and Identification of Perinatal and Postnatal HIV Exposure

Updated: January 31, 2024
Reviewed: January 31, 2024

Panel's Recommendations

- HIV testing is recommended for all sexually active people and should be a routine component of pre-pregnancy care (AII).
- All pregnant people should receive opt-out HIV testing as early as possible during each pregnancy (see Laboratory Testing for the Diagnosis of HIV Infection: Updated Recommendations and 2018 Quick Reference Guide: Recommended Laboratory HIV Testing Algorithm for Serum or Plasma Specimens from the Centers for Disease Control and Prevention [CDC]) (AII).
- Partners of all pregnant people should be referred for HIV testing when their status is unknown (AIII).
- Repeat HIV testing in the third trimester is recommended for pregnant people with negative initial HIV 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 people per year, those who reside in jurisdictions (states or counties) with elevated HIV incidence among females aged 15 to 45 years (>17 per 100,000 females aged 15–45 years), or those who reside in states or territories that require third-trimester testing (AII). Annual state and county-level HIV diagnosis rates are available at CDC's National Center for HIV, Viral Hepatitis, Sexually Transmitted Diseases, and Tuberculosis Prevention AtlasPlus webpage.
- Repeat HIV testing is recommended for pregnant people with a sexually transmitted infection, with signs and symptoms of acute HIV infection, or with ongoing exposure to HIV (AIII). Initiation of pre-exposure prophylaxis (PrEP) is recommended if HIV testing is negative (AIII). See Pre-Exposure Prophylaxis (PrEP) to Prevent HIV During Periconception, Antepartum, and Postpartum Periods for more information.
- Expedited[a] HIV testing should be performed during labor or after delivery for people 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). HIV antigen/antibody testing should be available 24 hours a day, and results should be available within 1 hour. If results of expedited[a] HIV testing are positive, intrapartum intravenous zidovudine prophylaxis should be initiated immediately (AI); see Intrapartum Care for People with HIV.
- When acute HIV infection is suspected during pregnancy or the intrapartum period or while breastfeeding, a plasma HIV RNA assay should be performed in conjunction with an antigen/antibody immunoassay (AIII).
- When a person has a positive HIV test result during labor and delivery or postpartum, an HIV-1/HIV-2 antibody differentiation assay and an HIV RNA assay should be performed on the birthing parent (AI). In these situations, an HIV nucleic acid test (NAT) should be performed on the infant, with immediate initiation of presumptive HIV therapy appropriate for an infant at high risk of perinatal HIV transmission (AI); see Diagnosis of HIV Infection in Infants and Children for additional information.
- If HIV test results of the birthing parent are unavailable at birth, the newborn should be tested using an expedited[a] antibody test to identify perinatal HIV exposure (AI). If positive, an HIV NAT should be performed on the infant, and the birthing parent should be offered standard HIV diagnostic testing as soon as possible (AI).
  - In this situation, presumptive HIV therapy appropriate for infants who are at high risk of perinatal HIV transmission should be initiated immediately (AI). See Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection for guidance.
  - For people with an initial positive HIV test during labor or delivery or immediately postpartum who were planning to breastfeed, the Panel recommends against breastfeeding. Breast milk should be expressed and stored appropriately until all supplemental HIV tests are reviewed and are negative (AI).
- For postpartum people at increased risk of HIV acquisition, HIV testing and PrEP should be offered. If the parent is breastfeeding, consult an HIV specialist regarding frequency of HIV testing for the breastfeeding parent and/or infant (AIII).

- HIV test results of the birthing parent should be documented in the newborn's medical record and communicated to the newborn's primary care provider (AIII).
- To identify perinatal HIV exposure and possible HIV infection, HIV testing is recommended for infants and children in foster care and adoptees for whom the HIV status of the birthing parent is unknown (AIII) (see Diagnosis of HIV Infection in Infants and Children).

[a] The term "expedited" is used to designate HIV testing performed in situations when a very short turnaround time is optimal. Expedited testing is dependent on the available HIV tests in each facility and may include antigen/antibody immunoassays or antibody-only assays; see Approved HIV Tests in the text below.

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 postpubertal adolescents

Overview

Incident HIV infection during pregnancy or postpartum among people who are breastfeeding represents a period of high viremia and significantly increased risk of infant HIV acquisition. Similarly, entering pregnancy without knowledge of HIV infection also presents a high risk of perinatal transmission. This section addresses HIV testing in pregnancy, during labor and delivery, and postpartum. The section also addresses HIV testing to identify HIV perinatal and postnatal exposure in infants. For guidance on diagnosis of HIV in infants and children, see Diagnosis of HIV in Infants and Children.

Approved HIV Tests and Recommended HIV Testing Algorithm

There are multiple U.S. Food and Drug Administration (FDA)–approved tests available for the diagnosis of HIV infection. Clinicians should familiarize themselves with the testing available at their facilities, including the turnaround time for receiving results and test performance characteristics (e.g. sensitivity, specificity). For the purposes of this section, three types of testing are discussed: antigen/antibody immunoassays; antibody-only immunoassays; and HIV nucleic acid tests (NATs).

- Antigen/antibody immunoassays: Most routine laboratory testing for HIV currently uses antigen/antibody tests. Because these tests also detect HIV p24 antigen, they can detect acute HIV infection as early as 1 to 2 weeks after appearance of HIV RNA and before appearance of HIV antibody. These tests also detect HIV-2 infection. Laboratory-based tests require trained laboratory staff, and results can be available within 1 hour, but in some hospitals the test may not be readily available 24 hours a day. One FDA-approved antigen/antibody test can be performed at the point of care (POC), provides results after 20 minutes, and must be read before 30 minutes. Using timed seroconversion panels, this POC antigen/antibody test has been shown to detect HIV infection just 1 day later than laboratory-based antigen/antibody tests. However, it has lower specificity than laboratory-based antigen/antibody tests; therefore, false positive results are more likely than with laboratory-based tests.[1]

- Antibody-only immunoassays: Many antibody-only immunoassays in current use can be performed using blood from a finger stick or oral fluid and provide results within 30 minutes. Because of this very short turnaround time, they are often referred to as rapid tests. Many of these tests are also approved by the FDA for POC usage. Because these tests detect only antibody, acute HIV infection may be missed.
- HIV NAT: HIV-1 NAT detects HIV viral nucleic acid in blood. Depending on the type of HIV NAT, it may detect acute HIV infection, help diagnose HIV infection, and assess response to HIV therapy. The HIV RNA assay is the preferred NAT for possible acute infection and perinatally acquired infection. Different laboratories may have varying turnaround times for HIV NAT; some require several days before results are available.

- In this section, the term expedited is used to designate testing performed in situations when a very short turnaround time is optimal, such as when the individual is in labor but HIV status is undocumented. Expedited testing should be available in all delivery units 24 hours a day, and results should be available within 1 hour. Expedited testing is dependent on the available HIV tests in each facility and may include any of the three test types. In a setting with low HIV prevalence and/or frequent testing, false positive initial test results will be common. Expedited and/or concurrent NAT can be helpful in managing an initial positive HIV test result. An HIV-1/HIV-2 antibody differentiation assay may be helpful if an antibody response has been mounted.

The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV and the Panel on Treatment of HIV During Pregnancy and Interventions to Reduce Perinatal HIV Transmission (the Panels) **recommend that clinicians initiate HIV testing with an immunoassay that can detect HIV-1 antibodies, HIV-2 antibodies, and HIV-1 p24 antigen (referred to as an HIV antigen/antibody immunoassay).** The Panels' recommendations for HIV testing are based on the Centers for Disease Control and Prevention's (CDC's) 2014 Laboratory Testing for the Diagnosis of HIV Infection: Updated Recommendations.[2]

Individuals with a reactive antigen/antibody 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 immunoassay and a nonreactive differentiation test should be tested with an FDA-approved plasma HIV RNA assay to assess for acute HIV infection (see the CDC's 2018 Quick Reference Guide: Recommended Laboratory HIV Testing Algorithm for Serum or Plasma Specimens).

In some clinical settings, initial testing may be conducted with a **rapid HIV test,** which may detect a combination of antigen and antibodies or only HIV antibodies. Positive results on POC rapid tests should be followed first by a laboratory-based antigen/antibody assay using serum or plasma and when reactive, followed by a differentiation assay.[3]

Clinicians should assess a pregnant person's risk of acute HIV infection, particularly late in pregnancy, because people may receive a negative result for HIV immunoassays when they are in the window period (the time between infection and when the infection can be detected by a specific laboratory test). The antigen/antibody immunoassay may detect infection as early as 18 days after infection; antibody-only assays may not detect infection until as long as 45 days post-infection. However, during this period, the person with acute HIV will be viremic,[4] with a high risk of perinatal transmission. The HIV RNA assay can detect the presence of HIV as early as 10 days post-infection. **When acute HIV infection is suspected** during pregnancy, during the intrapartum period, or while breastfeeding, **a plasma HIV RNA assay should be performed in conjunction with an antigen/antibody immunoassay.** See Early (Acute and Recent) HIV Infection for more information.

Discordant or False Positive HIV Tests

Discordant HIV testing results can occur, requiring careful evaluation and often repeat tests. Early in HIV infection, before HIV seroconversion, the test combination of a positive antigen/antibody screen, negative HIV-1/HIV-2 antibody differentiation assay, and positive HIV RNA assay may be seen. This combination of results can occur because the immunoglobulin G–based antibody differentiation assay is positive later in infection than the antigen capture or the immunoglobulin M result in the antigen/antibody screen.

False positive results do occur with HIV testing. The frequency of false positive HIV testing is dependent both on the specificity of the assay and the prevalence of HIV in the population, so frequency may vary considerably. In a large urban hospital in Dallas, 21,163 women were screened using a combination antigen/antibody immunoassay. Reactive initial screens were followed by supplemental testing recommended by the CDC algorithm. Of the 190 who tested positive, 28 were determined to have a false positive HIV test, yielding a positive predictive value of 83% (95% confidence interval [CI], 77% to 88%) and a false positive rate of 0.16% (95% CI, 0.11% to 0.22%), using the ARCHITECT HIV Ag/Ab assay.[5] For women screened a second time in pregnancy, the rate of false positive results relative to true positive results may be higher, as it depends on the community risk of HIV acquisition over a short time period (i.e., the 6 months between first- and third-trimester testing).

For any positive HIV screen late in pregnancy, during labor, or immediately postpartum, an HIV RNA assay should be done at the same time as the supplemental HIV-1/HIV-2 antibody differentiation assay. The HIV RNA assay will be needed to resolve questions raised by discordant results between the antigen/antibody screen and the antibody differentiation assay.

The combination of a positive HIV antigen/antibody screen with a negative supplemental HIV-1/HIV-2 antibody differentiation assay and a negative HIV RNA assay is seen in people without HIV who have a false positive antigen/antibody screen.

Timing and Benefits of HIV Testing Prior to Conception or During Pregnancy

HIV infection should be identified before pregnancy (see Prepregnancy Counseling and Care for Persons of Childbearing Age with HIV) or as early as possible in pregnancy. In the United States, approximately 20% to 34% of infants with perinatal HIV exposure were born to people whose HIV diagnosis was not known before pregnancy.[6] Early diagnosis provides the best opportunity to improve the pregnant person's health and pregnancy outcomes and to prevent infant acquisition of HIV. Universal voluntary HIV testing is recommended as the standard of care for all pregnant people in the United States by the Panels, CDC, American Academy of Pediatrics, American College of Obstetricians and Gynecologists, and U.S. Preventive Services Task Force.[7-11] For pregnant people, HIV testing should be performed wherever a person seeks care (including emergency departments and prenatal clinics) to avoid missed opportunities to identify HIV infection. Repeat HIV testing should be performed in the third trimester for people who are at increased risk of acquiring HIV or who are living in areas of high HIV incidence. Repeat testing is also recommended when pregnant individuals are diagnosed with sexually transmitted infection (STI), or when they show symptoms and signs of acute HIV infection. Pregnant people with unknown or undocumented HIV status who present to care in labor should be tested before delivery or as soon as possible after delivery.[12-15] Because women are more susceptible to HIV acquisition during pregnancy and the postpartum period,[16] HIV testing provides an opportunity for clinicians to initiate a discussion about preventive interventions, including educating and counseling about pre-exposure prophylaxis (PrEP) for a pregnant person who is at risk for acquiring HIV. See Pre-exposure Prophylaxis (PrEP) to Prevent

HIV During Periconception, Antepartum, and Postpartum Periods and guidance available on CDC's Pre-exposure Prophylaxis (PrEP) page for more information.

Determining an individual's HIV status before they become pregnant or during the antenatal period enables:

- People with HIV to receive appropriate antiretroviral therapy (ART) and prophylaxis against opportunistic infections;
- Initiation of treatment to maintain and improve health and to decrease risk of perinatal HIV transmission and transmission to partners[7,17,18];
- Referral of partners for testing, providing an opportunity for treatment initiation by partners testing positive, PrEP initiation by serodifferent partners testing negative, and counseling on other preventive measures (see Pre-exposure Prophylaxis (PrEP) to Prevent HIV During Periconception, Antepartum, and Postpartum Periods);
- Counseling of pregnant people with HIV about recommended modes of delivery based on individualized risks of perinatal transmission of HIV[19-21];
- Provision of an appropriate antiretroviral (ARV) prophylaxis regimen to the newborn to reduce risk of infant HIV acquisition (see Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection);
- Shared decision-making on infant feeding choice, specifically breastfeeding or use of replacement feeding (see Infant Feeding for Individuals with HIV in the United States); *and*
- Early diagnostic evaluation of infants exposed to HIV, as well as testing of other children, to permit prompt initiation of ART and any indicated prophylaxis measures (see Diagnosis of HIV Infection in Infants and Children, Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection, and Table 6. What to Start: Initial Antiretroviral Regimens During Pregnancy for People Who Are Antiretroviral-Naive).[8,22,23]

Finally, all HIV testing should be performed in a manner that is consistent with state and local regulations. The CDC recommends the "opt-out" approach, which is allowed in many jurisdictions and involves notifying a pregnant person that HIV testing will be performed as part of routine care unless they choose not to be tested.[7] The "opt-in" approach involves obtaining specific consent before testing, and this approach has been associated with lower testing rates.[24,25] Despite the guidelines for universal HIV screening of pregnant people, recent studies indicate that fewer than 80% of women report having been tested for HIV during pregnancy.[26,27] The mandatory newborn HIV testing approach, which has been adopted by several states, involves testing newborns with or without consent of the birthing parent. In some areas, this applies to all newborns; in others, it applies only when the birthing parent of the newborn has declined prenatal or intrapartum testing.

Repeat HIV Testing in the Third Trimester

Repeat HIV testing during the third trimester, before 36 weeks of gestation, is recommended for people with negative results on their initial HIV tests during pregnancy who:

- Are at high risk of acquiring HIV (i.e., those who inject drugs or have sex with people who inject drugs, those who exchange sex for money or drugs, those who have a sex partner with HIV who has a detectable or unknown HIV viral load, those who have had a new sex partner or more than one sex partner during the current pregnancy,[7] those who have a suspected or diagnosed STI during pregnancy,[10] those who have recently immigrated from a high-burden HIV setting, or

those who have a partner who either recently immigrated from a high-burden HIV setting or recently traveled to such a setting); *or*

- Are receiving health care in facilities where prenatal screening identifies one or more pregnant people with HIV per 1,000 screened or reside in a jurisdiction (state or county) that has an elevated incidence rate of HIV in females aged of 15 to 45 years. An annual HIV diagnosis rate ≥17 per 100,000 females aged 15 to 45 years can be used as a proxy for elevated HIV incidence. Annual state- and county-level HIV diagnosis rates by age are available at the CDC's National Center for HIV, Viral Hepatitis, Sexually Transmitted Diseases, and Tuberculosis Prevention AtlasPlus webpage[7,10]; *or*
- Reside in states or territories with statutes or regulations that require third-trimester testing. In a 2020 article, these included Arizona, Connecticut, Delaware, Florida, Georgia, Illinois, Louisiana, Maryland, Nevada, New Jersey, North Carolina, Tennessee, Texas, Virginia, and West Virginia.[28] Clinicians should check current requirements in their jurisdictions; *or*
- Have signs or symptoms of acute HIV (e.g., fever, lymphadenopathy, skin rash, myalgia, headaches, oral ulcers, leukopenia, thrombocytopenia, elevated transaminase levels).[7,10,29,30]
- In addition, third-trimester testing should be offered to pregnant people who perceive themselves as being at increased risk for HIV infection (regardless of whether or not they fit any of the above criteria). Pregnant people who decline testing earlier in pregnancy should be offered testing again during the third trimester.

An antigen/antibody immunoassay should be used for third-trimester testing because these tests have a higher sensitivity in the setting of acute HIV infection than older antibody tests.[2,31] If acute HIV infection is suspected, a plasma HIV RNA assay should be performed in conjunction with an antigen/antibody immunoassay. See Early (Acute and Recent) HIV Infection for more information.

Providers should be proactive in assessing a pregnant person's HIV acquisition risk and implementing third-trimester HIV retesting when indicated. A 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.[15] A study of data from 2007 to 2014 on children in Florida with perinatal HIV exposure found that perinatal HIV transmission was associated with poor or late prenatal care, diagnosis of HIV during labor and delivery or after birth, and, in some cases, acute maternal infection (as indicated by negative results for initial tests).[32]

HIV Testing During Labor in People with Unknown HIV Status

People in labor whose HIV status is undocumented and those who tested negative early in pregnancy but are at increased risk of HIV infection and were not retested in the third trimester should undergo expedited HIV testing.[7-9,22,33,34]

- Perform an expedited HIV test—either an antigen/antibody immunoassay that can provide results within 1 hour or the most sensitive rapid test (includes rapid POC tests) available for people in labor. An HIV RNA assay should also be performed for individuals with suspected acute HIV infection. In a setting with low prevalence and/or frequent testing, false positive initial test results will be common. Expedited and/or concurrent NATs can be helpful in managing an initial positive HIV test result.[35]
- If the initial HIV test result is negative (nonreactive), no further testing is required unless acute HIV infection is suspected (see Acute HIV Infection During Pregnancy or Breastfeeding below).[2]

- A positive antigen/antibody immunoassay or rapid HIV test result must be immediately followed by a supplemental HIV-1/HIV-2 antibody differentiation assay, as well as an HIV RNA assay for the birthing parent and an HIV NAT for the infant.[2] If possible, contact the laboratory to prioritize results.
- For delivery units, every effort should be made to have the ability to run a confirmatory supplemental test (HIV-1/HIV-2 antibody differentiation assay) seven days a week. If possible, results of HIV RNA assays should be available in 24 hours or less.
- For individuals with a positive HIV test result or suspected acute HIV infection during labor, provide counseling about HIV test results and implications for care.
    - Initiate IV zidovudine during labor (see Intrapartum Care for People with HIV).
    - Immediately initiate presumptive HIV therapy appropriate for infants who are at high risk of perinatal HIV transmission (see Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection or contact the National Clinician Consultation Center Perinatal HIV/AIDS hotline).
    - For individuals who were planning to breastfeed, the Panel strongly advises against initiating breastfeeding given the high risk of perinatal transmission. Breast milk should be expressed and stored appropriately until all supplemental HIV test results are reviewed and determined to be negative (see Infant Feeding for Individuals with HIV in the United States).

HIV Testing During the Postpartum Period

People who have not been tested for HIV during pregnancy or labor should be offered expedited testing during the immediate postpartum period. Postpartum HIV testing should be done using the antigen/antibody 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 the birthing parent is unavailable for testing, their newborn should receive HIV testing using an antigen/antibody immunoassay to assess perinatal HIV exposure, understanding that the results reflect the HIV status of the birthing parent. For infants testing positive, an HIV NAT should be sent immediately (see Diagnosis of HIV Infection in Infants and Children).[8,22]

Postpartum individuals who request HIV testing or are at increased risk of HIV acquisition (e.g., those who inject drugs or have sex with people who inject drugs, those who exchange sex for money or drugs, those who have a sex partner with HIV who has a detectable or unknown HIV viral load, those who have had a new sex partner or more than one sex partner during the current pregnancy,[7] those who have a suspected or diagnosed STI during pregnancy,[10] those who have recently immigrated from a high-burden HIV setting, or those who have a partner that either recently immigrated from a high-burden HIV setting or recently traveled to such a setting) should be offered HIV testing and PrEP. See Pre-exposure Prophylaxis (PrEP) to Prevent HIV During Periconception, Antepartum, and Postpartum Periods for more information. If the parent is breastfeeding, consult an HIV specialist regarding frequency of HIV testing in the birthing parent and/or infant.

When an initial HIV test is positive in birthing parents or infants, it is strongly recommended that clinicians initiate presumptive HIV therapy appropriate for infants who are at high risk of perinatal HIV transmission, ideally ≤6 hours after birth (see Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV). The birthing parent should be counseled against breastfeeding pending the results of supplemental testing, which should include a plasma HIV RNA assay. Breast milk can be expressed while HIV diagnostic testing is being completed, but it should not be given to the infant until testing confirms that the birthing parent 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 HIV exposure in the birthing parent, breastfeeding can be initiated. Consultation with a pediatric HIV specialist is strongly recommended if questions remain about the potential for acute infection in the birthing parent or ongoing infant risk of HIV exposure.

Infant HIV Testing When the Birthing Parent's HIV Test Results Are Unavailable

When the birthing parent's HIV test results are unavailable (e.g., they declined testing during pregnancy, infant or child is in foster care) or their accuracy cannot be evaluated (e.g., for internationally adopted infants and children), HIV testing of these infants or children is indicated to identify HIV exposure and possible infection.[8] If the birthing parent's HIV test results are unavailable at birth, the newborn should be tested using an expedited antibody test to identify perinatal HIV exposure. If positive, an HIV NAT should be performed on the infant, presumptive HIV therapy appropriate for infants at high risk for perinatal HIV transmission should be initiated immediately (see Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection for guidance), and the birthing parent should be offered standard HIV diagnostic testing as soon as possible. For older infants and children, the choice of test will vary based on the age of the child (see Diagnosis of HIV Infection in Infants and Children).

Acute HIV Infection During Pregnancy or Breastfeeding

Pregnancy and the early postpartum period are times of increased risk for HIV infection.[36] Risk of HIV exposure should be assessed in all people who are considering becoming pregnant, as well as in all pregnant and postpartum people who previously tested negative for HIV, including those who are breastfeeding. People with risk factors for HIV acquisition before, during, and after pregnancy should receive prevention counseling and appropriate interventions, including PrEP if indicated[36,37] (see Prepregnancy Counseling and Care for Persons of Childbearing Age with HIV and Pre-Exposure Prophylaxis [PrEP] to Prevent HIV During Periconception, Antepartum, and Postpartum Periods for more information). People who have acute HIV during pregnancy or lactation have an increased risk of perinatal transmission; acute HIV also increase risk for sexual transmission of HIV (see Early [Acute and Recent] HIV Infection).[38-42] The antigen/antibody immunoassay will detect acute HIV infection earlier than other immunoassays—within approximately 18 days of acquisition. When acute HIV infection is suspected, a plasma HIV RNA test should be sent as well as the antigen/antibody test, because virologic tests can detect the presence of HIV approximately 5 days earlier than the antigen/antibody immunoassay. People with possible acute HIV infection who are breastfeeding should cease breastfeeding immediately until HIV infection is confirmed or excluded.[43] 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 people with acute or early HIV, and their infants, should follow the recommendations in the Perinatal Guidelines (see Early [Acute and Recent] HIV Infection, Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection, and Infant Feeding for Individuals with HIV in the United States).

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 people 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 Prevent HIV During Periconception, Antepartum, and Postpartum Periods

Updated: January 31, 2024
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Panel's Recommendations
• Health care providers should discuss PrEP with all sexually active people without HIV, including individuals who are trying to conceive, pregnant, postpartum, or breastfeeding, to prevent HIV acquisition (AII); counseling should include the benefits of PrEP to prevent HIV acquisition and perinatal transmission (AI) and potential adverse effects of PrEP during periconception, pregnancy, postpartum, and breastfeeding periods (AII). Health care providers should offer PrEP to those who desire PrEP or have specific indications for PrEP (AII). • The preferred PrEP option for HIV prevention in people who have receptive vaginal sex during pregnancy and breastfeeding is tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) (AII). TDF/FTC is currently the only U.S. Food and Drug Administration (FDA)–approved PrEP option with known safety and efficacy data during pregnancy and breastfeeding. People who become pregnant while using TDF/FTC as PrEP can continue PrEP throughout pregnancy and breastfeeding. Risk for HIV acquisition should be reassessed, and people should be counseled regarding the benefits and risks of PrEP use in pregnancy and during breastfeeding (AII). • Providers should counsel patients about the importance of daily adherence to oral TDF/FTC PrEP to prevent HIV acquisition (AI). Patients should be counseled to use additional HIV prevention strategies (e.g., condoms) for the first 20 days after initiating TDF/FTC PrEP (BII). For patients with a planned PrEP discontinuation, people should continue use for 7 to 28 days after their last potential vaginal exposure (BII). Given the lack of data, episodic or non-daily PrEP is not recommended for protection against vaginal exposure to HIV (AIII). • 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 Center for Disease Control and Prevention's PrEP for the Prevention of HIV in the United States 2021 Update and Pregnancy and Postpartum HIV Testing and Identification of Perinatal and Postnatal HIV Exposure). Consider more frequent testing when clinically indicated (e.g., adherence challenges, nonstandard visit schedule). • Long-acting injectable cabotegravir (CAB-LA) is FDA-approved for people with vaginal exposure to HIV; however, for people with PrEP indications in pregnancy, CAB-LA dosing, efficacy, and safety remain unknown. If a person receiving cabotegravir (CAB) PrEP becomes pregnant, the limited available safety data and long half-life of CAB should be discussed with the patient with shared decision-making around ongoing PrEP use and options (AIII). Consider expert consultation.
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 pre-exposure prophylaxis (PrEP) is the use of specific antiretroviral (ARV) drugs to prevent HIV acquisition. Susceptibility to HIV acquisition is greater during the periconception period, throughout pregnancy, and through 6 months postpartum. Acute or recent HIV infection during pregnancy or breastfeeding is associated with an increased risk of perinatal HIV transmission (see Early [Acute and Recent] HIV Infection).[1,2] The Panel on Treatment of HIV Infection During Pregnancy and Prevention of Perinatal Transmission (the Panel) recommends that people without HIV who are planning to have a child or who are pregnant, postpartum, or breastfeeding should be

routinely counseled about PrEP for HIV prevention and offered PrEP or referred for PrEP services when indicated to prevent HIV acquisition and potential perinatal HIV transmission.[3] In cases when the individual has a partner with HIV and that partner is on antiretroviral therapy (ART) with sustained viral suppression, HIV is not transmitted through condomless sexual intercourse (see Reproductive Options When One or Both Partners Have HIV).

The use of combination tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) as daily oral PrEP to reduce HIV acquisition was approved by the U.S. Food and Drug Administration (FDA) in 2012 and the use of cabotegravir (CAB) as long-acting injectable PrEP was approved in 2021. When taken as prescribed, TDF/FTC provides greater than 90% protection against HIV acquisition. The HIV Prevention Trials Network (HPTN) 084 study found CAB to be 89% more effective than TDF/FTC.[4] Of the FDA-approved PrEP agents for people with receptive vaginal exposure, TDF/FTC is currently the only option with demonstrated safety in pregnancy and during breastfeeding. Tenofovir alafenamide (TAF)/FTC has not yet been studied for efficacy in people with vaginal exposure; therefore, TAF/FTC is not recommended for this population, including during pregnancy and postpartum.[5,6] The guidance in this section focuses on the use of TDF/FTC as PrEP during periconception, antepartum, and postpartum periods (through 6 months postpartum and/or throughout breastfeeding). Information about other PrEP agents is included below in "What Is Known About Other PrEP Agents During Periconception, Antepartum, and Postpartum Periods?"

Most research on PrEP cited in this section was conducted with participants who self-identified as women (presumed to be predominantly cisgender women). However, individuals who do not identify as women (i.e., transgender men, genderqueer or nonbinary individuals) can become pregnant, give birth, and breast/chestfeed. PrEP should be offered and promoted for all individuals with an indication for PrEP using a gender-affirming approach to care (see Perinatal HIV Prevention for Transgender and Gender-Diverse People Assigned Female at Birth and Transgender People with HIV in the Adult and Adolescent Antiretroviral Guidelines). Patients should be asked about their gender identity, including the pronouns they use, how they want to be referred to as a parent (e.g., birth parent, mother, father, another name), and terms they prefer to use (e.g., breastfeeding, chestfeeding).

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

Initiating PrEP

The Centers for Disease Control and Prevention (CDC) provides guidelines (see PrEP for the Prevention of HIV in the United States 2021 Update) for discussing PrEP with all adults and adolescents who have sex or inject drugs.[3] The Panel recommends that PrEP be discussed with all people without HIV who are planning for pregnancy and/or sexually active and those who are pregnant or postpartum. To address underutilization of PrEP and disparities in PrEP use among women,[7] it is important for clinicians and clinical programs to consider strategies such as provider education, standard protocols, clinic champions, and resource tools to optimize implementation and reduce barriers to accessing PrEP.[8-11] PrEP can be prescribed to those who request it and is also specifically indicated for individuals who—

- Have a history of bacterial sexually transmitted infection (STI), including gonorrhea, syphilis, or chlamydia[12,13];

- Have infrequent condom use with one or more partners of unknown HIV status, especially within a sexual network with high HIV prevalence;
- Are taking non-occupational post-exposure prophylaxis (nPEP) and anticipate ongoing indications for prevention, or have used multiple courses of nPEP[14];
- Engage in transactional sex;
- Have substance use disorder and/or substance use associated with sex;
- Have a partner with HIV with unknown or inconsistent virologic suppression;
- Have a history of experiencing intimate partner violence[15]; *or*
- Have a partner with any of the factors listed above.

Providers should counsel people with HIV whose partners may have indications for PrEP about benefits and indications for PrEP. When prescribing PrEP, clinicians should:

- Counsel individuals about potential risks and benefits of PrEP and all available strategies for reducing HIV acquisition risks during periconception, antepartum, and postpartum periods (see Reproductive Options When One or Both Partners Have HIV). People who become pregnant while using TDF/FTC PrEP can continue PrEP throughout their pregnancy.
- Explain that condomless sex with a partner who has sustained viral suppression is associated with no risk of HIV sexual transmission.[16-19]
- Explain that although it is unknown how long PrEP needs to be taken in order to be protected from vaginal HIV exposure, daily oral TDF/FTC must be taken for at least 20 days before drug levels are high in cervicovaginal tissues. Therefore, the Panel recommends 20 days of PrEP before considering an individual fully protected from HIV acquisition via vaginal exposure. See Time to Protection below for more details.
- Counsel about the importance of adherence and suggest adherence supports, such as use of a pillbox (see Adherence Support below).
- Counsel that episodic, "2-1-1," "on-demand," and/or non-daily PrEP has not been evaluated for vaginal exposure.
- Counsel individuals who are taking PrEP about the symptoms associated with acute HIV infection and instruct them to contact their provider immediately for HIV testing and further evaluation if symptoms occur (see Early [Acute and Recent] HIV Infection). Individuals experiencing symptoms of acute HIV infection should be advised to use a condom during sex, stop attempts at conception, and stop breastfeeding.
- Explain that PrEP does not protect against other STIs. Condom use is important for reducing STI acquisition.
- Regularly assess and discuss ongoing needs for PrEP.
- Inquire about partner status and offer partner HIV testing.
- Be aware that additional prescribing details, including for same day PrEP start and PrEP follow-up via telehealth, are offered in the CDC Guidelines for PrEP (see PrEP for the Prevention of HIV in the United States 2021 Update).[3]

- For people who become pregnant while receiving PrEP, clinicians are encouraged strongly to register them with the Antiretroviral Pregnancy Registry. The purpose of the Antiretroviral Pregnancy Registry is to detect any major teratogenic effect involving any of the registry drugs to which pregnant people are exposed, including ARV drugs used for PrEP.

An individual's indications for PrEP may change across periconception, antepartum, and postpartum periods. Therefore, discussions regarding the need for PrEP should be ongoing.

Laboratory Testing

Recommended laboratory testing for individuals receiving PrEP includes—

- HIV diagnostic testing with an antigen/antibody combination immunoassay at baseline. For people exposed to antiretrovirals as PrEP, delays can be seen in antigen/antibody detection during acute infection.[20] Therefore, the CDC recommends antigen/antibody combination immunoassay as well as HIV-RNA testing every 3 months, or more frequently if indicated based on clinical symptoms, for people taking tenofovir-containing PrEP regimens.
- HIV testing (i.e., antigen/antibody combination immunoassay, as well as HIV-RNA testing) for individuals taking PrEP during pregnancy should include HIV testing at entry into antenatal care, with re-testing in the second and third trimester. More frequent testing may be appropriate when clinically indicated (e.g., known adherence challenges) (see Pregnancy and Postpartum HIV Testing and Identification of Perinatal and Postnatal HIV Exposure).
- In the case of documented new HIV infection, discontinuation of PrEP and immediate referral to an HIV specialist for initiation of ART are recommended. If the patient is pregnant, they should receive appropriate care to prevent perinatal transmission. See Early (Acute and Recent) HIV Infection and Pregnant People with HIV Who Have Previously Received Antiretroviral Medications but Are Not Currently on Antiretroviral Medications.
- Renal function testing at baseline and then every 12 months for people <50 years of age and/or with estimated creatinine clearance (CrCl) over 90 mL/min. Otherwise, renal function should be monitored every 6 months. TDF/FTC as PrEP should not be initiated in patients with a confirmed calculated CrCl <60 mL/min. Clinicians should discontinue daily TDF/FTC as PrEP if a patient develops a confirmed calculated CrCl <50 mL/min.
- Testing for hepatitis B virus (HBV) infection for patients initiating PrEP, but PrEP initiation need not be delayed while awaiting results. 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 counseled regarding the risk for possible hepatitis flares when tenofovir-based PrEP is stopped.[21]
- Pregnancy testing at baseline and then as indicated.
- Testing for STIs (gonorrhea, chlamydia, syphilis) at baseline. Testing every 6 months is recommended for gonorrhea and syphilis for women. Annual testing for chlamydia is also recommended. More frequent testing can be offered as clinically indicated.
- Reference to additional information and details about recommended laboratory testing in the CDC's PrEP for the Prevention of HIV Infection in the United States 2021 Update, as needed.

Time to Protection

High adherence to daily pills is required to achieve effective drug concentrations of TDF and FTC in vaginal and cervical tissues. Studies in nonpregnant 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.[22-24] Although pharmacokinetic (PK) data are limited in pregnant women, they suggest that pregnant women taking daily PrEP experience lower tenofovir drug levels.[25,26] Given the increased volume of distribution and concomitant lower levels of TDF/FTC in plasma, the Panel recommends continued use of other prevention strategies until PrEP has been taken for at least 20 days and protection against transmission can be assumed in pregnant or postpartum PrEP users. Six or seven doses per week (or daily dosing) are needed to maintain drug levels in cervicovaginal tissue in nonpregnant women.[27] When people initiate PrEP and have not yet reached protective drug levels or struggle with daily adherence, other strategies (e.g., condoms) should be used to prevent HIV.

For people planning to discontinue daily oral PrEP, ongoing use for 7 to 28 days after last HIV exposure is recommended. This time frame aligns with recommendations for post-exposure prophylaxis.[28]

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. Opportunities to promote adherence and mitigate barriers to adherence should be addressed at each visit. Data suggest that some adherence challenges stem from adherence fatigue, low perceptions of personal risk, stigma, cost, misinformation about PrEP, peer perspectives, mental health challenges, and intimate partner violence.[29-31] Based on barriers, providers can discuss strategies tailored to each patient'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 patient's social network who can provide social support toward PrEP adherence. PrEP services are ideally delivered in a comprehensive manner and address social determinants of health—including how clients will access PrEP and related services—and address housing instability, access to health insurance, and transportation because these factors have been shown to interfere with adherence. The CDC provides a PrEP webpage and a PrEP chapter.

Contraception

Contraception is an important component of reproductive health care for people receiving PrEP who do not want to become pregnant.[16] No known significant drug–drug interactions exist between TDF and different modes of hormonal contraception used during periconception and the postpartum period.[32-34] For additional information, refer to CDC's U.S. Medical Eligibility Criteria for Contraceptive Use, 2016 and Update to U.S. Medical Eligibility Criteria for Contraceptive Use, 2016: Updated Recommendations for the Use of Contraception Among Women at High Risk for HIV Infection.

Background on Use of PrEP During Periconception, Antepartum, and Postpartum Periods

Women account for nearly 20% of new HIV diagnoses in the United States yet only account for 7% of people prescribed PrEP.[35,36] PrEP is recommended for all people with potential exposure to HIV.[3,37] Although data about the use of PrEP among periconception, pregnant, and postpartum people are less robust than for nonpregnant people,[38] PrEP is highly efficacious for women, and a large body of data from pregnant women using TDF/FTC as treatment for HIV and HBV suggests these agents are safe for pregnant and breastfeeding women and their infants.[39-42]

Susceptibility to HIV acquisition is greater during periconception, antepartum, and early postpartum periods through 6 months. Data suggest that people trying to conceive are at higher risk for HIV acquisition, likely due to increased condomless sex.[43,44] 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 trauma and microtrauma to the genital tract during delivery.[45-47] HIV incidence among women during pregnancy and postpartum is two to six times greater than HIV incidence outside of pregnancy.[47-51] Two large HIV prevention studies conducted in African countries demonstrated that 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% confidence interval [CI], 1.58–4.81).[52] In addition, people who acquire HIV while pregnant or breastfeeding are more likely to transmit HIV to their infant.[53-55]

For people who become pregnant while receiving PrEP, including drugs not yet approved for PrEP during pregnancy (e.g., long-acting injectable CAB [CAB-LA], TAF), clinicians are strongly encouraged to register them with the Antiretroviral Pregnancy Registry as early in pregnancy as possible.

Efficacy of Tenofovir Disoproxil Fumarate/Emtricitabine 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%. In women with detectable drug levels (or taking PrEP), PrEP protected against 90% of incident transmissions.[56] In a meta-analysis of all available clinical trial data, modeling suggested that if women adhere to at least 75% of doses, PrEP decreases HIV acquisition by 61% (relative risk 0.39; 95% CI, 0.25–0.60).[57]

Although people planning for pregnancy were not enrolled in these clinical trials, subsequent data suggest that PrEP uptake and adherence are high during periconception periods.[58-61]

Safety of Tenofovir Disoproxil Fumarate/Emtricitabine as PrEP for Women, Including Those Who Are Pregnant or Breastfeeding

Currently available data suggest that the benefits of TDF/FTC as PrEP to prevent HIV during periconception, pregnancy, and breastfeeding periods outweigh any potential toxicities. PrEP should be promoted as an HIV prevention strategy during periconception, pregnancy, and postpartum periods.[39,62] Additional data and primary sources describing what is known about TDF and FTC on birth outcomes, renal and bone effects for women, and renal and bone effects for infants exposed to TDF/FTC *in utero* or while breastfeeding are available in the Tenofovir Disoproxil Fumarate and Emtricitabine sections of these guidelines.

What Is Known About Other PrEP Agents During Periconception, Antepartum, and Postpartum Periods?

Efficacy studies evaluating TAF/FTC as PrEP in people with vaginal exposure have not been completed. Therefore, the Panel does not recommend TAF/FTC as PrEP for this population, including during pregnancy and postpartum. Additionally, TDF/FTC PK data cannot be readily extrapolated to TAF/FTC.[5,6]

Long-acting injectable CAB-LA is FDA-approved for use as PrEP in adults and adolescents. Data on the PK of CAB injections initiated or continued during pregnancy are not available; thus, the optimal dose and dosing interval during pregnancy are unknown. Limited PK tail data and safety data are reassuring for individuals who became pregnant on CAB-LA[63-69] (see Cabotegravir section). For people with PrEP indications who are planning for pregnancy, the optimal time to conceive after stopping injections is unknown.[69,70]

CDC guidance notes that CAB for PrEP may be initiated or continued in people who become pregnant while receiving injections when anticipated benefits outweigh the risks. For people with PrEP indications in pregnancy, as CAB dosing, efficacy, and other details are still unknown, TDF/FTC is preferred for initiation during pregnancy given the more robust safety and efficacy data.[39,42,71,72] If a person receiving CAB for PrEP becomes pregnant, the limited available safety data and long half-life of CAB should be discussed, and the patient and provider should engage in shared decision-making about whether to continue CAB or switch to TDF/FTC. Expert consultation may be beneficial to make the best decision about continuing or discontinuing CAB for PrEP in light of evolving data and knowledge. Important considerations include the following:

- Given the long half-life of injectable CAB, exposure from dosing during pre-pregnancy/early pregnancy is likely to continue throughout the pregnancy; thus, the benefit of stopping CAB at pregnancy is uncertain.
- CAB has structural similarities to other ARV drugs (e.g., dolutegravir) for which there are reassuring safety profiles in pregnancy.
- If CAB is stopped during pregnancy and HIV exposure is ongoing, TDF/FTC as PrEP and additional strategies for HIV prevention should be offered.

The dapivirine vaginal ring also reduces the risk of HIV acquisition via receptive vaginal exposure but has been permanently withdrawn from the FDA approval process.[73] Oral TAF/FTC has not yet been demonstrated to be effective for HIV prevention in people with receptive vaginal exposure.

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Prepregnancy Counseling and Care for People of Childbearing Age with HIV

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Panel's Recommendations
• Discuss reproductive desires and plans with all people with HIV who are of childbearing potential on an ongoing basis throughout the course of their care (AIII). • Provide information about effective and appropriate contraceptive methods to people who do not currently desire pregnancy (AI). Offer all contraceptive methods or refer for contraceptive services. Individuals with HIV can use all available contraceptive methods (e.g., pill, patch ring, injection, implant); however, the presence of other medical co-morbidities and drug–drug interactions between hormonal contraceptives, antiretroviral (ARV) drugs, and other medications should be considered (see Table 3) (AII). This information may help support shared decision-making about acceptable contraception options for people not currently desiring pregnancy. • During prepregnancy counseling, provide information on safer sex and ask about the use of alcohol, nicotine products, and other substances. Provide or refer to evidence-based interventions for substance use disorder, including medication-assisted treatment for opioid use disorder (e.g., methadone, buprenorphine), and counsel people on how to manage health risks (e.g., by accessing a syringe services program) when indicated (AII). • Provide education and counseling about interventions to prevent perinatal HIV transmission, including antiretroviral therapy (ART). Explain that people 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 fully suppressive ART is started before pregnancy and undetectable viral load is maintained throughout pregnancy and at delivery, the risk of HIV transmission to the infant is extremely low (<1%). • For people with HIV who are considering or planning a pregnancy, begin to provide patient-centered, evidence-based counseling to support shared decision-making about infant feeding (AIII) (see Infant Feeding for Individuals with HIV in the United States). Information and plans for infant feeding should be reviewed throughout pregnancy and again after delivery. • When selecting or evaluating an ARV regimen for people of childbearing potential with HIV, consider a regimen's effectiveness, changes in ARV pharmacokinetics in the second and third trimesters of pregnancy, a person's hepatitis B status, and the possible adverse outcomes for the pregnant person and their fetus (AII). See Teratogenicity and Recommendations for Use of Antiretroviral Drugs During Pregnancy: Overview for more information. The Panel on Treatment of HIV During Pregnancy and Prevention of Perinatal Transmission emphasizes the importance of counseling and shared decision-making regarding all ARV regimens for people with HIV (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*

Overview

The Centers for Disease Control and Prevention (CDC), the American College of Obstetricians and Gynecologists (ACOG), and other national organizations recommend offering all people of childbearing potential comprehensive family planning and the opportunity to receive prepregnancy counseling and care as a component of routine primary medical care. The purpose of prepregnancy care is to improve the health of each person before conception by identifying risk factors for adverse outcomes for the pregnant person and their fetus, tailoring education and counseling to individual

needs, and treating or stabilizing medical conditions to optimize outcomes for the pregnancy and the fetus/newborn.[1,2] Prepregnancy care is not something that occurs in a single clinical visit; rather, it requires integrating ongoing care and interventions into primary care to address people's needs during the different stages of reproductive life. Integrating comprehensive family planning and prepregnancy care into routine health care visits can help people with HIV reach their desired reproductive outcomes by supporting them to make informed decisions about their fertility and contraceptive use that are aligned with their preferences and reproductive goals.[3-6] Providers should initiate and document a nonjudgmental conversation with all people of reproductive age about their reproductive desires because they may be reluctant to bring up the subject themselves.[7-11]

A meta-analysis of 50 studies found a 42% prevalence of fertility desire among people with HIV. In a pooled analysis, fertility desire was associated with being on antiretroviral therapy (ART), male sex, age younger than 30, being married or cohabitating, a secondary education or higher, and being childless.[12] In a retrospective study among 255 women with HIV, 69 (27.1%) reported an intended pregnancy. Those with intended pregnancies were more likely to be older, White, married, privately insured, and college educated. They were less likely than those with unintended pregnancies to use tobacco, alcohol, opiates, or cocaine during pregnancy, more likely to disclose their HIV status to the father of the baby by delivery, and more likely to receive less effective contraception (e.g., condoms) postpartum. In a multivariate analysis, pregnancy intendedness was an important predictor of nondetectable viral load at pregnancy entry but not at delivery.[13] Pregnancy intentions may not be binary and may change over time, thus underscoring the need for health care providers to engage in ongoing discussions to support dynamic pregnancy intentions.[11]

Health care providers who routinely care for people of reproductive age with HIV play an important role in promoting prepregnancy health and informed reproductive decisions. However, even among providers who offer primary care to people with HIV, the delivery of comprehensive reproductive counseling often falls short of the current guidelines.[14-16]

The fundamental principles of prepregnancy 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 prepregnancy counseling and care that are appropriate for all people of reproductive age, people with HIV have specific needs that should be addressed.[17-20]

- Discuss reproductive options; actively assess their pregnancy intentions on an ongoing basis throughout the course of care; and, when appropriate, make referrals to HIV and reproductive health specialists, including experts in reproductive endocrinology and infertility when necessary. The HIV status of one or both parents should not be a reason to withhold standard of care infertility treatment and assist individuals and couples in reaching their desired reproductive outcomes.
- Offer all people who currently do not desire pregnancy a full range of contraceptive methods to help them achieve their fertility goals. People with HIV can use all available contraceptive methods, including hormonal contraception (e.g., pill, patch, ring, injection, implant) and intrauterine devices (IUDs); see Medical Eligibility Criteria for Contraceptive Use and the updated summary chart.[21] Providers should be aware of the presence of other medical co-morbidities and potential interactions between antiretroviral (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 IUDs (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.[22] AIDS Clinical Trials Group (ACTG) 5375 showed that doubling the dose of LNG from 1.5 mg to 3 mg in women receiving efavirenz (EFV)-based ART helped overcome the drug–drug interaction with this ARV.[23,24] 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).
- Use the prepregnancy period to modify the ARV regimen for people who are contemplating pregnancy to optimize virologic suppression and minimize potential adverse effects (see Recommendations for Use of Antiretroviral Drugs During Pregnancy and Table 7). Recognize that individuals with perinatally acquired HIV may have special needs (e.g., psychosocial support, adherence support)[25] (see Prenatal Care, Antiretroviral Therapy, and HIV Management in People with Perinatally Acquired HIV Infection).
- Recognize that transgender and gender-diverse people who were assigned female sex at birth may have special needs.[26] For transgender men attempting pregnancy, the use of testosterone may induce hypothalamic–pituitary–gonadal suppression, leading to decreased ovulation.[27]
- Recognize that the primary treatment goal for people with HIV who are planning a pregnancy should include sustained suppression of plasma viral load below the limit of detection before conception for their own health, to minimize the risk of perinatal HIV transmission, and to prevent sexual HIV transmission to a partner without HIV (see Reproductive Options When One or Both Partners Have HIV). Inform individuals who are considering or planning pregnancy that with ART started before pregnancy and an undetectable viral load maintained throughout pregnancy and delivery, their risk of HIV transmission to the infant is extremely low (<1%).[28,29]
- Explain that people with HIV who take ART as prescribed and who achieve and maintain an undetectable viral load will not transmit HIV through sex, commonly known as Undetectable = Untransmittable or U=U. For more information, see Let's Stop HIV Together.
- Encourage individuals to disclose their HIV status to their partner or co-parent before pregnancy if doing so is safe. However, this disclosure should not be a requirement of assisting couples in achieving pregnancy.
- Encourage sexual partners to receive HIV counseling and testing so that they can seek HIV care if they have HIV or seek advice about HIV prevention, including pre-exposure prophylaxis (PrEP), if they do not have HIV (see Pre-exposure Prophylaxis (PrEP) to Reduce the Risk of Acquiring HIV During Periconception, Antepartum, and Postpartum Periods).
- Ask about the use of alcohol, tobacco, and other substances. Provide or refer to evidence-based interventions for substance use disorder, including medication-assisted treatment for opioid use disorder (e.g., methadone, buprenorphine), and counsel people on how to manage health risks (e.g., access to a syringe services program). A 2019 analysis[30] reported that overall, 39% of women with HIV of reproductive age reported current drinking and 10% reported binge drinking. Compared to non-drinkers, binge drinkers were less likely to adhere to ART or be virally suppressed and more likely to smoke and use drugs. Between 2007 and 2019, marijuana use during pregnancy among women with HIV increased from 7.1% to 11.7%, whereas alcohol and opioid use were unchanged. Postpartum alcohol (44.4%), marijuana (13.6%), and concomitant

alcohol and marijuana (10%) use were common; marijuana use increased from 10.2% in 2006 to 23.7% in 2019, whereas postpartum alcohol use was unchanged.[31]

- Counsel on maintaining a healthy diet and healthy weight before and during pregnancy.
- Counsel people who are contemplating pregnancy to take a daily multivitamin that contains 400 mcg of folic acid to help prevent neural tube defects (NTDs). Individuals with a history of having a child with NTDs, with a family history of NTDs, or on certain anti-epileptic medications, especially valproic acid, are candidates for receiving a higher dose (1,000–4,000 mcg) of folic acid. Higher doses of folate may also be considered for people receiving trimethoprim/sulfamethoxazole who are trying to conceive (see Special Considerations in Pregnancy in *Pneumocystis* Pneumonia).
- Optimize the health of people with HIV prior to pregnancy (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).
- Educate and counsel about the risk factors for perinatal HIV transmission, the strategies to reduce those risks, and the potential effects HIV or taking ARV drugs during pregnancy may have on the course of pregnancy and health outcomes for the pregnant person and fetus.
- Support shared decision-making about ART. Educate and counsel on the factors that affect the selection of ARVs for people who are trying to conceive, are pregnant, or are postpartum. For more information, see Recommendations for Use of Antiretroviral Drugs During Pregnancy: Overview.
- Consider the following factors when prescribing ART to people of childbearing potential: the regimen's effectiveness, changes in ARV pharmacokinetics (PK) in the second and third trimesters of pregnancy, an individual's hepatitis B virus (HBV) status, possible adverse outcomes for the pregnant person and their fetus, and the likelihood of developing drug resistance.[32-34]
- Provide patient-centered, evidence-based counseling to support shared decision-making about infant feeding (see Infant Feeding for Individuals with HIV in the United States). Information about and plans for infant feeding should be reviewed throughout pregnancy and again after delivery.
- Evaluate and manage ART-associated adverse effects (e.g., hyperglycemia, anemia, hepatotoxicity) that may affect health outcomes for the pregnant person and fetus.
- Administer all vaccines as indicated (see CDC's Recommended Immunization Schedule and ACOG Maternal Immunization Practice Advisory 2022), which includes vaccination for influenza, pneumococcus, HBV, tetanus, and SARS-CoV-2.[35] All people, including those with HIV, should receive Tdap (tetanus, diphtheria, and pertussis) vaccination during each pregnancy, typically between 27 and 36 weeks of gestation but preferably as early in this time window as possible.
- Ask pregnant people whether they feel safe at home and offer assistance or referrals for those experiencing intimate partner violence (IPV) or requesting assistance.

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 PK and pharmacodynamics among the different forms of contraception and ARVs.[22,36-59] The contraceptive effectiveness of the LNG IUD is largely through local (i.e., intrauterine) release of LNG, not through systemic absorption. CDC's U.S. Medical Eligibility Criteria for Contraceptive Use lists the LNG 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 people with HIV without other contraindications. The contraception effect is usually attributable to the progestin component of contraceptives. Drug interactions that decrease concentrations of the progestin component may affect contraceptive efficacy. An alternative or additional contraceptive method may be recommended when drug interactions are known. For people receiving darunavir/ritonavir (DRV/r)-based ART, an alternative or additional contraception may be considered because the area under the curve (AUC) for oral contraceptive hormones may be decreased.[60] Cobicistat-boosted protease inhibitors (PIs) are contraindicated with drosperinone-containing hormonal contraceptives due to the potential for hyperkalemia.[54] 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.[37,39,49,61]

Several studies have shown that the use of EFV decreases the effectiveness of hormonal implants and hormonal vaginal rings. Although contraceptive implants (e.g., etonogestrel [ENG], LNG) generally can be used in people who are receiving ARVs, both PK and clinical data suggest that these implants have decreased efficacy when used with EFV-based regimens.[47,62-64] LNG implants are not available in the United States. A PK evaluation reported that 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 Week 36 and Week 48, whereas no pregnancies occurred in the ART-naive or nevirapine (NVP) groups.[51]

In a study of 570 women with HIV in Eswatini, formerly known as Swaziland, who had LNG implants (i.e., Jadelle), none of the women on NVP- or lopinavir/ritonavir-based regimens (n = 208 and n = 13, respectively) became pregnant, whereas 15 women on EFV (n = 121; 12.4%) became pregnant.[47] A prospective study in seven African countries collected data from 5,153 women with HIV who were followed for 1 to 3 years. During the follow-up period, 40% used injectables, 14% used oral contraceptives, and 9% of the women used implants (mostly LNG); 31% 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. A potential lesser degree of effectiveness of these methods may be due to their greater dependence on user action, as compared to longer acting methods. ART use did not significantly diminish contraceptive effectiveness, although all methods showed nonsignificant reduced contraceptive effectiveness when people used EFV concurrently.[65]

In a retrospective study among 1,152 women with HIV using either EFV or NVP and ENG or LNG implants, 115 pregnancies occurred, yielding a pregnancy incidence rate of 6.32 (5.27–7.59), with a rate of 9.26 and 4.74 among ENG and 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; $P > 0.01$).[66] A study of 42 women in Malawi (30 women with HIV on EFV and LNG, and 12 women without HIV on LNG) showed that EFV users had lower LNG concentrations that non-EFV users, and one-third of the EFV/LNG users had LNG concentrations <180 pg/mL, which is the suggested minimum level for efficacy. No pregnancies were reported over 60 women-years of follow-up.[67]

In a non-randomized, open label, parallel group, longitudinal pharmacokinetic study among Ugandan women aged 18 to 45, participants with HIV who were on EFV 600 mg received double-dose 300-mg LNG implants and were compared to women without HIV who received standard-dose 150-mg LNG implants. Plasma LNG concentration was quantified more than 48 weeks after implant insertion. LNG AUC from 0 to 24 weeks was 34% lower among women taking 300-mg LNG plus ART versus women taking 150-mg LNG (geometric mean 9,998 vs. 15,231 pg•week/mL, respectively). Double-dose LNG implants did not completely overcome the drug–drug interaction with EFV[58]; therefore, prescribing double-dose LNG implants is not recommended to overcome this drug–drug interaction. Since ovulatory activity was noted among women taking 300-mg LNG plus ART, another contraceptive method that does not interact with EFV is needed.

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, all received ENG implants. Women in the EFV group with CYP2B6 516 G>T had 43% lower ENG minimum plasma concentration (C_{min}) and 34% lower AUC from 0 to 24 hours postdose ($AUC_{0–24}$) at 24 weeks. For women on NVP, those with NR1I2 63396 C>T had lower ENG C_{min} and 37% lower $AUC_{0–24}$ at 24 weeks.[55] A PK study reported that EFV reduced the median ENG level by at least 93% in CYP2B6 slow metabolizers versus 75% in normal and intermediate metabolizers. EFV reduced median ethinyl estradiol (EE) concentration by 75% in slow metabolizers and 41% in normal and intermediate metabolizers among women using hormonal vaginal ring contraceptives.[68]

Tuberculosis Treatment, Antiretrovirals, and Contraception

Other medications, such as concomitant tuberculosis (TB) treatment and ARVs, may also have drug–drug interactions with contraceptives. A PK study of DMPA among women with HIV/TB coinfection who received EFV-based HIV treatment and rifampicin-based TB treatment showed that among 42 evaluable women, 5 women (11.9%; 95% CI, 4.0% to 25.6%) had medroxyprogesterone acetate (MPA) <0.1 ng/mL at Week 12, the level above which ovulation is prevented; of these women, 1 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% of women at Week 12.[69] After performing PK modeling with DMPA and ART, the authors of this study suggested redosing DMPA more frequently,[70] such as every 8 to 10 weeks. In a PK study of the interaction between DMPA, EFV, rifampicin, and isoniazid (INH) during treatment for HIV and tuberculosis, there were no associations between either CYP2B6 or N-acetyltransferase 2 genotype and MPA C_{min} at Week 12. The study was not designed to distinguish inductive effects of rifampicin from possible inhibitory effects of INH on MPA clearance.

Nevertheless, the authors recommended that more frequent DMPA dosing may be appropriate for women receiving all these medications.[71]

Long-Acting Cabotegravir

In a secondary analysis of 85 cisgender women enrolled in HPTN 077, compared to women reporting no hormonal contraception (n = 6), oral contraceptive use (n = 18) was associated with lower long-acting cabotegravir (CAB-LA) peak concentration but was not associated with other PK parameters, suggesting this association is not likely to be clinically significant. No other hormonal contraceptive type (injectable, implants, and other) was associated with significant differences in CAB-LA PK parameters.[72]

Vaginal Ring

A new contraceptive vaginal ring containing segesterone/EE (Annovera) has recently been approved by the U.S. Food and Drug Administration. No available drug–drug interaction studies with this contraceptive vaginal ring and ARV and CYP inducers/inhibitors are known. The contraceptive may possibly be metabolized in the same way as ENG and EE in the NuvaRing (see Table 3 below).[57]

Table 3

Because data are limited on pregnancy rates among people 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% decrease in norethindrone (with DRV/r). The Panel on Treatment of HIV During Pregnancy and Prevention of Perinatal Transmission does not recommend any change in EE dose in people who are receiving etravirine (EE increased 22%) or rilpivirine (EE increased 14%).

Table 3. Drug Interactions Between Antiretroviral Agents and Hormonal Contraceptives

Note: All recommendations in this table are based on consensus expert opinion. Additional information can be found in the Centers for Disease Control and Prevention Update to U.S. Medical Eligibility Criteria for Contraceptive Use, 2016: Updated Recommendations for the Use of Contraception Among Women at High Risk for HIV Infection.[73]

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	
Efavirenz (EFV)	
Dosing Recommendation/Clinical Comment for COC/P/R, POPs, and ENG Implants	If efficacy is of primary importance, consider an alternative method (or a reliable method of barrier contraception in addition to this method).
Dosing Recommendation/Clinical Comment for DMPA[a]	No additional contraceptive protection is needed.
Effect on Contraceptive Drug Levels and Contraceptive's Effects on ART and HIV	COC • No effect on EE concentrations • ↓ active metabolites of norgestimate; LNG AUC ↓ 83% and norelgestromin AUC ↓ 64%[40] • ENG (in COC) C_{24h} ↓ 61%[46] • ENG ↓ 79%; EE ↓ 59%[57] DMPA • No effect on DMPA levels[37,39] • DMPA AUC ↓ 33-35% when coadministered with EFV, rifampin, and INH. More frequent DMPA dosing may be appropriate.[69] ENG Implant • ENG ↓ below the level necessary to prevent pregnancy (90 pg/mL) in 60% of people on EFV[74] • ↓ 49% ENG concentration[56] • ENG AUC ↓ 63% to 82%[64,75] LNG Implant • ↓ 61% LNG concentration[56] • LNG AUC ↓ 47%[51] • ↑ pregnancy incidence rate among women using LNG or ENG implants, more among ENG users[66] • LNG AUC ↓ 40–73% over 30 months of use[67] • Doubling the dose of LNG implant from 150 mg to 300 mg did not overcome the decrease in LNG concentration.[58]

Table 3. Drug Interactions Between Antiretroviral Agents and Hormonal Contraception

	LNG Emergency Contraception (Oral Dosing) • LNG (emergency contraception) AUC ↓ 58%[22] • C_{max} was 51% higher with 3 mg LNG (24.9 ng/mL) compared to 1.5 mg (15.1 ng/mL), and the 48-hour concentration was 66% higher (0.6 vs. 0.3 ng/mL, respectively). Dose adjustment of LNG EC from 1.5 mg to 3 mg helped to overcome the drug–drug interaction in women receiving EFV-based ART.[23] Vaginally Administered ENG/EE (Vaginal Ring) • ENG ↓ 93% in CYP2B6 slow metabolizers and ↓ 75% in normal and intermediate metabolizers[68] • EE ↓ 75% in slow metabolizers and ↓ 41% in normal and intermediate metabolizers[68] Changes in ARV Levels and/or Effects on HIV *COC* • No effect on EFV concentrations[40] • EFV C_{12h} ↓ 22%; under therapeutic threshold in 3 of 16 subjects[46] *DMPA* • No effect on HIV disease progression[37,76,77] • No effect on EFV concentrations[37] LNG Implant • No effect on HIV disease progression[51]
Clinical Studies	COC • No difference in pregnancy rates[65] • Pregnancy rate was 13% higher in women using COCs and EFV than in women using COCs alone.[63,78] • Progesterone >3 ng/mL (a surrogate for ovulation) in 3 of 16 women[79] • No ovulations[40] DMPA • No increase in pregnancies[37,63,65,77] • Low endogenous progesterone, consistent with no ovulation[37,39,77] ENG Implant • Pregnancy rate higher with EFV compared with no ART but still lower with implants than with other hormonal methods of contraception[63] • Presumptive ovulation in 5%[75] LNG Implant • 12% pregnancy rate[47] • 15% pregnancy rate[51]

Table 3. Drug Interactions Between Antiretroviral Agents and Hormonal Contraception

	• Pregnancy rate higher with EFV compared with no ART but still lower with implants than with other hormonal methods of contraception[63] • No increase in pregnancy rate[65]
Justification/Evidence for Recommendation	For COCs, some studies suggest higher pregnancy rate and ovulation rate and decreased progestin levels. EFV may decrease, but clinical significance is 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. More frequent DMPA dosing may be appropriate for women receiving rifampicin, INH, and EFV. For implants, some studies suggest higher pregnancy rate and decreased hormone levels. For vaginally administered ENG/EE, PK evaluation showed that ENG levels were 79% lower and EE levels were 59% lower in participants on EFV than in controls after 21 days.[57]
Etravirine (ETR)	
Dosing Recommendation/Clinical Comment for COC/P/R, POPs, DMPA[a], ENG Implants	No additional contraceptive protection is needed.
Effect on Contraceptive Drug Levels and Contraceptive's Effects on ART and HIV	EE AUC ↑ 22%[80] No significant effect on NE[80]
Clinical Studies	COC • No ovulations[80]
Justification/Evidence for Recommendation	For COCs, one study found no ovulations and no significant change in progestin levels. No data on POPs
Nevirapine (NVP)	
Dosing Recommendation/Clinical Comment for COC/P/R, POPs, DMPA[a], ENG Implants	No additional contraceptive protection is needed.
Effect on Contraceptive Drug Levels and Contraceptive's Effects on ART and HIV	EE AUC ↓ 29%[81]; no change in EE AUC[82] NE AUC ↓ 18%[81] ENG (in COC) C_{24h} ↓ 22%[46] DMPA • No significant change[37] LNG Implant • LNG AUC ↑ 35%[51]

Table 3. Drug Interactions Between Antiretroviral Agents and Hormonal Contraception

	• ↑ pregnancy incidence rate among women using LNG or ENG implants, more among ENG users[66] Changes in ARV Levels and/or Effects on HIV *COC* • No significant effect on NVP levels[79,81,83] *DMPA* • No effect on HIV disease progression[37,76,77,84] *LNG Implant* • No effect on HIV disease progression[51,85]
Clinical Studies	COC • No increase in pregnancy rate[63,65,78,86,87] • No ovulations[79,82,87] DMPA • No increase in pregnancy rates[63,65,77,86] • Low serum progesterone, consistent with no ovulation[37] ENG Implant • No increase in pregnancy rate[63] LNG Implant • No increase in pregnancy rate[47,51,63,65,85]
Justification/Evidence for Recommendation	For COCs, evidence does not show effects on pregnancy rate or ovulations. Evidence demonstrated a 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.
Rilpivirine (Oral RPV)	
Dosing Recommendation/Clinical Comment for COC/P/R, POPs, DMPA[a], ENG Implants	No additional contraceptive protection is needed.
Effect on Contraceptive Drug Levels and Contraceptive's Effects on ART and HIV	EE AUC ↑ 14%[45] No significant change on NE[45] Changes in ARV Levels and/or Effects on HIV *COC* • No change in RPV levels compared to historical controls[45]

Table 3. Drug Interactions Between Antiretroviral Agents and Hormonal Contraception

Clinical Studies	COC • No change in progesterone[45]
Justification/Evidence for Recommendation	For COCs, evidence does not show effects on ovulation or progestin levels. No change in RPV levels. No data on POPs
Doravirine (DOR)	
Dosing Recommendation/Clinical Comment for COC/P/R, POPs, DMPA[a], ENG Implants	No additional contraceptive protection is needed.
Effect on Contraceptive Drug Levels and Contraceptive's Effects on ART and HIV	No clinically significant interaction with EE and LNG[88]
Clinical Studies	N/A
Justification/Evidence for Recommendation	No clinical data
Ritonavir (RTV)–Boosted Protease Inhibitors (PIs)	
Atazanavir/Ritonavir (ATV/r)	
Dosing Recommendation/Clinical Comment for COC/P/R, POPs, DMPA[a], ENG Implants	No additional contraceptive protection is needed.
Effect on Contraceptive Drug Levels and Contraceptive's Effects on ART and HIV	EE AUC ↓ 19%[89] Norgestimate AUC ↑ 85%[89] POP • NE AUC ↑ 50%[90] Vaginally Administered ENG/EE • ENG ↑ 71% • EE ↓ 38%[57]
Clinical Studies	N/A
Justification/Evidence for Recommendation	For COCs, increase in progestin levels seen in only one study. Using a COC with at least 35 mcg/day may decrease breakthrough bleeding. For POPs, increase in progestin levels seen in only one study RTV inhibits CYP3A4, which may increase contraceptive hormone levels.
Darunavir/Ritonavir (DRV/r)	
Dosing Recommendation/Clinical Comment for COC/P/R, POPs, and ENG Implants	If efficacy is of primary importance, can consider an alternative method (or a reliable method of barrier contraception in addition to this method)
Dosing Recommendation/Clinical Comment for DMPA[a]	No additional contraceptive protection is needed.

Table 3. Drug Interactions Between Antiretroviral Agents and Hormonal Contraception

Effect on Contraceptive Drug Levels and Contraceptive's Effects on ART and HIV	EE AUC ↓ 44%[60] NE AUC ↓ 14%[60]
Clinical Studies	N/A
Justification/Evidence for Recommendation	For COCs, small decrease in progestin levels No data on POPs
Lopinavir/Ritonavir (LPV/r)	
Dosing Recommendation/Clinical Comment for COC/P/R, POPs, DMPA[a], ENG Implants	No additional contraceptive protection is needed.
Effect on Contraceptive Drug Levels and Contraceptive's Effects on ART and HIV	EE AUC ↓ 55%[36] NE AUC ↓ 17% Patch • EE AUC ↓ 45%[36] • Norelgestromin AUC ↑ 83%[36] DMPA • DMPA AUC ↑ 46%[49] ENG Implant • ENG AUC ↑ 52%[75] Changes in ARV Levels and/or Effects on HIV *Patch* • LPV/r ↓ 19%[36] *DMPA* • No effect on HIV disease progression[49] • No change in LPV/r levels[49]
Clinical Studies	COC • Trend of increased pregnancy rate, but CIs overlap[63] Patch • Low serum progesterone consistent with no ovulations (n = 8)[36] DMPA • No pregnancies and no ovulations[49] • Trend of increased pregnancy rate, but CIs overlap[63] ENG Implant • No increase in pregnancy rate[63]

Table 3. Drug Interactions Between Antiretroviral Agents and Hormonal Contraception

	LNG Implant • No increase in pregnancy rate[47,63]
Justification/Evidence for Recommendation	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. For implants, evidence shows no effect on pregnancy rate. Progestin levels increased.
Cobicistat (COBI)-Boosted Protease Inhibitors (PIs)	
Atazanavir/Cobicistat (ATV/c)	
Dosing Recommendation/Clinical Comment for COC/P/R	**Contraindicated** with drospirenone-containing hormonal contraceptives due to potential for hyperkalemia
Dosing Recommendation/Clinical Comment for POPs, DMPA[a], ENG Implants	No additional contraceptive protection is needed.
Effect on Contraceptive Drug Levels and Contraceptive's Effects on ART and HIV	Drospirenone AUC ↑ 2.3-fold[54] No change in LNG concentration 25% decrease in EE C24[53]
Clinical Studies	N/A
Justification/Evidence for Recommendation	No data on POPs
Darunavir/Cobicistat (DRV/c)	
Dosing Recommendation/Clinical Comment for COC/P/R	Clinical monitoring is recommended when DRV/c is used in combination with drospirenone-containing COCs as a result of the potential for hyperkalemia.
Dosing Recommendation/Clinical Comment for POPs, DMPA[a], ENG Implants	No additional contraceptive protection is needed.
Effect on Contraceptive Drug Levels and Contraceptive's Effects on ART and HIV	Drospirenone AUC ↑ 1.6-fold EE AUC ↓ 30%[54]
Clinical Studies	N/A
Justification/Evidence for Recommendation	No data on POPs
Protease Inhibitors (PIs) without Ritonavir (RTV)	
Atazanavir (ATV)	
Dosing Recommendation/Clinical Comment for COC/P/R	Prescribe oral contraceptive that contains no more than 30 mcg of EE or recommend alternative contraceptive method.

Table 3. Drug Interactions Between Antiretroviral Agents and Hormonal Contraception

Dosing Recommendation/Clinical Comment for POPs, DMPA[a], ENG Implants	No additional contraceptive protection is needed.
Effect on Contraceptive Drug Levels and Contraceptive's Effects on ART and HIV	COC • EE AUC ↑ 48%[91] • NE AUC ↑ 110%[91]
Clinical Studies	N/A
Justification/Evidence for Recommendation	For COCs, increased concentrations of estrogen and progestin, but the only data available are from the product label. No data on POPs
CCR5 Antagonist	
Maraviroc (MVC)	
Dosing Recommendation/Clinical Comment for COC/P/R, POPs, DMPA[a], ENG Implants	No additional contraceptive protection is needed.
Effect on Contraceptive Drug Levels and Contraceptive's Effects on ART and HIV	COC • No significant effect on EE or LN[92]
Clinical Studies	N/A
Justification/Evidence for Recommendation	For COCs, no change in EE or progestin. No clinical data. No data on POPs
Integrase Strand Transfer Inhibitors (INSTIs)	
Bictegravir/Emtricitabine/Tenofovir Alafenamide (BIC/FTC/TAF)	
Dosing Recommendation/Clinical Comment for COC/P/R, POPs, DMPA[a], ENG Implants	No additional contraceptive protection is needed.
Effect on Contraceptive Drug Levels and Contraceptive's Effects on ART and HIV	No significant drug interactions with EE or norgestimate
Clinical Studies	N/A
Justification/Evidence for Recommendation	No clinical data
Dolutegravir (DTG)	
Dosing Recommendation/Clinical Comment for COC/P/R, POPs, DMPA[a], ENG Implants	No additional contraceptive protection is needed.
Effect on Contraceptive Drug Levels and Contraceptive's Effects on ART and HIV	COC • No significant effect on ENG implants[74] • No significant effect on norgestimate or EE • No change in DTG AUC[50]

Table 3. Drug Interactions Between Antiretroviral Agents and Hormonal Contraception

Clinical Studies	N/A
Justification/Evidence for Recommendation	For COCs, no change in EE or progestin. No clinical data. No data on POPs
Elvitegravir/Cobicistat (EVG/c)	
Dosing Recommendation/Clinical Comment for COC/P/R, POPs, DMPA[a], ENG Implants	No additional contraceptive protection is needed.
Effect on Contraceptive Drug Levels and Contraceptive's Effects on ART and HIV	COC • Norgestimate AUC ↑ 126% • EE AUC ↓ 25%[93,94]
Clinical Studies	N/A
Justification/Evidence for Recommendation	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
Raltegravir (RAL)	
Dosing Recommendation/Clinical Comment for COC/P/R, POPs, DMPA[a], ENG Implants	No additional contraceptive protection is needed.
Effect on Contraceptive Drug Levels and Contraceptive's Effects on ART and HIV	COC • No change in EE • Norgestimate AUC ↑ 14%[95]
Clinical Studies	N/A
Justification/Evidence for Recommendation	For COCs, no change in EE and a small increase in progestin. No clinical data. No data on POPs.
Long-Acting Cabotegravir (CAB-LA)	
Dosing Recommendation/Clinical Comment for COC/P/R, POPs, DMPA[a], ENG Implants	No additional contraceptive protection needed
Effect on Contraceptive Drug Levels and Contraceptive's Effects on ART and HIV	Oral contraceptive use was associated with ↓ CAB-LA C_{max} compared to women not on any hormonal contraception (GMR 0.75; 90% CI, 0.59–0.93; $P = 0.033$). However, oral contraceptive use did not result in significant differences in other CAB-LA PK parameters.
Clinical Studies	N/A
Justification/Evidence for Recommendation	Although oral contraceptive use was associated with lower CAB-LA peak concentration, no other PK parameters seen suggesting the association is not likely to be clinically significant.

[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.

Table 3. Drug Interactions Between Antiretroviral Agents and Hormonal Contraception

Key to Symbols:

↑ = increase
↓ = decrease

Key: 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 postdose; C_{24h} = concentration at 24 hours postdose; CAB-LA = long-acting cabotegravir; CI = confidence interval; $C_{max;}$ = minimum plasma concentration; COBI = cobicistat; COC = combined oral contraceptives; COC/P/R = COC/patch/ring; CYP = cytochrome P450; DMPA = depot medroxyprogesterone acetate; DOR = doravirine; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EC = emergency contraception; EE = ethinyl estradiol; EFV = efavirenz; ENG = etonogestrel; ETR = etravirine; EVG/c = elvitegravir/cobicistat; FTC = emtricitabine; GMR = geometric mean ratio; INH = isoniazid; INSTI = integrase strand transfer inhibitor; LNG = levonorgestrel; LPV/r = lopinavir/ritonavir; MVC = maraviroc; NE = norethindrone; NNRTI = non-nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; PK = pharmacokinetic; POP = progesterone-only oral contraceptive pills; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

Sources: Panel on Antiretroviral Guidelines for Adults and Adolescents; Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV; Table 24a, Table 24b, and Table 24d

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Reproductive Options When One or Both Partners Have HIV

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Panel's Recommendations
For People Who Want to Conceive When One or Both Partners Have HIV • People with HIV should achieve sustained viral suppression (e.g., two recorded measurements of plasma viral loads that are below the limits of detection and that have been taken at least 3 months apart) before attempting conception to maximize their health, prevent HIV sexual transmission (AI), and minimize the risk of HIV transmission to their infants once conception occurs (AI). • Both partners should be screened and treated for genital tract infections before attempting to conceive (AII). Rescreening for genital tract infections while attempting to conceive may be considered based on individual risk and duration of the preconception period (AII). • For partners with different HIV status when the person with HIV is on antiretroviral therapy and has achieved sustained viral suppression, sexual intercourse without a condom allows conception without sexual HIV transmission to the person without HIV (BII). • Expert consultation is recommended to tailor guidance to the specific needs of the person or people planning for pregnancy when indicated (e.g., infertility) (AIII). • Health care providers should discuss pre-exposure prophylaxis (PrEP) with all sexually active people without HIV, including individuals who are trying to conceive, to prevent HIV acquisition (AII); counseling should include the benefits of PrEP to prevent HIV acquisition and perinatal transmission (AI) and potential adverse effects of PrEP during periconception, pregnancy, postpartum, and breastfeeding periods (AII). Health care providers should offer PrEP to those who desire PrEP or have specific indications for PrEP (AII) (see PrEP to Prevent HIV During Periconception, Antepartum, and Postpartum Periods). o When partners with different HIV status attempt conception, the partner without HIV can choose to take PrEP as an additional method of HIV prevention 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. The section focuses on HIV prevention in the context of penile–vaginal intercourse to achieve pregnancy. The Panel on the Treatment of HIV During Pregnancy and Prevention of Perinatal Transmission (the Panel) also appreciates the diversity of parenting desires within lesbian, gay, bisexual, transgender, queer, intersex, asexual, and gender nonconforming communities (LGBTQIA+), as well as the importance of promoting family building while minimizing HIV transmission opportunities for people with HIV. Strategies for achieving pregnancy without penile–vaginal intercourse include gamete donation and surrogacy. When gamete donation and surrogacy occur through health care channels, HIV testing and viral load monitoring should be included within protocols.[1] When conducted informally, the same tenets for prevention outlined below should apply.[2] Clinicians also must consider that people of all gender identities may seek options to build families, including adoption, and should be supported to do so.[3]

For people who want to conceive when one or both partners have HIV, expert consultation (e.g., with an HIV specialist, maternal/fetal medicine specialist, infertility expert when indicated) is recommended so that approaches for safer conception can be tailored to their specific needs.

People with HIV who take antiretroviral therapy (ART) as prescribed and maintain a viral load below 200 copies/mL will not transmit HIV to their sex partners.[4,5] If one or both partners have HIV, they should be informed that condomless sex to achieve conception is associated with no risk of HIV sexual transmission once people with HIV initiate ART and maintain HIV viral suppression.[6-9] 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. Rescreening for genital tract infections while attempting to conceive may be considered based on individual risk and duration of the preconception period. With ART and sustained undetectable plasma viral load and/or pre-exposure prophylaxis (PrEP), sexually transmitted infections (STIs) do not increase the risk of HIV transmission. However, STI screening and treatment is important for the health of both partners and prevention of pregnancy complications.[10-12]

If conception does not occur within 12 months (or a shorter duration of time, if indicated, based on age or other obstetric indications), providers should pursue a workup for infertility, including a semen analysis.[13] 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, high rate of abnormal forms, and low semen volume. In some cases, earlier evaluation may be indicated because of concerns about higher rates of infertility among people with HIV.[14,15]

Coordination of care across multiple disciplines—including HIV primary care, obstetrics and gynecology (specifically, reproductive endocrinology and infertility), case management, and peer and social support—is advised.

People with Differing HIV Status

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

In two large studies that included heterosexual couples with differing HIV status (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 virologically suppressed (defined as <400 copies/mL for HPTN 052 and <200 copies/mL for the PARTNER study). HPTN 052 was a randomized clinical trial designed to evaluate whether immediately initiating ART in people with CD4 T lymphocyte cell counts of 350 to 550 cells/mm^3 could prevent sexual transmission of HIV between couples with differing HIV statuses more effectively than delaying ART. Most participants were from Africa (54%), 30% were from Asia, and 16% were from North and South America combined. This study showed that initiating ART earlier led to a 93% reduction in the rate of sexual transmission of HIV. No linked infections occurred between partners when the partner with HIV had a viral load that was suppressed by ART. Thus, this randomized trial clearly demonstrated that providing treatment to people with HIV can reduce the

risk of HIV transmission to their sexual partners.[16] In addition, the PARTNER study—which studied 1,166 couples of differing HIV statuses (mainly heterosexual couples and men who have sex with men) in which the partner with HIV was on suppressive ART with a plasma viral load <200 copies/mL 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.[17]

A prospective cohort study evaluated couples with differing HIV status who were planning to conceive. Among 161 couples (133 couples included a male partner with HIV) in which 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.[18]

For partners with differing HIV status in which the partner with HIV is on ART and has achieved sustained viral suppression, sexual intercourse without a condom is a method of conception that will not result in 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 ART and viral suppression as a prevention strategy.[4] Consider monitoring the viral load more frequently in these individuals than the current treatment guidelines recommend.

PrEP and Other Options for Partners with Differing HIV Status and Inconsistent or Unknown Viral Suppression

Health care providers should discuss PrEP with all sexually active people without HIV, including individuals who are trying to conceive, to prevent HIV acquisition. PrEP is the use of ARV drugs by a person without HIV to maintain blood and genital drug levels sufficient to prevent HIV acquisition. Counseling should include the benefits of PrEP to prevent HIV acquisition and perinatal transmission and the potential adverse effects of PrEP during periconception, pregnancy, postpartum, and breastfeeding periods. Health care providers should offer PrEP to those who desire PrEP or have specific indications for PrEP.

For people with differing HIV status who attempt conception through 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 Pre-Exposure Prophylaxis [PrEP] to Prevent HIV During Periconception, Antepartum, and Postpartum Periods). PrEP for the partner without HIV is an option that reduces their risk of sexual acquisition of HIV when the partner with HIV has not achieved sustained viral suppression, has an unknown HIV viral suppression status, and/or has potential for inconsistent ART adherence during the periconception period. In these situations, additional guidance for safer conception may be required if the person without HIV declines PrEP.

Combination of tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) currently is approved by the U.S. Food and Drug Administration for use as PrEP for all populations. Tenofovir alafenamide and FTC as a combination drug also has been approved for PrEP in men and transgender women but not for people who have receptive vaginal sex. The use of long-acting injectable cabotegravir (CAB-LA) for PrEP was approved in 2021 for men, transgender women, and cisgender women. For the person planning to become pregnant, there are limited safety data or pharmacokinetic data to inform efficacy or safety of CAB-LA for the pregnant person or fetus. If a person receiving cabotegravir (CAB) PrEP becomes pregnant, the limited available safety data and long half-life of CAB should be discussed with the patient with shared decision-making about

whether to continue CAB-LA or switch to TDF/FTC. When PrEP is indicated for a person planning to become pregnant, the Panel recommends TDF/FTC whenever possible. Adherence is critical.

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

When an inseminating partner with HIV and their a partner without HIV want to conceive, the use of sperm from a donor without HIV is an option for conception that eliminates the risk of HIV transmission to the partner without HIV. When an inseminating partner with HIV and their partner without HIV want to conceive, the use of sperm preparation techniques (e.g., "sperm washing" followed by testing the sample for HIV RNA), coupled with either intrauterine insemination, *in vitro* fertilization, or *in vitro* fertilization with intracytoplasmic sperm injection, is no longer routinely recommended. The appropriate role of semen preparation techniques in the current context is unclear, particularly given their expense and technical requirements. These sperm preparation techniques largely were developed before studies 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 infertility or for couples who are using donor sperm or a gestational surrogate.

Males in a same-sex partnership who have serodiscordant HIV test results may consider adoption or a gestational surrogate. Female partners in a same-sex relationship who have serodiscordant HIV test results may wish to consider adoption or choosing a partner without HIV to be the gestational partner.

In addition to reducing the risk of HIV transmission between partners, starting ART before people with HIV become pregnant also can further reduce the risk of perinatal transmission (see Antiretroviral Therapy for People with HIV Who are Trying to Conceive).[19] Evidence suggests that early and sustained control of HIV can decrease the risk of perinatal transmission.[20,21] Reports are mixed on the possible effects of ART on prematurity and low birthweight, with some data suggesting that such outcomes might be more frequent among women who are on ART at conception.[22-26] For more information, see Antiretroviral Drug Regimens and Pregnancy Outcomes.

Monitoring Pregnant People without HIV Who Have Partners with HIV

People without HIV who present during pregnancy and indicate that their partners have HIV should be notified that HIV screening is recommended for all people who are pregnant 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 Pregnancy and Postpartum HIV Testing and Identification of Perinatal and Postnatal HIV Exposure). Pregnant people who test HIV seronegative and have partners with HIV should continue to be counseled regularly regarding consistent condom use and the option for PrEP to decrease their risk of sexual acquisition of HIV if the partner with HIV has not achieved sustained virologic suppression. They also should be counseled on the importance of their partners' adherence to ART and the need for their partners to achieve sustained virologic suppression to reduce the risk of sexual transmission of HIV. The pregnant person without HIV may consider PrEP under several conditions as previously discussed in PrEP and Other Options for Partners with Differing HIV Status and Inconsistent or Unknown Viral Suppression above (see PrEP to Prevent HIV During Periconception, Antepartum, and Postpartum Periods). Pregnant people without HIV also should be counseled regarding the symptoms of acute retroviral syndrome (i.e., fever, pharyngitis, rash,

myalgia, arthralgia, diarrhea, headache) and the importance of seeking medical care and testing if they experience such symptoms. People with acute HIV infection during pregnancy or lactation are at high risk of transmitting HIV to their infants. When acute HIV infection is suspected in pregnancy, testing should include an HIV RNA polymerase chain reaction assay[27-29] (see Early [Acute and Recent] HIV Infection). Repeat HIV testing in the third trimester is recommended for pregnant people who initially test HIV negative but who are at increased risk of acquiring HIV (see Pregnancy and Postpartum HIV Testing and Identification of Perinatal and Postnatal HIV Exposure). More frequent testing is indicated when a pregnant person's partner has HIV; these pregnant persons should be tested every trimester.

Monitoring People without HIV Who Have Partners with HIV Who Are Trying to Conceive

People 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 the partner with HIV and PrEP for the one without HIV as a personal choice. The Centers for Disease Control and Prevention recommends HIV testing every 3 months for the partner who does not have HIV while the partners are attempting to conceive via condomless sex. The National Perinatal HIV Hotline (888-448-8765) is a resource for a list of institutions that offer reproductive services when one or both partners have HIV.

Considerations When Both Partners Have HIV

When both partners have HIV, both should be on ART with sustained viral suppression before attempting conception to optimize the health of the parents and reduce perinatal transmission. 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.[30]

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Antepartum Care for Individuals with HIV

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Panel's Recommendations
• In addition to the standard antepartum assessments for all pregnant people, the initial evaluation of people with HIV should include an assessment of HIV disease status and recommendations for HIV-related medical care (AI). See Initial Evaluation and Continued Monitoring of HIV-Related Assessments During Pregnancy and Table 4. Antepartum Screenings and Assessments for Pregnant People with HIV for the recommended schedule of HIV-related laboratory tests during pregnancy. • Amniocentesis, if clinically indicated, may be performed on pregnant people with HIV after thorough patient-centered counseling about the risks, benefits, and alternatives. o The pregnant person should be receiving an effective antiretroviral (ARV) regimen and, ideally, have HIV RNA levels that are undetectable (BIII). o If a pregnant person with detectable HIV RNA levels requires amniocentesis, consultation with an expert in the management of HIV during pregnancy should be considered (BIII). o Data are inadequate to guide decision-making about other invasive diagnostic or therapeutic procedures; an individualized process of shared decision-making is recommended. • People with HIV should be counseled on the known benefits and potential risks of all medications, including ARV drugs used during pregnancy and postpartum. Counseling about the importance of adherence should be addressed at each visit (AIII). • Coordination of services among prenatal care providers, primary care, 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 care and enables adherence to antiretroviral therapy (AII). • During pregnancy, providers should initiate counseling about key intrapartum and postpartum considerations, 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 antepartum assessments for all pregnant people, the initial evaluation of people with HIV should include an assessment of HIV disease status and recommendations for HIV-related medical care (see Recommendations for the Use of Antiretroviral Drugs During Pregnancy: Overview). See Initial Evaluation and Continued Monitoring of HIV-Related Assessments During Pregnancy and Laboratory Testing for Initial Assessment and Monitoring of People with HIV Receiving Antiretroviral Therapy for the recommended schedule of HIV-related laboratory tests during pregnancy. Initial assessment and ongoing care for pregnant individuals with HIV should include the following items (see Table 4. Antepartum Screenings and Assessments for Pregnant People with HIV):

- 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 B virus (HBV), hepatitis C virus, and tuberculosis (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*[1-4]; Repeat STI testing in the third trimester may be indicated based on individual risk factors or as required by state laws;
- Assessment of the need for HAV, HBV, influenza, pneumococcus, Tdap (tetanus, diphtheria, acellular pertussis), or SARS-CoV-2 immunizations (including boosters). Counseling on the importance of vaccinations for all pregnant individuals, and specifically for people with HIV, should be addressed and vaccinations provided when indicated[5-8]; consideration of other vaccinations, such as for meningococcus, may be warranted based on individual patient considerations. Human papillomavirus vaccination may be indicated postpartum if not previously vaccinated;
- Complete blood cell count and renal and liver function testing;
- HLA-B*5701 testing, if the use of abacavir is anticipated (see Table 14. Antiretroviral Drug Use in Pregnant People with HIV: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy);
- History of prior or current antiretroviral (ARV) drug use or experience with adverse events or toxicities. Counseling should also address prior or anticipated challenges with adherence;
- Screening for depression and anxiety (see Screening and Diagnosis of Mental Health Conditions During Pregnancy and Postpartum), as well as for substance use disorders, and referral for mental health care services if indicated[9];
- Assessment of the need for supportive care (e.g., social services, mental health services, substance use disorder treatment services, smoking cessation services, other community-based resources) for pregnancy-specific needs, as well as to help ensure lifelong adherence to antiretroviral therapy (ART);
- Screening for intimate partner violence (IPV) and assessment of the need for referrals for supportive care;
- Assessment of gender identity, pronouns used, desired terminology for anatomy, and use of testosterone or other gender-affirming hormonal therapy[10,11] (see Perinatal HIV Prevention for Transgender and Gender-Diverse People Assigned Female Sex at Birth and Transgender People with HIV);
- Assessment of the HIV status of sexual partner(s) and referral of partner(s) for HIV testing and ART or prophylaxis as needed (see Pre-Exposure Prophylaxis [PrEP] to Prevent HIV During Periconception, Antepartum, and Postpartum Periods);
- Referral of children for HIV testing if HIV status is unknown; *and*

- Counseling about key intrapartum and postpartum considerations, including mode of delivery, lifelong HIV therapy, family planning and contraceptive options, infant feeding choices, infant ARV prophylaxis, and timing of infant diagnostic testing.

Prenatal Screening, Diagnosis, and Therapy

According to the American College of Obstetricians and Gynecologists (ACOG), prenatal genetic screening and diagnostic testing options should be discussed and offered to all pregnant people, regardless of age or risk of chromosomal abnormality. After review and discussion, every patient has the right to pursue or decline prenatal genetic screening and diagnostic testing.[12] Prenatal screening for aneuploidy should be offered using noninvasive methods with high sensitivity and low false-positive rates, as recommended by ACOG. Counseling on noninvasive genetic screening options is no different for people with HIV than for those without HIV. Noninvasive screening can be accomplished using either of the following:

- Cell-free DNA screening with or without nuchal translucency; *or*
- Serum analyte screening alone or combined with nuchal translucency (sequential or integrated).

Patients with HIV who desire or have indications for diagnostic 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 informed decisions about invasive testing. Although the data on women who are receiving ART are 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.[13,14] This is in contrast to the era before effective ART, during which invasive procedures, such as amniocentesis and chorionic villus sampling, were associated with a twofold to fourfold increase in the risk of perinatal transmission of HIV.[15-18] 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.[19-22]

At a minimum, it should be recommended that pregnant patients receive effective ART before undergoing any invasive prenatal testing. Patients 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. Families often make complex personal decisions about continuing a pregnancy after a prenatal diagnosis, and those decisions are made even more complex by evolving state laws regarding access to abortion. A patient-centered discussion regarding delaying diagnostic procedures to allow for viral suppression should also consider the impact of that delay on the options available to a patient for terminating a pregnancy, if that is something they are considering. If a patient with detectable HIV RNA levels requires invasive prenatal testing, consultation with an expert in the management of HIV during pregnancy should be considered (see Intrapartum Care for People with HIV).

Fetal therapy is an area of maternal-fetal medicine in which insufficient data exist about the risk of HIV transmission through such procedures as selective fetoscopic laser photocoagulation, vesicoamniotic or thoracoamniotic shunts, intrauterine transfusions, *in utero* repair of neural tube defects, and other invasive procedures. In the absence of evidence to guide these decisions, it is recommended that patients with HIV who may require advanced care for fetal abnormalities receive consultation at specialized centers where they can receive coordinated, multidisciplinary counseling.

As with the above discussion regarding prenatal diagnosis, it is recommended that individuals have achieved viral suppression prior to procedures.

The National Perinatal HIV Hotline

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

ART Adherence Support During Pregnancy

In general, the recommendations for the use of ART in people who are pregnant are the same as for those who are not pregnant. However, the Perinatal Guidelines do 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 6. What to Start: Initial Antiretroviral Regimens During Pregnancy for People Who Are Antiretroviral-Naive and Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs in Pregnant People and Nonpregnant People Who Are Trying to Conceive and Recommendations for Use of Antiretroviral Drugs During Pregnancy: Overview).

Clinicians and patients should discuss the substantial benefits of ARV drugs for health of the pregnant person and for reducing the risk of HIV transmission to infants; this helps put the potential risks of using these drugs into perspective (see Table 14. Antiretroviral Drug Use in Pregnant People with HIV: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy and Appendix B: Supplement: Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy). Counseling of pregnant patients about ARV drug use should be directive and noncoercive, and providers should help patients make informed decisions regarding the use of ARV drugs.

Counseling about regimens should include information about the following:

- The risk of HIV disease progression and the benefits and risks of therapy for the health of the pregnant person[23];
- The benefits of ART for preventing perinatal transmission of HIV[24];
- The benefits of using ART to achieve and maintain viral suppression, which reduces the risk of sexual transmission of HIV to partners who do not have HIV[25];
- The need for strict adherence to the prescribed ARV drug regimen to avoid drug resistance, optimize health outcomes, and minimize the risk of perinatal HIV transmission;
- The potential adverse effects of ARV drugs for pregnant people, fetuses, and infants, including potential interactions with other medications the patient may already be receiving (see Recommendations for Use of Antiretroviral Drugs During Pregnancy: Overview)[26-29];
- The limited long-term outcome data for infants who were exposed to ARV drugs *in utero*, especially for newer ARV drugs; *and*
- The importance of considering pregnancy-specific challenges to adherence, such as nausea and vomiting or adverse social determinants of health. Patients should be advised to remain in close communication with their providers about these challenges.

Counseling at the onset of antepartum care and at each subsequent visit 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. Patients with poor adherence during pregnancy are more likely to have detectable viral loads at delivery.[30] In addition, multiple adverse social determinants of health—including housing instability,[31] nondisclosure of HIV status,[32,33] lack of social support,[34] and other factors—are known to affect adherence. As a result, adherence counseling should include careful attention to the patient's social needs, social support, and mental health.

Patient Counseling and Coordination of Care

Coordination of services among antepartum 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 patients with HIV are well supported during all stages of their pregnancies and the postpartum period. Medical care of pregnant people with HIV requires coordination and communication between HIV specialists and obstetric providers.

Anticipatory guidance provided during pregnancy for people with HIV is generally similar to counseling that is recommended for individuals without HIV.[35] However, HIV-specific antepartum 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 tobacco use, substance use disorders, alcohol consumption, and genital tract infections. In addition to improving health of the pregnant person and their offspring, cessation of tobacco and drug use and treatment of STIs and other genital tract infections may reduce the risk of perinatal transmission. Other risk factors for ART nonadherence, such as housing instability, food insecurity, mental health disorders,[36] and IPV,[37] also require particular attention for patients with HIV. Patients should be screened for mental health conditions, assessed for the risk of IPV, and counseled about disclosure of their HIV status when needed.[38]

Fears of stigma and violence that could result from undesired HIV status disclosure require comprehensive, culturally informed services to assist pregnant and postpartum patients who are planning to disclose their status,[39,40] and patients who have not disclosed their status require support to maintain privacy during health care encounters (including telemedicine visits and in-person care).[41] Transgender and gender-diverse individuals may have specific concerns and needs for added support related to receiving services in settings designed for the care of cisgender women and pregnant women (see Perinatal HIV Prevention for Transgender and Gender-Diverse People Assigned Female at Birth).

In addition, providers should counsel patients with HIV about what to expect during labor, delivery, and the postpartum period. This counseling should include discussing the mode of delivery and the possible use of intrapartum zidovudine, as well as unique disclosure circumstances that may occur in the context of intrapartum care. Guidance must also address reproductive choice and postpartum contraceptive options. Providers also should discuss the possibility of simplifying a patient's ARV regimen after delivery, which can help promote long-term adherence to ART. Discussions regarding the prevention of postnatal transmission to the neonate also should include recommendations about infant feeding, neonatal ARV prophylaxis, infant diagnostic HIV testing, and the avoidance of premastication of food (see Infant Feeding for Individuals with HIV in the United States). Anticipatory guidance about postpartum care also must include plans for transitioning health care from the obstetric team to the long-term health care team.

Table 4. Antepartum Screenings and Assessments for Pregnant People with HIV[a]

Antepartum Screenings and Assessments	At Entry into Antenatal Care	At Each Visit	As Clinically Indicated
Assessment of ART adherence, adherence challenges, and facilitators	✓	✓	✓
Assessment of the need for prophylaxis against opportunistic infections, e.g., *Pneumocystis jirovecii* pneumonia[b]	✓		✓
Screening for HAV, HBV, and HCV and assessment of vaccination or treatment needs[c]	✓		
Assessment and provision of other vaccination needs, e.g., influenza, pneumococcus, Tdap, SARS-CoV-2 (including boosters)[d]	✓		✓
Tuberculosis screening[e]	✓		✓
STI screening, e.g., syphilis, *Chlamydia trachomatis*, *Trichomonas vaginalis*, and *Neisseria gonorrhea*	✓		✓[f]
Screening for depression and anxiety	✓		✓
Screening for IPV	✓		✓
Assessment of the patient's gender identity and pronouns[g]	✓		
Assessment of the need for supportive care, e.g., social services, mental health services, substance use disorder treatment services, smoking cessation	✓	✓	✓

[a] Provide or refer for needed services based on the results of screenings and assessments, e.g., immunizations, treatment, referrals.

[b] Prophylaxis against *Pneumocystis jirovecii* pneumonia is recommended during pregnancy when CD4 count is <200 cells/mL. See Pneumocystis Pneumonia in the Adult and Adolescent Opportunistic Infections Guidelines.

[c] See Hepatitis B Virus/HIV Coinfection and Hepatitis C Virus/HIV Coinfection for guidance regarding immunizations and treatment.

[d] See Pregnancy and Vaccination and Maternal Immunizations for additional information.

[e] Includes screening for active and latent tuberculosis; stepwise screening for active tuberculosis may begin with exposure history and symptom screening (see Mycobacterium tuberculosis Infection and Disease). If screening for latent tuberculosis was performed and negative in the last year, repeat testing is not necessary for those at low risk for repeated or ongoing exposure to people with active tuberculosis.

[f] Repeat STI screening, particularly for syphilis, chlamydia, and gonorrhea, is often repeated in the third trimester (see Recommended Clinician Timeline for Screening for Syphilis, HIV, HBV, HCV, Chlamydia, and Gonorrhea).

[g] See Perinatal HIV Prevention for Transgender and Gender-Diverse People Assigned Female at Birth for additional guidance.

Key: ART = antiretroviral therapy; HAV = hepatitis A virus; HBV = hepatitis B virus; HCV = hepatitis C virus; IPV = intimate partner violence; STI = sexually transmitted infection; Tdap = tetanus, diphtheria, and pertussis vaccine

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Initial Evaluation and Continued Monitoring of HIV During Pregnancy

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Panel's Recommendations
• The plasma HIV RNA levels of pregnant people with HIV should be monitored at the initial antenatal visit with a review of prior HIV RNA levels (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 36 weeks gestation, or within 4 weeks of planned delivery, to inform decisions about mode of delivery (see Intrapartum Care for People 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 with review of prior CD4 counts (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). Patients who have been on ART for <2 years and have CD4 counts of <300 cells/mm^3, those with inconsistent adherence, or those with detectable viral loads should have CD4 counts monitored every 3 months during pregnancy; patients on ART <2 years and with CD4 counts ≥300 cells/mm^3 should have CD4 monitored every 6 months (CIII). • HIV drug-resistance testing (genotypic testing and, if indicated, phenotypic testing) should be reviewed in conjunction with antiretroviral (ARV) history (if prior results are available) and performed during pregnancy in those whose HIV RNA levels are above the threshold for resistance testing (usually >500 copies/mL to 1,000 copies/mL but may be possible for HIV RNA >200 to ≤500 copies in some laboratories). Testing should be conducted before— o Initiating ART in ARV-naive pregnant people who have not been previously tested for ARV drug resistance (AII); o Initiating ART in ARV-experienced pregnant people (including those who have received pre-exposure prophylaxis) (AIII); *or* o Modifying ARV regimens for people with HIV who become pregnant while receiving ARV drugs or people who have suboptimal virologic response to ARV drugs that were started during pregnancy (AII). See Antiretroviral Drug Resistance and Drug Resistance Testing in Pregnancy. • ART should be initiated in pregnant patients prior to receiving the results of ARV-resistance tests. ART should be modified, if necessary, based on the results of resistance testing (AII). • Laboratory testing to monitor complications of ARV drugs during pregnancy should be based on what is known about the adverse effects of the drugs an individual is receiving (AIII). • Pregnant people with HIV who are taking ART during pregnancy should undergo standard gestational diabetes screening (AIII). Some experts suggest performing this screening early in pregnancy for those who may be at high risk for gestational diabetes on protease inhibitor–based ART (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*

Viral Load and CD4 Cell Count Testing and Monitoring

Viral loads should be monitored more frequently in pregnant individuals than in nonpregnant individuals because of the importance of rapid and sustained viral suppression through delivery in preventing perinatal HIV transmission (see Table 5 below). Individuals who are adherent to their

antiretroviral therapy (ART) and who do not harbor resistance mutations to the prescribed drugs should generally achieve viral suppression within 3 to 12 weeks on preferred regimens, such as integrase inhibitor–based ART, depending on the initial viral load.[1-4] Individuals with higher viral loads and lower CD4 T lymphocyte (CD4) cell counts are more likely to require more time to achieve viral suppression[5,6] than those with lower viral loads and higher CD4 counts. Those using integrase strand transfer inhibitors (INSTIs) are more likely to achieve suppression in much shorter time frames.[7-9] 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.[10,11]

Viral load should be monitored in pregnant patients with HIV at the initial clinic visit with a review of prior viral load levels 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.[12-14] Similarly, pregnancy may reduce the drug exposure levels or the efficacy of some drugs; patients who are taking these drugs may require a change in therapy or more frequent viral load monitoring (see Table 6 and Table 7). More frequent viral load monitoring is recommended for those 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 People with HIV Who Are Taking Antiretroviral Therapy When They Become Pregnant).

Viral load also should be assessed at approximately 36 weeks gestation, or within 4 weeks of planned delivery, to inform decisions about the mode of infant delivery and optimal treatment for newborns (see Intrapartum Care for People with HIV).

In pregnant patients with HIV, CD4 count should be measured at the initial clinic visit with a review of prior CD4 counts (see Table 5 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.[10,15,16] Patients who have been on ART for <2 years and have CD4 counts of <300 cells/mm^3, those with inconsistent adherence, or those with detectable viral loads should have CD4 counts monitored every 3 months during pregnancy. Patients who have been on ART <2 years and have CD4 counts of ≥300 cells/mm^3 should have CD4 counts monitored every 6 months. 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 at least 1 year) are highly unlikely to experience a CD4 count <350 cells/mm^3 in the span of a year.[17]

HIV Drug–Resistance Testing

HIV drug–resistance testing should be reviewed in conjunction with ARV history if prior results are available and performed in pregnant patients with HIV before starting or modifying ART if HIV RNA levels are above the threshold for standard resistance testing (usually >500 copies/mL to 1,000 copies/mL but may be possible for HIV RNA >200 to ≤500 copies in some laboratories) (see Table 5 below). Genotypic testing should be performed. In cases of treatment-experienced

individuals with suspected multidrug resistance and who are on failing regimens, phenotypic testing also should be 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 adjusted subsequently. HIV drug–resistance testing also should be performed on patients who are on ART but have suboptimal viral suppression (i.e., failure to achieve undetectable levels of virus during an appropriate time frame, as noted above) or sustained viral rebound to detectable levels after prior viral suppression on ART (see Pregnant People Who Have Not Achieved Viral Suppression on Antiretroviral Therapy 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.

Other Laboratory Testing and Monitoring

The laboratory tests that are assessed initially and 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 patient is receiving (see Table 5 below). For example, HLA-B*5701 testing should be performed if the use of abacavir is anticipated.[18-22] Routine hematologic monitoring is recommended for patients who are receiving zidovudine-containing regimens, and routine renal monitoring is recommended for patients who are receiving tenofovir-containing regimens. Liver function should be monitored in all patients 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 protease inhibitors (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. Pregnant women in general are more likely than their nonpregnant counterparts to have elevated levels of liver enzymes.[23-25]

Pregnancy itself increases the risk of glucose intolerance. In a meta-analysis, the pooled prevalence of gestational diabetes among women with HIV was 4.42% (95% confidence interval, 3.48% to 5.35%). These rates do not appear to be higher than those in non-HIV populations.[26,27] The majority of studies in pregnant women have not demonstrated an association between HIV infection and gestational diabetes.[28-32] However, other studies, particularly those with stringent definitions of gestational diabetes, did show an increased risk of gestational diabetes in women who were taking PI-based regimens during pregnancy.[33,34] In addition, one study and several case series in nonpregnant adults with HIV have reported an increased risk for incident diabetes after initiation of INSTIs.[35-39] Patients with HIV who are on ART during pregnancy should receive the standard screening for gestational diabetes that is recommended for all pregnant people. However, some experts suggest performing this screening earlier in pregnancy for patients who are receiving PI-based ART that was initiated before pregnancy, in accordance with recommendations for patients with risk factors for glucose intolerance, such as obesity (see Table 5 below).[40]

In addition to gestational diabetes risk with some ARV classes, risk for weight gain and obesity both during pregnancy and postpartum may be present with integrase inhibitor use, although existing evidence is somewhat inconclusive,[41-50] with most published data collected in nonpregnant populations (see Considerations for Antiretroviral Use in Special Patient Populations in the

Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV and Maternal Health Outcomes in Recommendations for the Use of Antiretroviral Drugs During Pregnancy: Overview). Several studies in nonpregnant people with HIV have reported higher weight gain with the combined use of tenofovir alafenamide and integrase inhibitors,[45,51,52] with another study in pregnant people with HIV observing a similar finding.[53] Current guidelines from the American College of Obstetricians and Gynecologists and the National Academy of Medicine recommend that appropriate weight gain, diet, and exercise during pregnancy should be discussed with patients at initial antenatal visits and regularly thereafter.[54-56]

Table 5. HIV-Related Laboratory Monitoring Schedule for Pregnant People with HIV[a]

Laboratory Test	Timepoint or Frequency of Testing						
	Entry Into Antenatal Care[c]	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 Approximately 36 Weeks of Gestation or Within 4 Weeks of Planned Delivery to Inform Mode of Delivery and Infant ARV Regimen
HIV RNA Levels[b]	✓[c]	✓ 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[d]		✓
CD4 Count[e]	✓[c]				✓ Patients who have been on ART for <2 years and have CD4 counts of <300 cells/mm^3, those with inconsistent adherence, or those with detectable viral loads should have CD4 counts monitored every		

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					3 months during pregnancy.[e]		
Resistance Testing[f]		✓					
HLA-B*5701 Testing		✓ If abacavir use is anticipated					
Standard Screening for Gestational Diabetes[g]						✓	
Complete Blood Cell Count; Renal Function	✓	✓ With additional testing as clinically indicated				✓	

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Laboratory Test	Timepoint or Frequency of Testing						
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Liver Function	✓	✓			✓ With additional testing as clinically indicated		
Monitoring for ARV-Specific Toxicities[h]	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 people with HIV should be monitored at the initial antenatal visit with a review of prior HIV RNA levels (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] Prior HIV-related illnesses and past plasma HIV RNA levels and CD4 counts should be reviewed at entry into antenatal care.

[d] More frequent viral load monitoring (every 1–2 months) may be indicated for patients who are taking ARVs that have been shown to have reduced drug levels in the second and third trimesters (e.g., cobicistat, elvitegravir, rilpivirine) and are potentially at risk for loss of viral suppression (see Table 6, Table 7, and People with HIV Who Are Taking Antiretroviral Therapy When They Become Pregnant).

[e] CD4 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). Patients who have been on ART for <2 years and have CD4 counts of <300 cells/mm^3, those with inconsistent adherence, or those with detectable

Table 5. HIV-Related Laboratory Monitoring Schedule for Pregnant People with HIV

viral loads should have CD4 counts monitored every 3 months during pregnancy (CIII). Those on ART<2 years and with CD4 counts >300 cells/mm^3 should have CD4 monitored every 6 months.

[f] ARV drug-resistance testing (genotypic testing and, if indicated, phenotypic testing) should be performed in patients whose HIV RNA levels are above the threshold for standard resistance testing (usually >500 copies/mL to 1,000 copies/mL but may be possible for HIV RNA >200 to ≤500 copies in some laboratories). Testing should be performed before—

- Initiating ART in ARV-naive pregnant patients who have not been tested previously for ARV drug resistance (AII);
- Initiating ART in ARV-experienced pregnant patients (AIII); *or*
- Modifying ARV regimens for patients who become pregnant while receiving ARV drugs or patients who have suboptimal virologic response to ARV drugs that were started during pregnancy (AII).

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

[g] Patients who are taking ART during pregnancy should undergo standard gestational diabetes screening (AIII). Some experts suggest performing glucose screening early in pregnancy for patients who are receiving PI-based regimens that were initiated before pregnancy, in accordance with recommendations for patients who are at risk for glucose intolerance (BIII). For more information on PIs, see Antiretroviral Drug Regimens and Maternal and Neonatal Outcomes.

[h] 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 person is receiving (AIII).

Key: ART = antiretroviral therapy; ARV = antiretroviral; CD4 = CD4 T lymphocyte

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Antiretroviral Drug Resistance and Resistance Testing in Pregnancy

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Panel's Recommendations
• Drug-resistance testing should be performed for people with virologic failure and HIV RNA levels >200 copies/mL (AI for >1,000 copies/mL, AIII for 501–1,000 copies/mL, CIII for confirmed HIV RNA 201–500 copies/mL). For people with confirmed HIV RNA levels >200 copies/mL but <500 copies/mL, drug-resistance testing may be unsuccessful but should still be considered. Perform resistance testing before— o Initiating antiretroviral therapy (ART) in antiretroviral (ARV)-naive pregnant persons who have not been previously tested for ARV resistance (AII), o Initiating ART in ARV-experienced pregnant persons (including those who have received pre-exposure prophylaxis) (AIII), *or* o Modifying ARV regimens for those who are newly pregnant and receiving ARV drugs or who have suboptimal virologic response to the ARV drugs started during pregnancy (AII). • ART should be initiated in pregnant persons before receiving results of ARV-resistance testing; ART should be modified, if necessary, based on the results of resistance assays (AII). • Phenotypic resistance testing is indicated for treatment-experienced persons on failing regimens who are thought to have multidrug resistance (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 (AIII). INSTI resistance may be a concern if— o A patient received prior treatment or pre-exposure prophylaxis that included an INSTI, *or* o A patient has had a sexual partner on INSTI therapy who was not virologically suppressed or with unknown viral load. • Documented zidovudine (ZDV) resistance does not affect the indications for use of intrapartum intravenous ZDV (see Intrapartum Care for People with HIV) (BIII). • Choice of ARV regimen for an infant born to a person 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) (BIII). • Pregnant persons 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 individuals 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 Persons with HIV

Identification of baseline resistance mutations allows for the selection of more effective and durable antiretroviral (ARV) regimens. Drug-resistance testing should be performed for people with virologic failure and HIV RNA levels >200 copies/mL. For people with confirmed HIV RNA levels >200 copies/mL but <500 copies/mL, drug-resistance testing may be unsuccessful but should still be considered. Perform resistance testing before—

- Initiating antiretroviral therapy (ART) in ARV-naive pregnant patients who have not been previously tested for ARV resistance,
- Initiating ART in ARV-experienced pregnant patients (including those who have received pre-exposure prophylaxis [PrEP]), *or*
- Modifying ARV regimens for those who are newly pregnant and receiving ARV drugs or who have suboptimal virologic response to ARV drugs that were initiated during pregnancy.

It is also important to obtain a comprehensive history of ARV drug use, including ARVs used for HIV PrEP. 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 persons or ARV-experienced individuals who are not presently on ART without waiting for the results of resistance testing because earlier viral suppression is associated with lower risk of perinatal transmission. The regimen can be modified, if required, when test results return.

Integrase strand transfer inhibitors (INSTIs) are used increasingly in ART regimens for pregnant people,[1] and the INSTI cabotegravir (Apretude) has been approved for PrEP. Resistance to INSTIs is generally uncommon among ARV-naive individuals in the United States.[2] In studies of INSTI resistance in North Carolina, resistance was detected in 2.4% (95% confidence interval [CI], 1.5% to 3.6%) of ART-naive persons and 9.6% (95% CI, 8.3% to 11.0%) of ART-experienced persons with HIV[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% ($P = 0.04$) in 2013 in Washington, D.C.[5] During 2014 to 2018, among 50,747 persons, Centers for Disease Control and Prevention surveillance within 3 months of HIV diagnosis identified 0.8% with INSTI resistance. A systematic review of 103 studies identified "surveillance" drug-resistance mutations in 0.5% of INSTI-naive individuals.[6,7] A polymorphism or a substitution associated with INSTI resistance was found in 1.4% of INSTI-naive persons in 16 clinical trials.[8]

The development of INSTI resistance is infrequent among people who receive INSTI-based ART (only 1.5% to 3.8% of people develop resistance).[9-11] A modeling study found that testing for INSTI resistance at ART initiation was not cost effective and did not improve clinical outcomes.[12] Genotype testing for INSTI resistance also is not considered cost effective in the United States when initiating ART.[13] Routine INSTI-resistance testing generally is not indicated in pregnant persons. However, such testing can be considered when a patient received prior treatment or PrEP that included an INSTI or when a patient has had a sexual partner on INSTI therapy who was not virologically suppressed or with unknown viral load.

HIV drug-resistance genotype testing detects mutations that confer resistance to protease inhibitors, nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors, and INSTIs. Phenotypic resistance testing is reserved generally 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.

There are currently no commercially available resistance tests for the CD4 T lymphocyte post-attachment inhibitor ibalizumab, gp120 attachment inhibitor fostemsavir, or capsid inhibitor lenacapavir.

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.[14] The complexities of managing pregnant people with perinatally acquired HIV warrant consultation with an expert in HIV.[15] See Prenatal Care, Antiretroviral Therapy, and HIV Management in People with Perinatal-Acquired 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 those 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.

Managing Antiretroviral Resistance During Pregnancy

The most effective way to prevent the development of ARV drug resistance in pregnancy is to follow recommendations for resistance testing and viral load monitoring and to support adherence to an effective ARV regimen that achieves maximal viral suppression (see Monitoring During Pregnancy). Management of pregnant people who have received ART or ARV prophylaxis previously, including resistance testing, is discussed in Pregnant People with HIV Who Have Previously Received Antiretroviral Medication But Are Not Currently on Antiretroviral Medications. Inadequate adherence and viral resistance should be considered when there is a suboptimal virologic response or viral rebound to an ARV regimen (see Pregnant People Who Have Not Achieved Viral Suppression on Antiretroviral Therapy). Because studies have shown that adherence to ART may worsen during the postpartum period,[16-19] arrangements should be made during pregnancy for appropriate postpartum follow-up and adherence support to prevent loss of virologic control and the development of resistance (see Postpartum Follow-Up of People with HIV).

The optimal prophylactic regimen for newborns of persons with drug-resistant HIV is unknown. Therefore, ARV prophylaxis for infants born to persons with known or suspected drug-resistant HIV 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). No evidence exists that neonatal prophylaxis regimens that have been customized to address maternal drug resistance are more effective than standard neonatal prophylaxis regimens.

Zidovudine Resistance During Pregnancy

Those who have documented zidovudine (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 patients with HIV RNA >1,000 copies/mL or unknown HIV viral load near delivery (see Intrapartum Care for People with HIV). A patient's ARV regimen should be continued orally during labor to the extent possible. The rationale for including ZDV intrapartum when a patient is known to have HIV with ZDV resistance is based on several factors. First, 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[20]; drug-resistance mutations may diminish viral fitness and possibly decrease transmissibility.[21] Second, the efficacy of ZDV prophylaxis appears to be based not only on a reduction in maternal HIV viral load, but also on the on its role as both PrEP and post-exposure prophylaxis in the infant.[22-24] 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,[25] which may provide additional protection against transmission. Third, ZDV penetrates the central nervous system better than other recommended nucleoside analogues; this may help eliminate a potential reservoir for transmitted HIV in the infant.[26] 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.

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Recommendations for the Use of Antiretroviral Drugs During Pregnancy: Overview

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Panel's Recommendations
• All pregnant people with HIV should initiate antiretroviral therapy (ART) as early in pregnancy as possible, regardless of their HIV RNA level or CD4 T lymphocyte cell count, to maximize their health and prevent perinatal HIV transmission and sexual transmission (AI). • In addition to benefiting an individual's health and preventing HIV transmission to sexual partners, the goal of ART during pregnancy is to achieve and maintain HIV viral suppression to undetectable levels (i.e., HIV RNA below the lower limits of detection of an ultrasensitive assay) to reduce the risk of perinatal transmission and maximize the pregnant person's health (AI). • Pregnant people are often excluded from clinical trials of antiretroviral (ARV) drugs, resulting in limited data regarding pharmacokinetics (PK), drug safety, and efficacy of new ARV drugs in pregnancy and lactation. However, **pregnancy, lactation, or the potential for pregnancy should not preclude the use of drug regimens that would be chosen for people who are not pregnant,** unless adequate drug levels are not likely to be attained in pregnancy or known adverse effects outweigh potential benefits (AIII). • The selection of which ARV drugs to use during pregnancy is best made through shared decision-making between the health care provider and patient after discussion of the known and potential risks and benefits to the patient and fetus, acknowledging limited data (AIII). See Appendix C: Antiretroviral Counseling Guide for Health Care Providers, Table 6. What to Start: Initial Antiretroviral Regimens During Pregnancy for People Who Are Antiretroviral-Naive, and Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs in Pregnant People and Nonpregnant People Who Are Trying to Conceive. • The Panel on Treatment of HIV During Pregnancy and Prevention of Perinatal Transmission (the Panel) uses a variety of data sources to assign ARV drugs to one of five categories for use in pregnancy: *Preferred*, *Alternative*, *Insufficient Data to Recommend*, *Not Recommended Except in Special Circumstances*, and *Not Recommended*, as outlined in Table 6. What to Start: Initial Antiretroviral Regimens During Pregnancy for People Who Are Antiretroviral-Naive and Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs in Pregnant People and Nonpregnant People Who Are Trying to Conceive for a variety of clinical scenarios. o When selecting ARV drugs for use in pregnancy or for people who are trying to conceive, the Panel recommends use of ARV drugs in the *Preferred* or *Alternative* categories whenever possible (AIII) but also tailors its recommendations to a variety of clinical scenarios; see Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs in Pregnant People and Nonpregnant People Who Are Trying to Conceive. • When choosing an ARV drug regimen and weighing the benefits and risks of specific ARVs for use during pregnancy or in people who are trying to conceive, providers and pregnant people should consider multiple factors, including adverse effects, drug interactions, PK, convenience of the individual drugs and drug combinations in the regimen, available pregnancy safety and outcome data, virologic efficacy in nonpregnant adults (and pregnant individuals if available), and the individual's resistance test results and comorbidities (AIII). • In most cases, people with HIV who are receiving ART and present for pregnancy care should continue their current ART, provided that the regimen is tolerated, safe, and effective in suppressing viral replication (defined as a regimen that maintains an HIV RNA level (viral load) less than the lower limits of detection of the assay) (AII) (see People with HIV Who Are Taking Antiretroviral Therapy When They Become Pregnant).

- Important changes in physiology and volume of distribution during pregnancy may impact drug concentrations and effectiveness in suppressing HIV viral replication, especially later in pregnancy when viral rebound may increase transmission risk and impact the need for intrapartum zidovudine or cesarean delivery (see Table 9 in Intrapartum Care for People with HIV). Pregnant people and clinicians should review these potential impacts as early in pregnancy as possible when choosing to start, modify, or continue an ARV regimen (AIII) (see People with HIV Who Are Taking Antiretroviral Therapy When They Become Pregnant).
- The Panel strongly recommends against discontinuing ART during pregnancy (AII).
- If an ARV drug regimen must be stopped during pregnancy, all ARV drugs should be stopped simultaneously, and a complete, effective ARV regimen should be reinitiated as soon as possible (AII).
- Throughout the prepregnancy, pregnancy, and postpartum periods, clinicians should discuss current and future reproductive desires and contraceptive options, as well as the risks and benefits of conceiving or conceiving again on the current ARV regimen (AIII). See Prepregnancy Counseling and Care for Persons of Childbearing Age with HIV and Postpartum Follow-Up of People with HIV 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

Selection of Antiretroviral Drugs During Pregnancy

Selection of antiretroviral (ARV) drugs **should be individualized** for people with HIV who are pregnant or are trying to conceive. The availability of data about the use of each medication in pregnancy is a primary consideration. In addition, 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 people who are pregnant, as well as factors that will vary for individuals.

Pregnancy-related factors include potential short-term and long-term adverse effects on fetuses or newborns, such as possible risk of teratogenicity, preterm birth, or effects on growth and development, and the degree to which data are available about these risks; pharmacokinetic (PK) changes in pregnancy; and potential adverse effects for pregnant people, especially those that may be exacerbated during pregnancy.

Individual-level factors include potential drug interactions with other medications; results of resistance testing and the patient's prior exposure to ARV drugs; comorbidities; ability of the patient to tolerate and adhere to a regimen; and convenience and individual preference, including a pregnant individual's preferences for balancing known and unknown risks and benefits.

This section provides an overview of the key clinical and PK issues that are relevant to the selection of specific ARV drugs for use in pregnancy.

After reviewing key concepts about balancing the risks and benefits and PK, this section will define the categories of ARV drug recommendations in pregnancy: *Preferred*, *Alternative*, *Insufficient Data*, *Not Recommended Except in Special Circumstances*, and *Not Recommended*. Whenever possible, ARV drugs that are *Preferred* for use in pregnancy should be used. However, it is important to note that most individuals with HIV will be receiving antiretroviral therapy (ART) when they become pregnant and often are receiving *Preferred* or *Alternative* ARV drugs.[1]

The sections that follow focus on the benefits of ART and recommendations for the use of ARV drugs in specific scenarios:

- Use of Antiretroviral Drugs to Prevent Perinatal HIV Transmission and Improve Health for Pregnant People
- Antiretroviral Therapy for People with HIV Who Are Trying to Conceive
- Pregnant People with HIV Who Have Never Received Antiretroviral Drugs (Antiretroviral-Naive)
- People with HIV Who Are Taking Antiretroviral Therapy When They Become Pregnant
- Pregnant People with HIV Who Have Previously Received Antiretroviral Medications but Are Not Currently on Antiretroviral Medications
- Pregnant People Who Have Not Achieved Viral Suppression on Antiretroviral Therapy
- Discontinuation of ART (see below)

Table 6. What to Start: Initial Antiretroviral Regimens During Pregnancy for People Who Are Antiretroviral-Naive provides advantages and disadvantages of specific ARV drugs and drug combinations in pregnancy, focusing primarily on considerations for people who are ARV naive, with additional information about other clinical scenarios.

Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs in Pregnant People and Nonpregnant People Who Are Trying to Conceive for a variety of clinical scenarios consolidates these scenario-specific recommendations for the use of ARV drugs in people with HIV who are trying to conceive or are pregnant into a single table for ease of reference.

Table 14. Antiretroviral Drug Use in Pregnant People with HIV Infection: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy and Appendix B: Supplement: Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy provide information about individual drugs, including dosing and PK data in pregnancy.

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 with HIV.

Balancing Risks and Benefits of ART in the Face of Limited Data

The selection of which ARV drugs to use during pregnancy or when trying to conceive is best made through **shared decision-making** between the pregnant individual and the health care provider following comprehensive discussion of the known benefits, as well as potential risks to the pregnant individual and the fetus[2] (see Appendix C: Antiretroviral Counseling Guide for Health Care Providers). Data about the PK, teratogenicity, and safety of individual ARV drugs during pregnancy are provided in Appendix B: Supplement: Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy.

During discussions, it can be helpful to point out that **ARV regimens taken during pregnancy can be modified after delivery.** After delivery, people may be able to use some regimens that could not be used during pregnancy due to insufficient or problematic safety and or PK data. These decisions

should take several factors into consideration, including the current ART recommendations for nonpregnant adults and adolescents, the patient's plans for contraceptive use and future pregnancies, and individual adherence considerations and medication preferences (see Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents and Postpartum Follow-Up of People with HIV).

Pregnant people often are excluded from clinical trials of ARV drugs. As a result, data regarding the PK, drug safety, and efficacy of new ARV drugs often are limited to nonpregnant adults.[3,4] Information about the efficacy of ARV drugs for treatment of pregnant people can be extrapolated from evidence of efficacy in nonpregnant adults, as long as direct PK evaluation in pregnant people demonstrates drug exposures in pregnancy that are within the effective range in nonpregnant adults. Similarly, ART regimens that result in viral suppression throughout pregnancy are likely to be effective in preventing vertical transmission of HIV. To expedite the investigation of new ARV drugs during pregnancy, it is essential that studies evaluate the PK of these drugs during pregnancy as soon as possible after dosing in nonpregnant people is established. In addition, clinical trials should carefully evaluate the safety of ARV drugs in people of childbearing potential, and measurement of efficacy should be included as a secondary endpoint in pregnant people.[5]

Drugs with known benefits to people who are not pregnant should not be withheld during pregnancy unless they have known adverse effects in pregnant people, fetuses, or infants and these adverse effects outweigh the benefits to pregnant patients or adequate drug levels are not likely to be attained during pregnancy. Pregnancy or the potential for pregnancy **should not preclude** the use of optimal drug regimens.

It is important to discuss the clear benefits of ART for maternal health and prevention of HIV transmission to the infant and sexual partners, as well as the limitations of available data on individual drugs.[6] Data about the benefits of ART are summarized and discussed in Recommendations for the Use of Antiretroviral Drugs to Prevent Perinatal HIV Transmission and Improve Health for Pregnant People. Overall, data are limited on the risks associated with using *Preferred* and *Alternative* ARV drugs other than tenofovir disoproxil fumarate (TDF), emtricitabine (FTC), lamivudine (3TC), efavirenz (EFV), and dolutegravir (DTG) when used during preconception or in very early pregnancy. Importantly, this **lack of data indicates neither the presence nor the absence of risk.** For more details and information about other drugs, please see Teratogenicity, Antiretroviral Drug Regimens and Pregnancy Outcomes, Appendix C: Antiretroviral Counseling Guide for Health Care Providers, and Appendix B: Supplement: Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy.

Birth Defect Risk

Although a few concerns exist about teratogenicity of currently used ARV drugs, the Panel on Treatment of HIV During Pregnancy and Prevention of Perinatal Transmission (the Panel) continues to use a longstanding, systematic approach for evaluating birth defect risk for all ARV drugs. Large-scale, systematic birth defect surveillance data following periconception exposure are available only for TDF, FTC, 3TC, zidovudine (ZDV), EFV, and DTG.[7,8] To determine whether a drug carries an increased risk of a rare birth defect, more than 2,000 periconception exposures need to be monitored to detect a threefold increase in risk. Data from more than 1,000 first-trimester exposures are needed to detect a 1.5-fold increase in the risk of overall birth defects and a twofold increase in the risk of the most common classes (cardiovascular and genitourinary) of birth defects.[9] The Antiretroviral Pregnancy Registry is an international registry that also provides data on birth defects with periconception exposures for all available ARV drugs, but reporting is voluntary, and the number of

reports to the registry depends on clinicians' reporting. Data are more limited on newer ARV drugs and on periconception exposures. See Teratogenicity, Appendix B: Supplement: Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy, and the Antiretroviral Pregnancy Registry for information about individual ARV drugs.

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.

Preterm Birth and Other Adverse Pregnancy Outcomes

The risk of other adverse pregnancy outcomes that are more common than birth defects also should be considered when selecting ART regimens (see Antiretroviral Drug Regimens and Pregnancy Outcomes). For example, the use of some protease inhibitors, particularly lopinavir/ritonavir (no longer recommended except in special circumstances), has been associated with an increased risk of preterm birth, which may lead to an increase in infant morbidity and mortality.[7,8,10]

Maternal Health Outcomes

Data on maternal health outcomes (e.g., hypertension, weight gain) with all ARV regimens are needed (see Antiretroviral Drug Regimens and Pregnancy Outcomes).[11-13] Substantial weight gain on DTG-based regimens has been observed in nonpregnant populations, especially among women and among people also receiving tenofovir alafenamide (TAF) (see Dolutegravir and Tenofovir Alafenamide).[14,15] However, it is difficult to extrapolate data about weight gain in nonpregnant adults to determine the effects of ARV drugs on gestational weight gain. DTG-associated weight gain has been observed in pregnancy, but this may reflect better maternal health (e.g., lower rates of insufficient weight gain or weight loss during pregnancy with DTG-based ART). Some studies have shown greater weight gain during pregnancy with TAF/FTC/DTG (0.08 kg/week)[16] and TDF/FTC/DTG (0.03–0.05 kg/week)[16,17] than with TDF/FTC/EFV, while others found no increased weight gain during pregnancy with DTG.[18] However, the weekly weight gain during pregnancy in women on DTG- or EFV-based ART remained less than in women without HIV[17] and less than the recommended weight gain in pregnancy for the general population.[16] In the Tshilo Dikotla Study, postpartum weight gain was greater in women receiving DTG than in those receiving EFV-based ART but was similar to weight gain in postpartum women without HIV.[19] The DolPHIN-2 (Dolutegravir in pregnant HIV mothers and their neonates) perinatal trial found no differences in postpartum weight changes between women initiating EFV-based or DTG-based ART late in pregnancy.[20] The Surveillance Monitoring for ART Toxicities study found that gestational weight gain was not associated with ARV class. However, among those who were overweight or obese when they entered pregnancy, weekly gestational weight gain in the second and third trimesters was greater in those receiving integrase strand transfer inhibitors (INSTIs) than other classes of ARV drugs.[21]

In the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) 2010 trial, no differences were observed in viral suppression, grade 3 or higher adverse events, or estimated creatinine clearance among people randomized to initiate TDF/FTC versus TAF/FTC with DTG at >14 weeks gestational age. However, more women in the TAF/FTC arm had high gestational weight gain than in the TDF/FTC arm. High gestational weight gain was not associated with adverse outcomes in this study, but modeling suggests that, over time, excess weight gain with regimens containing TAF and DTG may lead to increased prepregnancy weight and obesity-related adverse pregnancy outcomes.[22] Additionally, in infants who were exposed to TDF *in utero*, there have been

concerns about bone and growth abnormalities, but the duration and clinical significance of study findings require further evaluation (see Tenofovir Disoproxil Fumarate).[23]

Pharmacokinetic Considerations for ARV 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.[24-26] 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 PK in the pregnant person.

In general, the PK of nucleoside reverse transcriptase inhibitors and non-nucleoside reverse transcriptase inhibitors (NNRTIs) are similar in pregnant and nonpregnant people (although PK data for some drugs are limited or not available). The PK of protease inhibitors and INSTIs are more variable, particularly during the second and third trimesters. Because dosing may differ in pregnancy, clinicians should review the currently available data on the PK and dosing of ARV drugs in pregnancy (see Appendix B: Supplement: Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy and Table 14. Antiretroviral Drug Use in Pregnant People with HIV: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy) and information about how PK changes affect recommendations for use of specific ARV drugs in pregnancy (see Categories for Drug Recommendations in Pregnancy below, Table 6. What to Start: Initial Antiretroviral Regimens During Pregnancy for People Who Are Antiretroviral-Naive, and Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs).

Categories of Drug Recommendations in Pregnancy

The Panel assigns U.S. Food and Drug Administration–approved ARV drugs to one of five categories, described below, for use in people who are pregnant. Table 6. What to Start: Initial Antiretroviral Regimens During Pregnancy for People Who Are Antiretroviral-Naive lists all ARV drugs and drug combinations and summarizes advantages and disadvantages of each. Situation-Specific Recommendations for Use of Antiretroviral Drugs in Pregnant People and Nonpregnant People Who Are Trying to Conceive provides an overview of Panel recommendations for ARV drugs in different clinical scenarios that are described in the following sections: Antiretroviral Therapy for People With HIV Who Are Trying to Conceive, People with HIV Who Are Taking Antiretroviral Therapy When They Become Pregnant, Pregnant People With HIV Who Have Previously Received Antiretroviral Medications but Are Not Currently on Antiretroviral Medications, and Pregnant People Who Have Not Achieved Viral Suppression on Antiretroviral Therapy. 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 shared decision-making (see Appendix C: Antiretroviral Counseling Guide for Health Care Providers).

- **Preferred:** 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 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; this assessment of risks and benefits should incorporate outcomes for pregnant people, fetuses, and infants. Some *Preferred* drugs or regimens may have minimal toxicity or incompletely evaluated teratogenicity risks that are offset by other advantages for people with HIV who are pregnant or trying to conceive.
- **Alternative:** Drugs or drug combinations are designated as *Alternative* options for therapy in pregnant people 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 risks that are offset by other advantages for people 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 people. In some cases, it may be appropriate to continue using these drugs or drug combinations in patients 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 people because of specific safety concerns or very limited safety and efficacy data in pregnancy, there may be circumstances in which ART-experienced people 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 because of inferior virologic efficacy or potentially serious safety concerns for the pregnant person or fetus. 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 viremia in the pregnant person occurs.

In some situations, it may be appropriate to continue using drugs or drug combinations designated as *Insufficient Data*, *Not Recommended Except in Special Circumstances*, or *Not Recommended* in people who become pregnant on fully suppressive ART that has been well tolerated, although viral load monitoring and, in some cases, safety monitoring should be performed more frequently in these instances. See People with HIV Who Are Taking Antiretroviral Therapy When They Become Pregnant and Initial Evaluation and Continued Monitoring of HIV-Related Assessments During Pregnancy.

In assigning these categories, the Panel uses information from several sources to develop recommendations on specific drugs or regimens for pregnant people. 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 when data are available, evidence of high rates of viral suppression during pregnancy, or evidence of high rates of viral suppression in nonpregnant patients with PK (drug exposure) data in pregnancy demonstrating exposures similar to those in nonpregnant patients;
- PK (drug exposure) data during pregnancy;
- Data from animal teratogenicity studies; *and*
- Antiretroviral Pregnancy Registry data and other postmarketing surveillance data.[9]

Discontinuation of ART

The Panel strongly recommends against discontinuing ART. However, 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. If an ARV drug that is known to have a long serum half-life (e.g., NNRTIs) must be stopped for more than a few days, clinicians should consider assessing the patient for rebound viremia after a new regimen is started and viral suppression would be expected; if optimal viral suppression has not been achieved, potential drug resistance should be assessed (see Antiretroviral Drug Resistance and Resistance Testing in Pregnancy).[27]

Temporary discontinuation of 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. Possible toxicity or intolerance to a single ARV agent should prompt discussion about options for modifying rather than stopping an entire ARV regimen (see People with HIV Who Are Taking Antiretroviral Therapy When They Become Pregnant).[27]

Discontinuation of therapy could lead to an increase in viral load, with possible disease progression and decline in immune status for the pregnant person and increased risk of *in utero* transmission of HIV. An analysis from a prospective cohort of 937 mother–child pairs from the Italian Register for HIV Infection in Children found that interruption of ART during pregnancy, including interruption in the first and third trimesters, was independently associated with an increased rate of perinatal HIV transmission.[28] Although the perinatal transmission rate for the entire cohort was only 1.3%, transmission occurred in 4.9% of mother–child pairs with first-trimester interruption (95% confidence interval [CI], 1.9% to 13.2%; adjusted odds ratio [aOR] 10.33; $P = 0.005$) and 18.2% of mother–child pairs with third-trimester interruption (95% CI, 4.5% to 72.7%; aOR 46.96; $P = 0.002$).[28]

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Use of Antiretroviral Drugs to Prevent Perinatal HIV Transmission and Improve Health for Pregnant People

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Reviewed: January 31, 2024

Panel's Recommendations
• All pregnant people with HIV should initiate antiretroviral therapy (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). • Persons with HIV initiating ART should receive the support necessary to achieve viral suppression to undetectable levels as rapidly as possible and maintain an HIV viral load that is below the limit of detection prior to conception, during pregnancy, postpartum, and throughout their lives (AII). (See Recommendations for Use of Antiretroviral Drugs During Pregnancy: Overview.) • Neonates should receive antiretroviral prophylaxis or presumptive HIV therapy appropriate to their risk of perinatal HIV acquisition (AI). (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*

All pregnant people with HIV should receive antiretroviral therapy (ART) early in pregnancy, preferably prior to conception, regardless of their viral load or CD4 T lymphocyte (CD4) cell count, to maximize their health and to prevent perinatal HIV transmission and secondary sexual transmission (see Recommendations for Use of Antiretroviral Drugs During Pregnancy: Overview). Antiretroviral (ARV) drugs are important for maintaining health before, during, and after pregnancy because they decrease the rate of HIV disease progression, reduce the risk of opportunistic diseases, and reduce the risk of death.[1] Use of an ARV regimen that successfully reduces plasma HIV RNA to undetectable levels substantially lowers the risk of vertical transmission of HIV to <1%, improves pregnancy outcomes, 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.

ARV drugs reduce the risk of perinatal transmission of HIV in all pregnant people, regardless of their CD4 counts and HIV RNA levels, through several mechanisms. Antenatal drug administration decreases viral load in blood and genital secretions.[2-4] **Early and sustained control of HIV viral replication with a suppressed viral load at the time of delivery markedly reduces the risk of perinatal HIV transmission.** In the prospective multicenter French Perinatal Cohort, both viral load at delivery and the timing of ART initiation were independently associated with perinatal HIV transmission rate.[5] Among women treated at conception who had detectable viral load near delivery, transmission risk was 1.08% (95% confidence interval [CI], 0.49–2.04), but among women treated at conception with undetectable viral load near delivery, there were no infections in 5,482 infants (95% CI, 0.00–0.07).[6] Other studies have similarly found lack of early and sustained viremic control to be strongly associated with increased risk of perinatal HIV transmission.[7,8]

In addition, several studies have found that higher viral load during pregnancy is associated with adverse pregnancy outcomes, including preterm birth and pregnancy loss through miscarriage or stillbirth.[9,10] These data suggest that ideally, ART should be initiated and viral suppression should be achieved prior to conception. When not started prior to conception, **ART should be initiated as early as possible in pregnant people. Prompt initiation of ART is particularly important in pregnant people with acute HIV infection or who have high baseline viral loads.**[11-14]

Antenatal drug administration also provides infant pre-exposure prophylaxis (PrEP); this is important because viremia during pregnancy is not the only risk factor for perinatal HIV transmission and ART use during pregnancy reduces vertical transmission.[7,15-17] Infant PrEP is achieved by administering ARV drugs during pregnancy that cross the placenta and produce adequate drug levels that prevent HIV acquisition by inhibiting viral replication in the fetus. This is particularly important during the birth process, when there can be extensive viral exposure during passage through the birth canal. All *Preferred* nucleoside reverse transcriptase inhibitors—as well as integrase strand transfer inhibitors, such as dolutegravir and raltegravir—are known to have high transplacental passage (see Table 14. Antiretroviral Drug Use in Pregnant People with HIV: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy).[18-22]

ARV drugs administered to the infant after birth provide post-exposure prophylaxis by providing protection from cell-free or cell-associated virus that may have entered the fetal/infant systemic circulation during labor and delivery (see Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection).[23] The importance of the pre- and post-exposure components of prophylaxis in reducing the risk of perinatal HIV transmission is demonstrated by the lower efficacy of interventions that involve administration of ARV drugs only during labor and/or as a single dose to the newborn compared to regimens that include postnatal infant antiretroviral medications.[24-31]

In conclusion, the most effective way to prevent perinatal transmission of HIV is (1) to begin ART as early as possible in pregnancy (ideally before conception) to achieve antepartum plasma viral load suppression as quickly as possible and to provide infant PrEP, (2) to maintain viral suppression throughout pregnancy, and (3) to provide infant ARV post-exposure prophylaxis or presumptive HIV therapy appropriate to their risk of HIV acquisition to reduce the risk of peri-partum transmission. Information about the historical context of perinatal HIV prevention is available in the Archived Guidelines (see Appendix A: Review of Clinical Trials of Antiretroviral Interventions to Prevent Perinatal HIV Transmission in the guidelines archived on January 31, 2024).

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Antiretroviral Therapy for People with HIV Who Are Trying to Conceive

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Panel's Recommendations
• Reproductive intentions should be reviewed at each health care encounter. The time before a planned attempt to conceive is an important opportunity to review current and alternative antiretroviral (ARV) regimens and underscore the goal of reaching viral suppression (i.e., undetectable HIV RNA) before and throughout pregnancy, along with many other aspects of preconception planning (see Prepregnancy Counseling and Care for Persons of Childbearing Age with HIV) (AIII). • Use of contraception, regardless of type, should never be a requirement to initiate or continue ARV regimens, even if there are limited data on these ARV regimens in pregnancy (e.g., long-acting injectable cabotegravir and rilpivirine) (AIII). Clinicians should engage in shared decision-making, counsel patients on the potential benefits and risks, and be aware of the potential for reproductive coercion (AIII). • Whenever possible, regimen initiation or changes should be made with sufficient time to achieve viral suppression before attempting to conceive or becoming pregnant (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*

Antiretroviral therapy (ART) should be initiated and viral suppression (i.e., undetectable HIV RNA) should be achieved prior to pregnancy whenever possible. People should be given information about the benefits and risks of initiating specific antiretroviral (ARV) regimens when trying to conceive so they can make informed decisions about their care (see Appendix C: Antiretroviral Counseling Guide for Health Care Providers). Prevention of perinatal HIV transmission is maximized in individuals who are on fully suppressive ART prior to conception and remain suppressed during pregnancy and through delivery.[1] For more information, see Prepregnancy Counseling and Care for Persons of Childbearing Age with HIV.

In general, the Panel on Treatment of HIV During Pregnancy and Prevention of Perinatal Transmission recommendations for *Preferred* and *Alternative* ARV medications are the same for both pregnant people and people who are trying to conceive and are initiating treatment (see Table 7. Situation-Specific Recommendations for the Use of Antiretroviral Drugs in Pregnant People and Nonpregnant People Who Are Trying to Conceive). However, the time before a planned attempt at conception is an important opportunity to review current ARV regimens and other ARV options, if indicated. This is especially important for regimens that lack pharmacokinetic or safety data and those with possible risk of viral rebound later in pregnancy when medication changes may be more difficult. For people on long-acting injectable ARVs who are considering switching regimens prior to conceiving to prevent fetal exposure, it is important to recognize that these injections must be stopped at least 1 year before conceiving to ensure that the long-acting drugs are fully eliminated. Additionally, among those on long-acting injectable ART who have a history of poor adherence to oral medications, switching from long-acting injectable cabotegravir (CAB) and rilpivirine (RPV) to

oral ART to prepare for conception may be associated with increased risk of viral rebound and non-nucleoside reverse transcriptase inhibitor resistance.[2]

Importantly, many people who are not trying to conceive, but who are of childbearing potential, may choose ARV regimens that are not designated as *Preferred* for people trying to conceive. Use of contraception, regardless of type, should never be a requirement to initiate or continue ARVs, even if there are limited data on these ARVs in pregnancy (e.g., long-acting injectable CAB and RPV). Clinicians should engage in shared decision-making, counsel patients on the potential risks and benefits, and be aware of the potential for reproductive coercion.[3]

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

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Panel's Recommendations
• For pregnant people who have never received antiretroviral therapy (ART), ART should be initiated as soon as possible, even before results of drug-resistance testing are available, as viral suppression earlier in pregnancy has been associated with lower risk of transmission (AI). When ART is initiated before the results of the drug-resistance assays are available, the antiretroviral (ARV) regimen should be modified, if necessary, based on the resistance assay results (AII). • ARV regimens that are *Preferred* for the treatment of pregnant people with HIV who have never received ARV drugs consist of the integrase strand transfer inhibitor (INSTI) dolutegravir (DTG) plus a dual-nucleoside reverse transcriptase inhibitor combination (see Table 6. What to Start: Initial Antiretroviral Regimens During Pregnancy for People Who Are Antiretroviral-Naive; Early (Acute or Recent) HIV) (AIII). *Preferred* regimens include: o DTG plus (tenofovir disoproxil fumarate [TDF] or tenofovir alafenamide [TAF]) plus (emtricitabine [FTC] or lamivudine [3TC]) *or* o DTG plus abacavir (ABC) plus 3TC – only for individuals who are HLA-B*5701 negative and without chronic hepatitis B virus (HBV) coinfection • ARV regimens that are *Preferred* for pregnant people with HIV with any prior use of long-acting injectable cabotegravir (CAB-LA) as pre-exposure prophylaxis (PrEP) consist of the ritonavir-boosted protease inhibitor darunavir/ritonavir (DRV/r), rather than an INSTI (i.e., DTG), plus a dual-nucleoside reverse transcriptase inhibitor combination (see Pregnant People with HIV Who Have Previously Received Antiretroviral Medications but Are Not Currently on Antiretroviral Medications) (AIII). *Preferred* regimens include: o DRV/r plus (TDF or TAF) plus (FTC or 3TC) *or* o DRV/r plus ABC plus 3TC – only for individuals who are HLA-B*5701 negative and without chronic HBV coinfection • *Alternative* ARVs for the treatment of pregnant people with HIV who have never received ARV drugs are shown in Table 6. What to Start: Initial Antiretroviral Regimens During Pregnancy for People Who Are Antiretroviral-Naive. • Choice of ART regimen should be based on results of resistance testing, concurrent medical conditions, and current recommendations for ART in pregnancy (AII). For additional information, see Recommendations for Use of Antiretroviral Drugs During Pregnancy: Overview.
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 (ARV) regimens designated by the Panel on Treatment of HIV During Pregnancy and Prevention of Perinatal Transmission (the Panel) as *Preferred* regimens for pregnant people who have never received antiretroviral drugs (ARV naive) consist of the integrase strand transfer inhibitor (INSTI) dolutegravir (DTG) plus a dual–nucleoside reverse transcriptase inhibitor (NRTI) combination. *Preferred* regimens for the treatment of pregnant people who have never received ARV drugs include:

- DTG plus (tenofovir disoproxil fumarate [TDF] or tenofovir alafenamide [TAF]) plus (emtricitabine [FTC] or lamivudine [3TC])

- DTG plus abacavir (ABC) plus 3TC – only for individuals who are HLA-B*5701 negative and without chronic hepatitis B virus (HBV) coinfection

The NRTI components are *Preferred* because they are recommended for nonpregnant adults and have several advantages, including reassuring pharmacokinetic (PK) data, extensive experience with use in pregnancy, once-daily dosing, and less toxicity than zidovudine plus 3TC.[1-3] Use of ABC requires testing for the HLA-B*5701 gene variant before initiating therapy. For this reason, providers may choose to use TDF or TAF rather than ABC to avoid delays in antiretroviral therapy (ART) initiation while awaiting HLA-B*5701 test results. In addition, ABC is not active against HBV; therefore, TDF and TAF with either 3TC or FTC—drugs that are active against hepatitis B virus—should be used for individuals with chronic HBV coinfection.

DTG is the *Preferred* INSTI for use in pregnancy because it has been studied extensively in pregnancy, is associated with high rates of viral suppression, fast rates of viral load decline, high tolerability, and a high genetic barrier to drug resistance.[4-6] For example, two randomized clinical trials that compared DTG plus two NRTIs to efavirenz (EFV) plus two NRTIs in ART-naive women who initiated therapy during pregnancy found that DTG-based ART produced more rapid viral suppression than EFV-based ART, with a greater proportion of women reaching an undetectable viral load (<50 copies/mL) at the time of delivery.[7,8] Higher rates of viral suppression did not translate into statistically significantly lower rates of observed vertical transmission with DTG compared with EFV; transmission rates were low with both regimens, and the studies were not powered to detect small differences.[8-10] Safety and efficacy data extending to 50 and 72 weeks postpartum supported use of DTG-based ART in pregnancy.[10,11] DTG is *Preferred* for use in pregnant people with early (acute or recent) HIV infection without prior use of long-acting injectable cabotegravir (CAB-LA) as pre-exposure prophylaxis (PrEP) (see Early [Acute or Recent] HIV).

Ritonavir-boosted darunavir (DRV/r) is *Preferred* over an INSTI-based regimen for pregnant people with any prior CAB-LA use, pending results of genotypic resistance testing for INSTI mutations (see Early [Acute or Recent] HIV and Pregnant People with HIV Who Have Previously Received Antiretroviral Medications but Are Not Currently on Antiretroviral Medications). For pregnant people without prior CAB-LA use, DRV/r is now classified as an *Alternative* ARV drug for use in pregnancy. Its efficacy in pregnancy is well documented; in a recent large observational study, viral suppression with DRV/r was not statistically significantly different than viral suppression with DTG.[12] Importantly, however, although the use of once-daily dosing for DRV/r is approved for nonpregnant adults, PK data do not support once-daily dosing in pregnancy[13]; therefore, twice-daily dosing is recommended (see Darunavir).

The INSTI bictegravir (BIC) is now classified as an *Alternative* ARV drug for use in pregnancy because data about safety, PK, and efficacy in pregnancy are available but are more limited than data about drugs classified as *Preferred*. Detailed advantages and disadvantages of each of these *Preferred* medications in pregnancy, as well as of those in the *Alternative*, *Insufficient Data*, *Not Recommended*, and *Not Recommended Except in Special Circumstances* categories, are shown in Table 6. What to Start: Initial Antiretroviral Regimens During Pregnancy for People Who Are Antiretroviral-Naive.

Recommendations for Regimens Other Than Combination (Three-Drug) ART

Although the Adult and Adolescent Antiretroviral Guidelines recommend some two-drug ARV regimens for nonpregnant ARV-naive people in certain clinical circumstances, two-drug ARV

regimens **are not recommended** for initiation of ART in ARV-naive pregnant people because of a lack of data in pregnancy.

ARV-Naive People Who Present in the Third Trimester

INSTIs have an important role when ART is initiated late in pregnancy, particularly for people who have high viral loads, because of the documented ability of DTG and raltegravir (RAL) to suppress viral load rapidly (a decrease of approximately 2 $\log_{10}$ copies/mL occurs by Week 2 of therapy with these drugs).[14-18]

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 minimum of 28 weeks gestational age (median: 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, with a faster time to reach viral loads <50 copies/ml (4.1 vs. 12.1 weeks).[7] 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% confidence interval, 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.[19]

RAL and DTG are likely to be similarly effective in reducing viral load rapidly for people who present in the third trimester. However, DTG is *Preferred* and RAL is *Alternative* when initiating ART in people who have never received ARV drugs, because RAL requires twice-daily dosing and has a lower barrier to development of drug resistance than DTG (see Adult and Adolescent Antiretroviral Guidelines). BIC is now an *Alternative* INSTI-based regimen when initiating ART during pregnancy, but data are not available for its use when initiating ART during the third trimester. Other INSTIs (i.e., elvitegravir [EVG] and cabotegravir [CAB]) are not recommended when initiating ART in pregnancy due to either concern for insufficient levels (EVG) or lack of data during pregnancy as initial treatment for ARV-naive adults or adolescents (CAB). For more information, see Table 6. What to Start: Initial Antiretroviral Regimens During Pregnancy for People Who Are Antiretroviral-Naive.

People who present after early (acute or recent) HIV infection at any time in pregnancy are discussed in Early (Acute or Recent) HIV.

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People with HIV Who Are Taking Antiretroviral Therapy When They Become Pregnant

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Panel's Recommendations
• In most cases, people 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 on Treatment of HIV During Pregnancy and Prevention of Perinatal Transmission recommends patient counseling to support informed decision-making (AIII). See Appendix C: Antiretroviral Counseling Guide for Health Care Providers. • Clinicians need to consider whether pharmacokinetic changes in pregnancy, especially in the second and third trimester, may lead to a lower plasma level of some antiretroviral (ARV) drugs and necessitate increased doses, more frequent dosing, boosting, more frequent viral load monitoring, or a change in the ARV regimen (AII). See Appendix B: Supplement: Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy. • Although there are no data on the use of two-drug oral regimens during pregnancy (e.g., dolutegravir [DTG] plus lamivudine [3TC], DTG plus rilpivirine [RPV]), the component drugs are recommended as *Preferred* or *Alternative* for use in pregnancy. Pregnant persons who present to care on DTG/3TC or DTG/RPV and have successfully maintained viral suppression can continue the two-drug regimen (BIII) with more frequent viral load monitoring every 1 to 2 months throughout pregnancy (CIII). • Data about the use of long-acting injectable cabotegravir and RPV during pregnancy are extremely limited and insufficient to make a recommendation for or against use in pregnancy. Pregnant people who present to care on this regimen should be counseled about limited data. Clinicians and pregnant people should reach a shared decision about continuing this regimen with frequent viral load monitoring (every 1–2 months) or switching to one of the *Preferred* or *Alternative* three-drug ARV regimens in conjunction with an HIV expert (CIII). • The use of cobicistat (COBI)-containing 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. When pregnant people present to care on one of these regimens, clinicians and pregnant people should reach a shared decision about whether to continue the regimen with frequent viral load monitoring or to switch to a different regimen that is recommended for use during pregnancy (BIII) (see Table 6. What to Start: Initial Antiretroviral Regimens During Pregnancy for People Who Are Antiretroviral-Naive and Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs). If a COBI-containing regimen is continued, absorption should be optimized by taking the drugs with food and following instructions for administration (e.g., spacing administration of vitamins containing iron and calcium) (AII). Viral load should be monitored more frequently (i.e., every 1–2 months) (CIII). • People 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 ARV drugs that are recommended for use during pregnancy (AIII). See Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs for more information. • People who present in pregnancy on a regimen that is not fully suppressive should be evaluated carefully for adherence barriers, drug–drug and drug–food interactions, and HIV drug resistance to determine whether a change in ART regimen is indicated. See Pregnant People Who Have Not Achieved Viral Suppression for additional guidance. • For pregnant people on ART, ARV drug-resistance testing should be performed prior to changing an ARV regimen for people with HIV RNA levels >200 copies/mL (AI for >1,000 copies/mL, AIII for 501–1,000 copies/mL, CIII for 201–500 copies/mL). For people with confirmed HIV RNA levels >200 copies/mL but <500 copies/mL, drug-resistance testing may be unsuccessful but should still be considered. See Antiretroviral Drug Resistance and Resistance Testing in Pregnancy.

- If an ARV regimen is altered during pregnancy, drugs in the new regimen should include ARV drugs that are recommended for use in pregnancy (BIII) (see Table 6. What to Start: Initial Antiretroviral Regimens During Pregnancy for People Who Are Antiretroviral-Naive and Table 7. Situation-Specific Recommendations for Use of ARVs), and more frequent virologic monitoring is warranted until viral suppression is stably observed (CIII).

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

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

People on Fully Suppressive Antiretroviral Therapy

In general, **people who are already on a fully suppressive antiretroviral regimen when pregnancy occurs should continue their antiretroviral therapy (ART) regimens.** The Panel on Treatment of HIV During Pregnancy and Prevention of Perinatal Transmission (the Panel) recommends that effective ART regimens should not be changed just because the regimen includes antiretroviral (ARV) drugs that are not *Preferred* or *Alternative* for use in pregnancy. 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] In a study from the French Perinatal cohort among 1,797 women with HIV RNA levels <50 copies/mL before 14 weeks gestation, change in ARV regimen in 411 women due to safety concerns based on existing guidelines at the time of pregnancy did not result in loss of virologic control.[2] However, among 662 pregnancies that were followed in Italy between 2001 and 2008, treatment modification during pregnancy was independently associated with HIV RNA level >400 copies/mL in late pregnancy (adjusted odds ratio [aOR] 1.66; 95% CI, 1.07–2.57; $P = 0.024$).[1] This highlights the importance of establishing potent and well-tolerated regimens prior to pregnancy, using Preferred and Alternative ARVs for use in pregnancy whenever possible, to maximize effectiveness and minimize the need for modifying treatment in pregnancy.

Regimens that involve medications that are not recommended for use in adults because of high risk for toxicity (e.g., stavudine, indinavir, didanosine, and treatment-dose ritonavir) or inferior virologic efficacy (nelfinavir) should not be continued when pregnancy occurs; fortunately, these drugs are rarely used now. In this case, these drugs should be stopped and people switched to other ARV drugs that are recommended for use in pregnancy (see Table 6. What to Start: Initial Antiretroviral Regimens During Pregnancy for People Who Are Antiretroviral-Naive and Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs in Pregnant People and Nonpregnant People Who Are Trying to Conceive).

Physiologic changes that occur during pregnancy may result in lower levels of certain ARVs, resulting in loss of virologic control with the potential for perinatal transmission. For patients who have achieved viral suppression and become pregnant while receiving regimens with a potential increased risk of virologic failure during pregnancy due to pharmacokinetic (PK) concerns (e.g., cobicistat [COBI]-boosted regimens, oral rilpivirine) or regimens with insufficient data about dosing and/or safety in pregnancy (e.g., doravirine [DOR], oral two-drug regimens, and long-acting injectable cabotegravir/rilpivirine), clinicians need to consider whether to continue the regimen or switch to a different regimen that is recommended for use during pregnancy[3-5] (see Table 6. What to Start: Initial Antiretroviral Regimens During Pregnancy for People Who Are Antiretroviral-Naive

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

For regimens with PK concerns or those with insufficient data about dosing in pregnancy, pregnant people and clinicians may elect to continue the suppressive regimen with frequent viral load monitoring (every 1–2 months, understanding that switching may be needed later in pregnancy and that potential viral rebound may increase vertical transmission risk and lead to cesarean delivery), or they may elect to switch to a recommended oral regimen as soon as pregnancy is recognized. In these cases, the Panel emphasizes the importance of patient counseling and informed decision-making, including consideration of individual factors (such as ARV resistance or intolerance, or difficulty with adherence to other regimens) that may increase the risk of virologic failure with a switch to a new regimen. When choosing to switch any ART regimen in pregnancy in people who are already virologically suppressed, clinicians should closely monitor tolerability of the new regimen, evaluate for adverse effects, and consider more frequent viral load monitoring (i.e., every 1–2 months). For additional information, see Appendix C: Antiretroviral Counseling Guide for Health Care Providers.

Bictegravir

PK data on bictegravir (BIC) in human pregnancy are now available from two clinical studies and a case series.[6,7] Drug levels are lower in the second and third trimesters than in nonpregnant or postpartum individuals and are reduced in later pregnancy to a greater degree for BIC than dolutegravir (DTG). However, viral suppression was generally maintained. BIC levels remained above the 95% maximal effective concentration and thus are anticipated to suppress viral load (see Bictegravir for additional information). As a result, BIC is now recommended as an *Alternative* ARV for use in pregnancy (see Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs in Pregnant People and Nonpregnant People Who Are Trying to Conceive).

Cobicistat-Boosted Regimens

Clinicians and pregnant people should be aware that the use of atazanavir/COBI, darunavir/COBI, or elvitegravir/cobicistat (EVG/c) is associated with lower plasma drug exposures (both of COBI and of the drug being boosted) 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 person presents to care on one of these regimens, providers should consider continuing the regimen with more frequent viral load monitoring (i.e., every 1–2 months) or switching to a different regimen that is recommended for use during pregnancy (see Table 6. What to Start: Initial Combination Regimens for Antiretroviral-Naive Pregnant People and Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs in Pregnant People and Nonpregnant People Who Are Trying to Conceive).[3-5] A 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.[8] If one of these regimens is continued, absorption should be optimized by taking the drugs with food. Pregnant people who are taking regimens that include EVG/c should take ARV drugs and prenatal vitamins ≥2 hours apart.

Doravirine

PK data on DOR in human pregnancy are available only from PK modeling data based on *ex vivo* studies of placental transfer.[9,10] Patients who become pregnant with viral suppression while receiving regimens with DOR should be counseled about limited available data, see Doravirine. Clinicians and patients should reach a shared decision about continuing DOR with frequent viral load monitoring (i.e., every 1–2 months) or switching to one of the *Preferred* or *Alternative* regimens.

Oral Two-Drug Regimens

Currently, no data exist on the use of oral two-drug regimens in pregnancy (e.g., DTG plus lamivudine [3TC] and DTG plus rilpivirine [RPV]). However, for both DTG/3TC and DTG/RPV, there are data in nonpregnant persons showing noninferiority when compared to a standard three-drug regimen.[11,12] The component drugs in each of the oral two-drug regimens (DTG, 3TC, RPV) have well described PK that are adequate in pregnancy, and the individual drug components are recommended as *Preferred* or *Alternative* ARV drugs by the Panel. Note that although PK data indicate that RPV plasma concentration is reduced during the second and third trimesters of pregnancy, the reduction is less than the reductions seen with the COBI-containing regimens described above, and most pregnant people will have adequate exposure. A recent observational study of 188 pregnant people on oral RPV as part of a three-drug regimen at delivery found that 182 (96.8%) had viral load <200 copies/mL.[13] Standard RPV dosing is recommended when used as part of a three-drug regimen, and viral load should be monitored frequently (e.g., every 1–2 months; see Rilpivirine, Table 6. What to Start: Initial Antiretroviral Regimens During Pregnancy for People Who Are Antiretroviral-Naive, and Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs in Pregnant People and Nonpregnant People Who Are Trying to Conceive.

Long-Acting Injectable Cabotegravir and Rilpivirine

Data on long-acting injectable cabotegravir (CAB) and RPV are currently limited to a small number of patients without HIV who became pregnant while enrolled in trials of long-acting injectable CAB for pre-exposure prophylaxis and stopped the medication once pregnancy was recognized, usually in the first trimester.[14-16] In these patients, the pharmacologic washout was similar in pregnant and nonpregnant adults.[14,17] No data are available about the pharmacokinetics of CAB in the second and third trimesters, with either oral or injectable formulations. While data in nonpregnant adults suggest slower washout (and thus potentially higher CAB levels) with intramuscular CAB among people with obesity,[18] this may not be applicable to the weight gain that is due to pregnancy, as the volume of distribution in pregnancy differs from that in obesity. No data exist on the PK of injectable RPV in pregnancy. Prior data have shown concern for lower concentrations of oral RPV in the third trimester,[19] as above. Some patients who have achieved virologic suppression on injectable CAB and RPV experienced previous challenges with oral ART, such that switching back to oral ART could increase the risk of virologic rebound. Clinicians and pregnant people should reach a shared decision about continuing this regimen with frequent viral load monitoring (every 1–2 months) or switching to one of the *Preferred* or *Alternative* three-drug ARV regimens in conjunction with an HIV expert.

When switching from long-acting injectable CAB and RPV to an oral regimen in pregnancy, the timing of the switch must take into account the long half-life of the long-acting injectable formulation (median 5.6–11.5 weeks) with persistence of the drug for up to 12 months.[20] When the dosing schedule is monthly, the change to an oral regimen should occur within 1 month of the last CAB and RPV injections.[21] When the dosing schedule is every 2 months, the change to an oral

regimen should occur within 2 months of the last CAB and RPV injections.[22,23] Dosing recommendations, including guidance for switching to an oral regimen, can be found in the prescribing information.[20,23] For additional information, see Optimizing Antiretroviral Therapy in the Setting of Viral Suppression and Discontinuation or Interruption of Antiretroviral Therapy in the Adult and Adolescent Antiretroviral Guidelines.

People Not on Fully Suppressive ART When Becoming Pregnant

People who are not fully suppressed and who are currently taking ART should be evaluated carefully for adherence barriers, drug–drug interactions, drug–food requirements, and HIV drug resistance, with every effort made to achieve rapid and full viral suppression through adherence interventions or medication changes (see Pregnant People Who Have Not Achieved Viral Suppression on Antiretroviral Therapy).

For pregnant people on ART, ARV drug-resistance testing should be performed prior to changing an ARV regimen if HIV RNA levels are >200 copies/mL. For people with HIV RNA levels >200 copies/mL but <500 copies/mL, drug-resistance testing may be unsuccessful but should still be considered (see Antiretroviral Drug Resistance and Resistance Testing in Pregnancy).

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Pregnant People with HIV Who Have Previously Received Antiretroviral Medications but Are Not Currently on Antiretroviral Medications

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Reviewed: January 31, 2024

Panel's Recommendations
• In choosing an antiretroviral therapy (ART) regimen for pregnant people who have previously received antiretroviral (ARV) drugs, clinicians should obtain an accurate history of all prior ARV medications used for HIV treatment or prevention of HIV transmission, including virologic efficacy, tolerance of the medications, results of prior resistance testing, and barriers to adherence (AIII). • ART should be restarted before receiving the results of ARV drug-resistance testing, because longer durations of ART during pregnancy have been associated with reduced perinatal transmission rates. ART should be modified, if necessary, based on the results of resistance assays (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*

Pregnant people with HIV who are currently not receiving antiretroviral therapy (ART) may have received antiretroviral (ARV) medications in the past either as treatment for themselves (i.e., ART) or to prevent HIV transmission to their infant (i.e., perinatal prevention), as post-exposure prophylaxis, as pre-exposure prophylaxis (PrEP) for prevention of HIV transmission to themselves prior to having HIV infection, or for prevention of HIV transmission to their sexual partner.[1,2] Data show 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.[3-7] Standard genotyping has shown that 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,[8-10] but not in those who previously received protease inhibitor (PI)–based therapies.[8] To date, there are no data on the risk of developing resistance among people who stop using long-acting ART (e.g., long-acting cabotegravir [CAB-LA] and long-acting rilpivirine) without starting alternative ART. In contrast to time-limited exposure to ART for people with HIV, recent studies suggest that individuals receiving CAB-LA for PrEP and who acquire HIV may be at risk for selection of integrase inhibitor mutations.[11] For this reason, the Panel on Treatment of HIV in Pregnancy and Prevention of Perinatal Transmission recommends the use of the PI darunavir boosted with ritonavir, rather than the integrase strand transfer inhibitor (INSTI) dolutegravir, as the *Preferred* ARV for people with prior CAB-LA exposure who are pending genotype test results. See Early (Acute and Recent) HIV Infection in the Adult and Adolescent Antiretroviral Guidelines, Table 6. What to Start: Initial Antiretroviral Regimens During Pregnancy for People Who Are Antiretroviral Naive, and Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs in Pregnant People and Nonpregnant People Who Are Trying to Conceive for more information.

Individuals may choose to discontinue ART for a variety of reasons, and the length of time off treatment before pregnancy may vary. A person's HIV treatment history and all prior drug resistance test results should be considered when choosing ART for pregnant people who previously have

received ARV medications, 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. 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. Therefore, when selecting a new ART regimen, all information—including prior regimens received, virologic response, laboratory testing (including HLA-B*5701 results), tolerance or adherence problems, food requirements, concomitant medications, prior medical conditions, and results of all prior resistance testing—should be considered.

Resistance testing should be performed before initiating a new ART regimen in people who have previously received ARVs (see Antiretroviral Drug Resistance and Resistance Testing in Pregnancy). 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.[12,13] ART should be modified, when necessary, based on subsequent resistance assay results. Careful monitoring of virologic response is essential. For specific guidance on timing and frequency, see Initial Evaluation and Continued Monitoring of HIV-Related Assessments During Pregnancy.

A person may restart a previous ART regimen that successfully suppressed their viral load if the regimen was tolerated well and no evidence of resistance to that regimen is identified. Ideally, the regimen should also be recommended currently as a *Preferred* or *Alternative* regimen for initial ART in pregnancy (see Table 6. What to Start: Initial Antiretroviral Regimens During Pregnancy for People Who Are Antiretroviral Naive and Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs in Pregnant People and Nonpregnant People Who Are Trying to Conceive). Drugs that are not recommended for initial use because of concerns about viral breakthrough during pregnancy should be avoided if *Preferred* or *Alternative* regimens exist; if not, they should be discussed with the patient using a shared decision-making approach. Even experienced health care providers may have difficulty with the selection of appropriate ART for people 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 individuals. Consultation is also available through the National HIV Perinatal Hotline (1-888-448-8765).

If ART produces an insufficient viral response (e.g., a 1 $\log_{10}$ drop or less within 4 weeks), clinicians should repeat resistance testing, including testing for resistance to INSTIs, if indicated (see Antiretroviral Drug Resistance and Resistance Testing in Pregnancy). Clinicians should also 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 Pregnant People Who Have Not Achieved Viral Suppression on Antiretroviral Therapy).

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Pregnant People Who Have Not Achieved Viral Suppression on Antiretroviral Therapy

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Panel's Recommendations
• Regular viral load monitoring is needed in pregnancy to quickly detect lack of viral suppression (AII). See Initial Evaluation and Continued Monitoring of HIV-Related Assessments During Pregnancy. • To detect problems with viral suppression early, more frequent viral load monitoring (every 1–2 months) is recommended when individuals are receiving regimens associated with lower drug levels in the third trimester or drugs with limited or no pharmacokinetic (PK) data about use in pregnancy (AII). See Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs in Pregnant People and Nonpregnant People Who Are Trying to Conceive. • When lack of suppression is identified, a thoughtful evaluation of potential contributing factors is needed, including barriers to adherence, drug resistance, drug–drug and drug–food interactions, PK changes in pregnancy that affect drug levels, and combinations of these factors. Viral suppression management should address each of these factors, if relevant (AII) (see Virologic Failure in the Adult and Adolescent Antiretroviral Guidelines). After these factors are addressed, repeat viral load monitoring within 2 to 4 weeks (AII). • In general, adding a single antiretroviral drug to a virologically failing regimen is not recommended because this would rarely result in full virologic suppression and, therefore, may cause the development of resistance to one or more drugs in the regimen (BII). • Consider consulting with an HIV treatment specialist when modifying ART due to inadequate viral suppression (BIII). Consultation is also available through the National Perinatal HIV hotline (1-888-448-8765). • Discontinuing or briefly interrupting ART may lead to a rapid increase in HIV RNA, a decrease in CD4 T lymphocyte cell count, and an increase in the risk of perinatal HIV transmission and clinical progression. Therefore, this strategy is not recommended (AI). Please see Intrapartum Care for People with HIV for guidance about use of intrapartum intravenous zidovudine prophylaxis and scheduled cesarean delivery for pregnant people who have not achieved viral suppression on ART.
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 to undetectable levels is defined as a confirmed plasma HIV RNA level that is below the lower limits of detection of an ultrasensitive assay. Suppression of HIV RNA to undetectable levels should be achieved as rapidly as possible in pregnancy because viral load affects the risk of perinatal transmission, with the lowest risk associated with viral load <50 copies/mL.[1,2] 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.[3-5]

HIV RNA levels should be assessed regularly in pregnancy (see Initial Evaluation and Continued Monitoring of HIV-Related Assessments During Pregnancy for guidance on timing and frequency). Physiologic changes that occur during pregnancy may result in lower levels of certain antiretrovirals (ARVs), resulting in loss of virologic control with the potential for perinatal transmission. To detect problems with viral suppression early, more frequent viral load monitoring (every 1–2 months) is recommended when individuals are receiving regimens associated with lower

drug levels in the third trimester or drugs with limited or no pharmacokinetic (PK) data about use in pregnancy (see Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs in Pregnant People and Nonpregnant People Who Are Trying to Conceive).

In the Adult and Adolescent Antiretroviral Guidelines for nonpregnant individuals, virologic failure is defined as the inability to achieve or maintain an HIV RNA level of <200 copies/mL (see Virologic Failure).[6] Incomplete virologic response is defined as two consecutive HIV RNA level test results ≥200 copies/mL after 24 weeks on an ARV regimen in a patient who has not yet had documented virologic suppression on that regimen. Virologic rebound is defined as a confirmed HIV RNA level of ≥200 copies/mL after virologic suppression. During pregnancy or breastfeeding, any detectable viral load or, in some cases, a viral load >50 copies/mL is considered lack of viral suppression; these observations would indicate viral rebound if they occurred after viral suppression was achieved. If an HIV RNA level below the lower limit of detection of an ultrasensitive assay has not been achieved or viral rebound has occurred, causes of detectable viremia should be evaluated and addressed before considering a change in an ARV regimen.

For patients initiating or changing antiretroviral therapy (ART), HIV RNA is expected to decline fairly quickly, ideally achieving at least a 10-fold (1 $\log_{10}$) drop within 4 weeks. With the use of integrase strand transfer inhibitors (INSTIs) as part of an ARV regimen, the decline may be even faster (e.g., a decrease of approximately 100-fold [2 $\log_{10}$] in HIV RNA levels can be expected by week 2 of therapy).[6,7] 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.[8]

Situations in which virologic suppression is not achieved (i.e., viral load is detectable) remain a common problem for pregnant people in the United States and globally. For example, a report from the HIV Outpatient Study noted that among 119 pregnancies between 2005 and 2015, 33 women (27.7%) were not virally suppressed (HIV RNA >500 copies/mL) at the end of pregnancy.[9]

Evaluating Factors Contributing to Detectable Viremia

Lack of virologic suppression is frequently associated with inadequate adherence. Other potential causes of detectable viremia include drug–drug interactions and lack of attention to food requirements with some ARV agents (e.g., rilpivirine [RPV], darunavir) that affect adequate drug absorption; concomitant administration or inadequate spacing of vitamins or foods containing calcium or iron (e.g., dolutegravir, bictegravir, raltegravir, elvitegravir; see Appendix B: Supplement: Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy); and overall poor tolerability of the ARV drug, exacerbated by nausea and vomiting associated with pregnancy or hyperemesis gravidarum.

Barriers to adherence should be addressed when the viral load does not decline as expected (see Adherence to the Continuum of Care in the Adult and Adolescent Antiretroviral Guidelines). 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% of pregnant women achieved adequate (>80%) ART adherence.[10] Factors that can contribute to suboptimal adherence in pregnancy include depression and other mental health disorders, barriers to HIV seropositive status disclosure, adverse drug reactions, a history of intimate partner violence,

substance use, a lack of prior experience with taking ART, and a lack of knowledge about the role of ART in preventing perinatal transmission.[11-13] Other factors that have been associated with lack of viral suppression in pregnancy, and are likely associated with difficulties with adherence, include unintended pregnancy and social and economic vulnerabilities (e.g., living in the United States for less than 5 years with no family/friends' support, neighborhood exposures to crime), as well as poor engagement in prenatal care.[14-16]

A retrospective study of 318 pregnant women addressed the risk of a viral rebound to HIV RNA >50 copies/mL in pregnancy among women who received ART for ≥4 weeks and who had had one or more prior undetectable viral load test result. Nineteen women (6%) had a viral rebound (HIV RNA >50 copies/mL) within 1 month before delivery; 6 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.[17] Viral load testing is currently recommended at 34 to 36 weeks gestation for delivery planning; providers may consider repeat testing subsequently in selected patients who are at increased risk for viral rebound. Risk for viral rebound may be greater in people receiving regimens with PK concerns for lower drug levels in late pregnancy (e.g., cobicistat-boosted regimens and RPV) (see Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs and People Taking Antiretrovirals When They Become Pregnant).

The lack of virologic suppression by late pregnancy may indicate virologic failure, but it may also represent inadequate time on ART for people who initiated ART in pregnancy. Among 1,070 ART-naive pregnant women with HIV who participated in the prospective cohort study International Maternal, Pediatric, Adolescent AIDS Clinical Trials (IMPAACT) P1025, initiating three-drug ART at >32 weeks gestation (with a protease inhibitor– or non-nucleoside inhibitor–based regimen or a nucleoside transcriptase inhibitor–only regimen) also was associated with a significantly higher risk of having a viral load >400 copies/mL at delivery.[18] A recent cross-sectional analysis of 10,052 pregnant women with HIV receiving antenatal care in public facilities in South Africa reported that failure to achieve viral suppression (HIV RNA <50 copies/mL) was associated primarily with late registration for antenatal care and late initiation of ART.[19] In the French Perinatal Cohort of 14,630 women with HIV and delivering from 2000 to 2017, both HIV RNA level at delivery and timing of ART initiation were independently associated with risk of perinatal transmission of HIV.[1]

Pregnant people with acute HIV generally have high viral loads and may take longer than nonpregnant people to achieve viral suppression (see Early [Acute and Recent] HIV Infection).

Pregnant people with perinatally acquired HIV may also face additional barriers to adherence and virologic suppression. Several studies from the United States and Europe have demonstrated that among pregnant people, perinatally acquired HIV is a risk factor for detectable viral load near the time of delivery and a higher perinatal transmission rate than non–perinatally acquired HIV.[20,21] If needed, ARV 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 People with Perinatally Acquired HIV Infection).

Managing Lack of Viral Suppression

A three-pronged approach is indicated for evaluating and managing pregnant people on ART who have lack of suppression of HIV RNA, taking time on treatment into account. The approaches include the following—

- Assessing adherence, tolerability, correct dosing, or potential problems with absorption (e.g., nausea/vomiting, use of gastroesophageal reflux disease medications, coadministration of prenatal vitamins and iron with INSTIs,[22,23] lack of attention to food requirements); Ordering ARV drug–resistance tests should be considered before changing regimens if plasma HIV RNA levels >200 copies/mL while on the current regimen. For people with confirmed HIV have RNA levels >200 copies/mL but <500 copies/mL, drug-resistance testing may be unsuccessful but should still be considered; *and*
- Considering modifying the ARV regimen (see People with HIV Who Are Taking Antiretroviral Therapy When They Become Pregnant, Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs in Pregnant People and Nonpregnant People Who Are Trying to Conceive, and Virologic Failure in the Adult and Adolescent Antiretroviral Guidelines) *and*
- Repeating viral load monitoring within 2 to 4 weeks after relevant factors contributing to delectable viral load are addressed.

Evaluation of and support for adherence during pregnancy are critical to achieving and maintaining maximal viral suppression. Pre-pregnancy counseling and family planning services should be promoted and accessible to reduce unintended pregnancy, help those with HIV achieve their childbearing aspirations, and provide an important opportunity to support ART adherence. Early attention to the special need for adherence support among immigrant communities affected by HIV and other communities with adverse neighborhood exposures is also critical to achieving and maintaining maximal viral suppression. In a retrospective cohort study at a Texas community center, group prenatal care for pregnant women with HIV, as compared to individual care, showed promise in achieving viral suppression by the time of delivery (adjusted odds ratio 2.29; 95% confidence interval [CI], 0.94–5.55; $P = 0.068$).[24] 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 (see Table 14. Antiretroviral Drug Use in Pregnant People with HIV: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy), and directly observing drug administration in the home or hospital setting.[25]

When considering altering an ARV regimen because viral suppression targets have not been reached, resistance testing should be performed while the pregnant person is still taking their current regimen (see Antiretroviral Drug Resistance and Resistance Testing in Pregnancy). Resistance testing generally can be performed when HIV RNA levels are >500 copies/mL. For HIV RNA >200 to <500 copies/mL, drug-resistance testing may be unsuccessful but should still be considered. The results can be used to select a new ARV regimen with a greater likelihood of suppressing viral replication to undetectable levels. For patients with current or prior INSTI exposure, INSTI resistance testing in addition to standard genotype testing should be obtained.

The Adult and Adolescent Antiretroviral Guidelines offer specific regimen modifications for situations in which viral suppression has not been achieved or where there has been a rebound of viral load (see Virologic Failure).

In addition, when poor adherence is the reason that the patient has not achieved or maintained virologic suppression, it is unclear whether adding a new drug to the existing regimen will improve adherence. In general, adding a single ARV drug to a virologically failing regimen is not recommended because this would rarely result in full virologic suppression and, therefore, may risk the development of resistance to one or more drugs in the regimen.

Before modifying an ARV regimen, consultation with a specialist in clinical care for ARV-experienced adults is recommended (e.g., the National Perinatal HIV hotline at 1-888-448-8765). 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.

Finally**,** discontinuing or briefly interrupting therapy may lead to a rapid increase in HIV RNA, a decrease in CD4 T lymphocyte cell count, and an increase in the risk of perinatal transmission and clinical progression.[26-28] Therefore, this strategy **is not recommended** in the setting of virologic failure**.**

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Table 6. What to Start: Initial Antiretroviral Regimens During Pregnancy for People Who Are Antiretroviral-Naive

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Recommendations for initial antiretroviral therapy (ART) during pregnancy are intended for people **who have never received ART or antiretroviral (ARV) drugs for prophylaxis** (i.e., people who are ARV-naive) and show no evidence of significant resistance to regimen components (see Pregnant People with HIV Who Have Never Received Antiretroviral Drugs [Antiretroviral-Naive]). Recommendations about the use of ARVs in other scenarios are detailed in Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs in Pregnant People and Nonpregnant People Who Are Trying to Conceive.

In general, the Panel on Treatment of HIV During Pregnancy and Prevention of Perinatal Transmission (the Panel) recommends that people **who are already on fully suppressive ARV regimens when pregnancy occurs should continue with those regimens,** unless they are receiving an ARV drug or ARV regimen that is not recommended for use in nonpregnant adults or concerns exist about safety and inferior efficacy during pregnancy (see Table 7 and People with HIV Who Are Taking Antiretroviral Therapy When They Become Pregnant). Clinicians may need to consider additional factors when initiating ART in patients who previously received ART or ARV drugs for prophylaxis (see Pregnant People with HIV Who Have Previously Received Antiretroviral Medications but Are Not Currently on Antiretroviral Medications and Table 7).

Whenever possible, changes in ARV regimens should be timed so that individuals are able to achieve viral suppression before they begin trying to become pregnant (see Table 7).

Regimens are listed alphabetically within each drug class and recommendation category for initial therapy in people who are ARV-naive, so the order does not indicate a ranking of preference. In addition, except where noted below, the Panel makes no recommendation for one agent or regimen over another within each category (e.g., among *Preferred* or *Alternative* medications). The table also indicates ARV drugs or regimens that are available in fixed-dose combination tablets. Patients and providers should make shared decisions about which ARV drugs to use during pregnancy after discussing the benefits of ART and the known and potential risks to pregnant people and their fetuses (see Appendix C: Antiretroviral Counseling Guide for Health Care Providers and Recommendations for Use of Antiretroviral Drugs During Pregnancy: Overview).

Note: For more information about the use of specific drugs and dosing in pregnancy, see Table 7, the individual drug sections in Appendix B: Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy, and Table 14. Antiretroviral Drug Use in Pregnant People with HIV: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy.

Table 6. What to Start: Initial Antiretroviral Regimens During Pregnancy for People Who Are Antiretroviral-Naive

Preferred Initial Regimens in Pregnancy		
Drugs or drug combinations are designated as *Preferred* for therapy during pregnancy 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 the health of the pregnant person, fetus, and infant. 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 to read all the information on each drug in the Perinatal Guidelines before administering any of these medications to patients (see Appendix B: Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy).		
Preferred Dual-NRTI Backbones	Advantages	Disadvantages
ABC/3TC	• Once-daily dosing • Available as an FDC • Well-tolerated during pregnancy • Reassuring PK data during pregnancy	• Requires HLA-B*5701 testing before use. ABC **should not be used** in patients who test positive for HLA-B*5701 because of the risk of developing a hypersensitivity reaction. Requires education about hypersensitivity reactions. • ABC is not active against HBV; see Hepatitis B Virus/HIV Coinfection for recommended dual NRTI backbones. • ABC/3TC administered with ATV/r or EFV is not recommended if pre-treatment HIV RNA is >100,000 copies/mL. • ABC is not recommended as part of regimens for initial treatment of acute HIV infection unless the patient previously tested negative for the HLA-B*5701 gene variant; using TDF or TAF rather than ABC will avoid delays in ART initiation while awaiting HLA-B*5701 test results.
TAF/FTC *or* TAF plus 3TC	• Once-daily dosing • Available as an FDC • Reassuring PK data and extensive use during pregnancy; no dose adjustment required in pregnancy • Both NRTI combinations active against HBV • Minimal toxicity compared with ZDV/3TC • When combined with DTG, the efficacy and toxicity of TAF/FTC and TDF/FTC for treatment of pregnant patients are similar, but TAF/FTC is associated with fewer adverse birth outcomes and less risk of insufficient weight gain in pregnancy.	• When combined with DTG, TAF/FTC is associated with more treatment-emergent obesity in nonpregnant adult women compared to TDF/FTC. (Notably, the impact on weight gain in pregnancy may be beneficial, as noted in the Advantages column.)

Table 6. What to Start: Initial Antiretroviral Regimens During Pregnancy for People Who Are Antiretroviral-Naive

TDF/FTC *or* TDF/3TC	• Once-daily dosing • Available as an FDC • Reassuring PK data and extensive use during pregnancy; no dose adjustment required in pregnancy • Both NRTI combinations active against HBV • When combined with DTG, the efficacy and toxicity of TAF/FTC and TDF/FTC for treatment of pregnant patients are similar.	• Potential concerns about fetal bone and early-life growth abnormalities exist with TDF, although clinical findings are reassuring to date. • TDF has potential renal toxicity; thus, TDF-based, dual-NRTI combinations should be used with caution in patients with renal insufficiency.
Preferred INSTI Regimens	Advantages	Disadvantages
DTG/ABC/3TC (FDC) *or* DTG plus a *Preferred* Dual-NRTI Backbone	• Once-daily dosing • DTG/ABC/3TC is available as an FDC. • Sufficient data about PK, efficacy, and safety of DTG in pregnancy • High rates of viral suppression • Dose adjustments during pregnancy are not needed. • May be particularly useful when drug interactions or the potential for preterm delivery with a PI-based regimen are a concern. • DTG has been shown to rapidly decrease viral load in ARV-naive pregnant women who present to care later in pregnancy. In nonpregnant adults, DTG is associated with lower rates of INSTI resistance than RAL, and DTG allows for once-daily dosing; for these reasons, DTG is particularly useful for pregnant people presenting late in pregnancy. • DTG with a NRTI backbone of TAF or TDF with 3TC or FTC is the *Preferred* regimen for initial treatment in people with early (acute or recent) HIV infection in people without a history of CAB exposure for PrEP; see Early (Acute or Recent) HIV Infection.	• Potential concerns about excess weight gain with DTG • DTG/ABC/3TC requires HLA-B*5701 testing before use (see ABC/3TC above). • Specific timing and/or fasting recommendations apply if DTG is taken with calcium or iron (e.g., in prenatal vitamins; see Table 14). • DTG is not *Preferred* for initial treatment in people with early (acute or recent) HIV infection *and* a history of CAB exposure for PrEP due to concerns about INSTI resistance mutations; DRV/r is *Preferred* in this situation.

Table 6. What to Start: Initial Antiretroviral Regimens During Pregnancy for People Who Are Antiretroviral-Naive

Preferred PI Regimens	Advantages	Disadvantages
DRV/r plus a *Preferred* Dual-NRTI Backbone	• DRV/r is a *Preferred* PI for initial therapy only in certain circumstances (e.g., exposure to CAB-LA). See DRV/r under *Alternative* PI Regimens below for full details.	• See DRV/r under *Alternative* PI Regimens below.

Table 6. What to Start: Initial Antiretroviral Regimens During Pregnancy for People Who Are Antiretroviral-Naive

Alternative Initial Regimens in Pregnancy		
Drugs or drug combinations are designated as *Alternative* options for therapy during pregnancy 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 people 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 (see Appendix B: Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy).		
Alternative INSTI Regimens	Advantages	Disadvantages
BIC/TAF/FTC (FDC)	• Coformulated as a single, once-daily pill • High barrier to resistance • No food requirement • No dose adjustment required in pregnancy • No safety concerns observed • High rates of viral suppression	• PK and safety data in pregnancy remain limited to small studies. Drug levels are lower in a pregnant person who is in the second and third trimester than in nonpregnant or postpartum patients and are reduced in later pregnancy to a greater degree for BIC than for DTG. BIC levels remained above the EC_{95} during pregnancy and therefore are anticipated to suppress viral load. • May be associated with weight gain • Specific timing and/or fasting recommendations apply if BIC is taken with calcium or iron (e.g., in prenatal vitamins; see Table 14 and Bictegravir for details).
RAL plus a *Preferred* Dual-NRTI Backbone	• No safety concerns observed. Like DTG, RAL may be particularly useful when drug interactions or the potential for preterm delivery with PI-based regimens are a concern. • PK data are available for RAL in pregnancy when using the twice-daily formulation (400 mg twice daily). • Like DTG, RAL has been shown to rapidly decrease viral load in ARV-naive pregnant women who present to care later in pregnancy. In nonpregnant adults, DTG is associated with lower rates of INSTI resistance than RAL, and DTG permits once-daily dosing; for these reasons, DTG is *Preferred* and RAL is *Alternative* for use during pregnancy.	• Twice-daily dosing in pregnancy is recommended due to low drug level with once-daily dosing during pregnancy. • Not available as an FDC • Lower barrier to resistance than DTG; for this reason, RAL is *Alternative* for use during pregnancy • PK data are not available for the once-daily 1,200 mg (2 × 600 mg) extended-release formulation (raltegravir HD) in pregnancy. • Specific timing and/or fasting recommendations apply if RAL is taken with calcium or iron (e.g., in prenatal vitamins; see Table 14 and Raltegravir for details).

Table 6. What to Start: Initial Antiretroviral Regimens During Pregnancy for People Who Are Antiretroviral-Naive

Alternative PI Regimens	Advantages	Disadvantages
ATV/r plus a *Preferred* Dual-NRTI Backbone	• Once-daily dosing • Extensive experience during pregnancy	• Not available as an FDC • Associated with increased maternal indirect bilirubin levels, which theoretically may increase the risk of neonatal hyperbilirubinemia. No clinically significant neonatal hyperbilirubinemia or kernicterus reported, but neonatal bilirubin monitoring is recommended. • Requires increased dosing in the second or third trimester • Has been associated with small but significant reductions in language and social-emotional scores and late language • PIs may increase the risk of preterm birth. • Cannot be used with PPIs • Requires consideration of timing when dosed with H2 blockers, which are commonly used during pregnancy (see Table 14).
DRV/r plus a *Preferred* Dual-NRTI Backbone	• When a PI-based regimen is indicated, DRV/r is recommended over ATV. However, DRV/r requires twice-daily dosing in pregnancy, and dosing frequency affects adherence. For that reason, when use of a PI-based regimen is indicated during pregnancy, some Panel members would use ATV/r rather than DRV/r for ART. • DRV/r with a NRTI backbone of TAF or TDF with 3TC or FTC is the *Preferred* regimen for initial treatment in people with early (acute or recent) HIV infection *and* a history of CAB-LA exposure for PrEP, see Early (Acute or Recent) HIV Infection.	• Not available as an FDC • Requires twice-daily dosing during pregnancy • Requires administration with food • PIs may increase the risk of preterm birth.
Alternative Dual-NRTI Backbone	Advantages	Disadvantages
ZDV/3TC	• Available as an FDC • Significant experience during pregnancy	• Requires twice-daily dosing • Associated with higher rates of side effects, including nausea, headache, and reversible maternal and neonatal anemia and neutropenia • Other regimens have demonstrated similar or greater efficacy and fewer side effects.

Table 6. What to Start: Initial Antiretroviral Regimens During Pregnancy for People Who Are Antiretroviral-Naive

Alternative NNRTI Regimens	Advantages	Disadvantages
EFV/TDF/FTC (FDC) *or* EFV/TDF/3TC (FDC) *or* EFV plus a *Preferred* Dual-NRTI Backbone	• Once-daily dosing • Available as an FDC • Extensive experience in pregnancy • Not associated with increased risk of NTDs or other congenital anomalies in human studies (although cautionary text based on animal studies remains in the package insert); see Efavirenz and Table 14. • No dose changes required during pregnancy • Useful for patients 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	• Overall higher rates of adverse events than some *Preferred* drugs • Requires enhanced surveillance for depression and suicidality • Increased risk of adverse birth outcomes has been observed with EFV/TDF/FTC versus DTG/TAF/FTC started during pregnancy. • Increased risk of toxicity, including dizziness, fatigue, hepatotoxicity, vivid dreams/nightmares
RPV/TDF/FTC (FDC) *or* RPV/TAF/FTC (FDC) *or* RPV (oral) plus a *Preferred* Dual-NRTI Backbone	• Once-daily dosing • Available as an FDC • Useful for patients 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	• Limited use for individuals with high pre-treatment HIV RNA. RPV is not recommended in patients with pre-treatment HIV RNA >100,000 copies/mL or CD4 counts <200 cells/mm^3. • Requires close viral monitoring in second and third trimesters because PK data suggest lower drug levels. Insufficient data to suggest dosing changes. • Do not use with PPIs. • Requires consideration of timing when dosed with H2 blockers or PPIs, which are commonly used during pregnancy (see Table 14) • Requires administration with food

Table 6. What to Start: Initial Antiretroviral Regimens During Pregnancy for People Who Are Antiretroviral-Naive

Insufficient Data for Use as Initial Regimens in Pregnancy		
These drugs and drug combinations are approved for use in adults, but pregnancy-specific PK or safety data are too limited to make recommendations for use in pregnant people. When a pregnant person presents to care while virally suppressed on one of these drugs or drug combinations, providers should consider whether to continue their current regimen or switch to a recommended ARV regimen (see People with HIV Who Are Taking Antiretroviral Therapy When They Become Pregnant and Table 7). It is critical that providers report exposures to these medications in pregnancy to the Antiretroviral Pregnancy Registry.		
Insufficient Data	Advantages	Disadvantages
DOR *or* DOR/TDF/FTC	• Coformulated with TDF/FTC • No food requirement	• Limited PK, toxicity, and efficacy data in pregnancy • Initial studies suggest potentially lower drug levels in third trimester.

Table 6. What to Start: Initial Antiretroviral Regimens During Pregnancy for People Who Are Antiretroviral-Naive

Not Recommended for Use as Initial Regimens in Pregnancy		
Drugs and drug combinations listed in this category are *Not Recommended* for use in pregnancy because of inferior virologic efficacy or potentially serious safety concerns for the pregnant person or fetus or because they are not recommended for initial therapy in nonpregnant adults. 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 viremia in the pregnant person occurs (see Table 7 and Table 14). Note: When a pregnant person presents to care while virally suppressed on one of these drugs or drug combinations, providers should consider whether to continue their current regimen with more frequent viral load monitoring or switch to a *Preferred* ARV regimen (see People with HIV Who Are Taking Antiretroviral Therapy When They Become Pregnant and Table 7).		
Not Recommended	Advantages	Disadvantages
ATV/c		• Limited existing data suggest insufficient levels of both COBI and ATV in second and third trimesters. • Changing COBI component to RTV is likely to improve efficacy but will increase pill burden.
Long-Acting Injectable CAB plus RPV (Co-packaged Formulation)	• Injectable delivery may be more effective and/or more convenient than oral ART for some patients. • Approved for nonpregnant adults who have RNA levels <50 copies/mL for at least 3 months on a stable oral ARV regimen, with no history of treatment failure and no known or suspected resistance	• Limited PK, toxicity, and efficacy data during pregnancy • Not recommended as initial treatment for ARV-naive adults or adolescents (pregnant or nonpregnant) • Due to the long half-life of injectable CAB and RPV, drug levels may persist up to 12 months after the last dose. Optimal timing of switch to an oral regimen is not known (see Management of the Treatment-Experienced Patient in the Adult and Adolescent Antiretroviral Guidelines).
DRV/c (FDC) *or* DRV/c/FTC/TAF (FDC)	• DRV/c/FTC/TAF is coformulated as a single-tablet, once-daily regimen.	• Limited existing data suggest insufficient levels of both COBI and ATV in second and third trimesters; viral breakthroughs have been reported. • Changing COBI component to RTV is likely to improve efficacy but will increase pill burden; in addition to adding RTV as separate pill, both DRV and RTV should be dosed twice daily.
EVG/c/FTC/TAF (FDC) *or* EVG/c/FTC/TDF (FDC)	• Coformulated as single-tablet, once-daily regimen	• Limited existing data suggest insufficient levels of both COBI and EVG in second and third trimesters. • Viral breakthrough at delivery was identified in 26% of previously suppressed individuals in IMPAACT P1026. Data are insufficient to suggest dosing changes. • Unlike for DRV/c and ATV/c, there is no option to replace COBI with RTV boosting. • Specific timing and/or fasting recommendations apply, especially if taken with calcium or iron (e.g., in prenatal vitamins; see Table 14 and Elvitegravir for details).

Table 6. What to Start: Initial Antiretroviral Regimens During Pregnancy for People Who Are Antiretroviral-Naive

Not Recommended for Initial Use in Pregnancy, but May Be Used in Special Circumstances for Pregnant People Who Are Treatment-Experienced		
These drugs are *Not Recommended* for use in pregnant people who have never received ART. Except for NVP and LPV/r, data on the PK, safety, and efficacy of these drugs during pregnancy are limited. These drugs also are categorized as *Not Recommended* during pregnancy, except in special circumstances, because the Panel recognizes that circumstances may exist in which patients who are ART-experienced may need to initiate or continue these drugs during pregnancy to reach or maintain viral suppression (see Table 7).		
Not Recommended Except in Special Circumstances for Pregnant People Who Are Treatment-Experienced	Advantages	Disadvantages
ETR	• Standard adult dose is appropriate during pregnancy in the special circumstance where ETR is used.	• Not recommended in nonpregnant individuals who are ART-naive • Limited PK, toxicity, and efficacy data during pregnancy
FTR		• Not recommended in nonpregnant individuals who are ART-naive • Limited PK, toxicity, and efficacy data during pregnancy
IBA		• Not recommended in nonpregnant individuals who are ART-naive • Limited PK, toxicity, and efficacy data during pregnancy • Requires IV administration
LEN		• Not recommended in nonpregnant individuals who are ART-naive • Limited PK, toxicity, and efficacy data during pregnancy • Use is limited to multidrug-resistant HIV
LPV/r plus a *Preferred* Dual-NRTI Backbone	• Extensive experience during pregnancy • Available as a liquid formulation when needed. LPV/r solution contains approximately 42% (v/v) ethanol and 15% (w/v) propylene glycol; it should be used with caution in pregnancy.	• Not recommended in nonpregnant individuals who are ART-naive • Requires twice-daily dosing in pregnancy; data suggest that once-daily LPV/r will not achieve sufficient plasma concentrations. • Some experts recommend increased dosing in the second and third trimesters (see Table 14 and Lopinavir/Ritonavir). • Associated with nausea and diarrhea • Associated with increased risk of preterm birth and small-for-gestational-age neonatal status (see Antiretroviral Drug Regimens and Pregnancy Outcomes)

Table 6. What to Start: Initial Antiretroviral Regimens During Pregnancy for People Who Are Antiretroviral-Naive

MVC	• Limited data suggest standard adult dose is appropriate during pregnancy.	• Not recommended in nonpregnant individuals who are ART-naive • Limited PK, toxicity, and efficacy data during pregnancy • Requires tropism testing before use
NVP	• Standard adult dosing is appropriate in pregnancy in the special circumstance where NVP is used.	• Not recommended in nonpregnant individuals who are ART-naive • Greater potential for adverse effects • Low barrier to resistance • Requires complex lead-in dosing • 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 in nonpregnant individuals who are ART-naive • Limited PK, toxicity, and efficacy data during pregnancy

Note: The following drugs and drug combinations (not listed above) should not be used during pregnancy; people 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; CAB = cabotegravir; CAB-LA = long-acting cabotegravir; COBI = cobicistat; d4T = stavudine; ddI = didanosine; DOR = doravirine; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EC_{95} = 95% maximal effective concentration; EFV = efavirenz; ETR = etravirine; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FDC = fixed-dose combination; FPV = fosamprenavir; FPV/r = fosamprenavir/ritonavir; FTC = emtricitabine; FTR = fostemsavir; HBV = hepatitis B virus; HD = high dose; IBA = ibalizumab; IDV = indinavir; IDV/r = indinavir/ritonavir; IMPAACT = International Maternal Pediatric Adolescent AIDS Clinical Trials; INSTI = integrase strand transfer inhibitor; IV = intravenous; LEN = lenacapavir; 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 HIV During Pregnancy and Prevention of Perinatal Transmission; PI = protease inhibitor; PK = pharmacokinetic; PPI = proton pump inhibitor; PrEP = pre-exposure prophylaxis; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SQV = saquinavir; SQV/r = saquinavir/ritonavir; T-20 = enfuvirtide; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TPV = tipranavir; TPV/r = tipranavir/ritonavir; ZDV = zidovudine

Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs in Pregnant People and Nonpregnant People Who Are Trying to Conceive

Updated: January 31, 2024
Reviewed: January 31, 2024

People should be given information about the benefits and risks of initiating an antiretroviral regimen or making changes to an existing regimen during pregnancy or when trying to conceive so that they can make informed decisions about their care (see Appendix C: Antiretroviral Counseling Guide for Health Care Providers). Patient autonomy and informed choice should be considered in all aspects of medical care, including HIV and obstetric care. These are primary guiding principles in all the recommendations of the Panel on Treatment of HIV During Pregnancy and Prevention of Perinatal Transmission.

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 Starting or Restarting ART[a]	New ART Regimen for Pregnant People Whose Current Regimen Is Not Well Tolerated and/or Is Not Fully Suppressive	ART for Nonpregnant People Who Are Trying to Conceive[b]
Integrase Strand Transfer Inhibitor (INSTI) Drugs Used in combination with a dual–nucleoside reverse transcriptase inhibitor (NRTI) backbone[c,d]					
DTG[a]	Preferred[a]	Continue	Preferred[a]	Preferred	Preferred
BIC[a,e]	Alternative[a]	Continue	Alternative[a]	Alternative	Alternative
RAL	Alternative	Continue	Alternative	Alternative	Alternative
CAB[d] Oral (lead-in) Long-acting (IM)	Not recommended	Continue with frequent viral load monitoring or consider switching due to insufficient data[d]	Insufficient data	Insufficient data	Insufficient data

Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs in Pregnant People and Nonpregnant People Who Are Trying to Conceive

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 Starting or Restarting ART[a]	New ART Regimen for Pregnant People Whose Current Regimen Is Not Well Tolerated and/or Is Not Fully Suppressive	ART for Nonpregnant People Who Are Trying to Conceive[b]
EVG/c[f]	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[g]	Alternative	Continue	Alternative	Alternative	Alternative
DRV/r[a,g]	Alternative[a]	Continue	Alternative[a]	Alternative	Alternative
LPV/r[g]	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[f]	Not recommended	Continue with frequent viral load monitoring or consider switching.	Not recommended	Not recommended	Not recommended
DRV/c[f]	Not recommended	Continue with frequent viral load monitoring or consider switching.	Not recommended	Not recommended	Not recommended

Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs in Pregnant People and Nonpregnant People Who Are Trying to Conceive

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 Starting or Restarting ART[a]	New ART Regimen for Pregnant People Whose Current Regimen Is Not Well Tolerated and/or Is Not Fully Suppressive	ART for Nonpregnant People Who Are Trying to Conceive[b]
Non-nucleoside Reverse Transcriptase Inhibitor (NNRTI) Drugs Used in combination with a dual-NRTI backbone[c,d]					
EFV	Alternative	Continue	Alternative	Alternative	Alternative
RPV[h] Oral	Alternative	Continue	Alternative	Alternative	Alternative
RPV Long-acting (IM)[d]	Not recommended	Continue with frequent viral load monitoring or consider switching due to insufficient data.[d]	Insufficient data	Insufficient data	Insufficient data
DOR[i]	Insufficient data	Continue with frequent viral load monitoring or consider switching due to insufficient data.	Insufficient data	Insufficient data	Insufficient data
ETR[j]	Not recommended	Continue	Not recommended, except in special circumstances	Not recommended, except in special circumstances	Not recommended, except in special circumstances
NVP[j]	Not recommended	Continue	Not recommended, except in special circumstances	Not recommended, except in special circumstances	Not recommended, except in special circumstances
NRTI Drugs[c,k]					
ABC[c,k]	Preferred[c]	Continue	Preferred[c]	Preferred	Preferred[c]
FTC	Preferred	Continue	Preferred	Preferred	Preferred

Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs in Pregnant People and Nonpregnant People Who Are Trying to Conceive

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 Starting or Restarting ART[a]	New ART Regimen for Pregnant People Whose Current Regimen Is Not Well Tolerated and/or Is Not Fully Suppressive	ART for Nonpregnant People Who Are Trying to Conceive[b]
3TC	Preferred	Continue	Preferred	Preferred	Preferred
TDF[c]	Preferred[c]	Continue	Preferred	Preferred	Preferred
ZDV	Alternative	Continue	Alternative	Alternative	Alternative
TAF[c]	Preferred[c]	Continue	Preferred	Preferred	Preferred
Entry, Attachment, Fusion, and Capsid Inhibitor Drugs					
FTR[j]	Not recommended	Continue[j]	Not recommended, except in special circumstances	Not recommended, except in special circumstances	Not recommended, except in special circumstances
IBA[j]	Not recommended	Continue[j]	Not recommended, except in special circumstances	Not recommended, except in special circumstances	Not recommended, except in special circumstances
LEN[j]	Not recommended	Continue[j]	Not recommended, except in special circumstances	Not recommended, except in special circumstances	Not recommended, except in special circumstances
MVC[j]	Not recommended	Continue[j]	Not recommended, except in special circumstances	Not recommended, except in special circumstances	Not recommended, except in special circumstances

Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs in Pregnant People and Nonpregnant People Who Are Trying to Conceive

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 Starting or Restarting ART[a]	New ART Regimen for Pregnant People Whose Current Regimen Is Not Well Tolerated and/or Is Not Fully Suppressive	ART for Nonpregnant People Who Are Trying to Conceive[b]
T-20[j]	Not recommended	Continue[j]	Not recommended, except in special circumstances	Not recommended, except in special circumstances	Not recommended, except in special circumstances
Fixed-Dose Combination (FDC) and Coadministered Regimens[e,l] The individual drug component that is most responsible for the overall recommendation is indicated in parentheses.					
DTG/ABC/3TC[a,c,k]	Preferred[a,c]	Continue	Preferred[a,c]	Preferred	Preferred[a,c]
BIC/FTC/TAF[e]	Alternative (BIC)	Continue	Alternative (BIC)	Alternative (BIC)	Alternative (BIC)
EFV/FTC/TDF	Alternative (EFV)	Continue	Alternative (EFV)	Alternative (EFV)	Alternative (EFV)
EFV/3TC/TDF	Alternative (EFV)	Continue	Alternative (EFV)	Alternative (EFV)	Alternative (EFV)
RPV/TDF/FTC[h]	Alternative (RPV)	Continue (RPV)	Alternative (RPV)	Alternative (RPV)	Alternative (RPV)
RPV/TAF/FTC[h]	Alternative	Continue	Alternative	Alternative	Alternative
DOR/3TC/TDF[i]	Insufficient data (DOR)	Continue with frequent viral load monitoring or consider switching due to insufficient data (DOR).	Insufficient data (DOR)	Insufficient data (DOR)	Insufficient data (DOR)
IM CAB and RPV[d] As a complete regimen	Not recommended	Continue with frequent viral load monitoring or consider switching due to insufficient data.[d]	Insufficient data	Insufficient data	Insufficient data
DRV/c/FTC/TAF[f]	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)

Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs in Pregnant People and Nonpregnant People Who Are Trying to Conceive

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 Starting or Restarting ART[a]	New ART Regimen for Pregnant People Whose Current Regimen Is Not Well Tolerated and/or Is Not Fully Suppressive	ART for Nonpregnant People Who Are Trying to Conceive[b]
EVG/c/FTC/TDF[f]	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[f]	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)
DTG/3TC As a complete regimen[m]	Not recommended	Continue with frequent viral load monitoring.	Not recommended	Not recommended	Not recommended
DTG/RPV As a complete regimen[m]	Not recommended	Continue with frequent viral load monitoring.[m]	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. DTG and BIC are not recommended for initial treatment in people with a history of CAB exposure for PrEP due to concerns about INSTI resistance mutations in the absence of INSTI genotype information; DRV/r is *Preferred* in this situation.

[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, TAF plus FTC, and TDF plus 3TC are *Preferred* dual-NRTI backbones, and ZDV plus 3TC is an *Alternative* dual-NRTI backbone for ARV regimens. ABC is not recommended as part of regimens for initial treatment of early (acute or recent) HIV infection because it requires HLA-B*5701 testing before use. When results of HLA-B*5701 testing are not available, use of TDF or TAF rather than ABC will avoid delays in initiating ART.

[d] Long-acting injectable formulations of CAB and RPV are available only as a co-packaged product. Coadministration of CAB plus RPV is a complete two-drug ART regimen for nonpregnant adults with HIV RNA levels <50 copies/mL for at least 3 months, on a stable ARV regimen, with no history of treatment failure, and with no known or suspected resistance to CAB or RPV. Oral lead-in dosing with CAB and RPV for at least 28 days may be used to assess tolerability before starting monthly long-acting IM injections. CAB plus RPV (oral or injectable) should not be administered with NRTIs or other ARV drugs. Oral and injectable CAB and injectable RPV are not recommended for initiation in pregnancy due to lack of dosing, PK, and safety data for injectable RPV and for injectable or oral CAB. However, people who conceive while suppressed on injectable CAB/RPV may have few other treatment options, and the Panel recommends a shared decision-making process to decide whether to continue this regimen with viral load monitoring every 1 to 2 months or to switch to a recommended oral regimen. If a switch is made, the timing of the switch must take into account the long half-life of the long-acting injectable formulations with persistence of the drug for up to 12 months. With the current dosing schedule of monthly injections, change to an oral regimen should occur within 4 weeks of

the last CAB and RPV IM doses. Dosing recommendations, including guidance for switching to an oral regimen, can be found in the prescribing information. (See Cabotegravir in the Perinatal Guidelines and Optimizing Antiretroviral Therapy in the Setting of Viral Suppression in the Adult and Adolescent Antiretroviral Guidelines.)

[e] Data about BIC in nonpregnant adults show efficacy. PK and safety data in pregnancy remain limited to small studies. No safety concerns have been observed. Drug levels are lower in pregnant people who are in the third trimester than in nonpregnant or postpartum patients and are reduced in later pregnancy to a greater degree for BIC than for DTG. BIC levels remained above the 95% maximal effective concentration during pregnancy and thus are anticipated to suppress viral load.

[f] 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 (every 1–2 months) viral load monitoring or can be switched to a recommended or alternative agent. If concerns about switching exist, see People with HIV Who Are Taking Antiretroviral Therapy When They Become Pregnant. If the cobicistat pharmacologic booster is replaced with RTV for ATV and DRV, attention to dosing in pregnancy is critical; in the second and third trimesters, higher doses of ATV are required if coadministered with TDF or antacids, and twice-daily dosing is required for DRV.

[g] DRV/r, rather than ATV/r, is recommended as an option for initial ART in nonpregnant adults. However, DRV/r requires twice-daily dosing in pregnancy, and dosing frequency affects ARV adherence. For these reasons, when use of a PI-based regimen is indicated during pregnancy, some Panel members would use ATV/r rather than DRV/r for initial ART. LPV/r is not recommended for use in pregnancy but may be needed in special circumstances because it is safe for use in pregnancy and provides an option if a liquid formulation is needed (e.g., G-tube administration). However, because LPV/r solution contains approximately 42% (v/v) ethanol and 15% (w/v) propylene glycol, it should be used with caution in pregnancy.

[h] Although PK data indicate that RPV plasma concentration is reduced during the second and third trimesters, the reduction is less than that 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 (every 1–2 months).

[i] Data on the safety, PK, and dosing of DOR in pregnancy are limited. Viral load should be monitored more frequently (every 1–2 months). Because fewer than 200 first-trimester and periconception exposures have been reported in the Antiretroviral Pregnancy Registry, it is not yet possible to exclude a risk of birth defects greater than that in the general population. Please report all exposures to the Antiretroviral Pregnancy Registry.

[j] Although these drugs are not recommended for initial treatment in ART-naive pregnant people, in special circumstances, ART-experienced people may need to continue or initiate ETR, FTR, IBA, LEN, NVP, MVC, and T-20 to maintain or achieve viral suppression. Safety and efficacy data about the use of ETR, FTR, IBA, LEN, MVC, and T-20 in pregnancy are limited. For highly treatment-experienced patients, consider switching to a regimen approved for use in pregnancy, or for patients without therapeutic alternatives, continue with frequent (every 1–2 months) viral load monitoring and counsel patients that safety data are not available during 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 6. What to Start: Initial Antiretroviral Regimens During Pregnancy for People Who Are Antiretroviral-Naive and Nevirapine for more information.

[k] 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.

[l] When using FDC tablets, refer to Table 14. Antiretroviral Drug Use in Pregnant People with HIV: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy and the drug sections in Appendix B: Supplement: Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy for information about the dosing and safety of individual components of the FDC tablet during pregnancy.

Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs in Pregnant People and Nonpregnant People Who Are Trying to Conceive

[m] Two-drug oral ARV regimens are not recommended for use in pregnancy due to lack of available data about use in pregnancy. However, pregnant people who present to care on an oral DTG/3TC or DTG/RPV regimen with successfully maintained virologic suppression can continue it with more frequent viral load monitoring (every 1–2 months) throughout pregnancy because the component drugs are recommended for use in pregnancy.

Note: The following drugs and drug combinations, which are not listed above, should not be used during pregnancy: 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). If a person becomes pregnant while taking any of these medications, they should switch to a recommended regimen. 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 AR.V regimens that are not recommended or should not be used in adults. Refer to the table above and Table 6. What to Start: Initial Antiretroviral Regimens During Pregnancy for People Who Are Antiretroviral-Naive 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; CAB = cabotegravir; d4T = stavudine; ddI = didanosine; DOR = doravirine; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG/c = elvitegravir/cobicistat; FDC = fixed-dose combination; FPV = fosamprenavir; FPV/r = fosamprenavir/ritonavir; FTC = emtricitabine; FTR = fostemsavir; IBA = ibalizumab; IDV = indinavir; IDV/r = indinavir/ritonavir; IM = intramuscular; IM CAB and RPV = long-acting intramuscular formulations of cabotegravir and rilpivirine; INSTI = integrase strand transfer inhibitor; LEN = lenacapavir; LPV/r = lopinavir/ritonavir; MVC = maraviroc; NFV = nelfinavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; the Panel = Panel on Treatment of HIV During Pregnancy and Prevention of Perinatal Transmission; PI = protease inhibitor; PK = pharmacokinetic; PrEP = pre-exposure prophylaxis; 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

Teratogenicity

Updated: January 31, 2024
Reviewed: January 31, 2024

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, people should be counseled that ARV drugs during pregnancy generally do not increase the risk of birth defects (BIII). Providers should be aware that data on the risks of birth defects for many ARV drugs are limited and evolving (see Appendix B: Supplement: Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy). • All pregnant people with HIV should initiate antiretroviral therapy (ART) as early in pregnancy as possible (AI). Pregnant people with HIV should not delay initiating ART due to concerns about teratogenicity with first-trimester exposure (AIII). • The Panel on Treatment of HIV During Pregnancy and Prevention of Perinatal Transmission 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. • 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 unplanned pregnancies (AIII). See Prepregnancy Counseling and Care for Persons of Childbearing Age with HIV, Introduction to the Selection of Antiretroviral Drugs In Pregnancy, People with HIV Who are Trying to Conceive, and Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs in Pregnant People and Nonpregnant People Who Are Trying to Conceive.
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 people with HIV are advised strongly to report instances of prenatal exposure to antiretroviral (ARV) drugs (either single-drug exposure or exposure to a combination of ARV drugs) to the Antiretroviral Pregnancy Registry as early in pregnancy as possible. The purpose of the Antiretroviral Pregnancy Registry is to detect any major teratogenic effect involving any of the registry drugs to which pregnant people are exposed. Registry data are used to supplement animal toxicology studies and assist clinicians in weighing the potential risks and benefits of treatment for individual patients. The Antiretroviral Pregnancy Registry is a collaborative project of pharmaceutical manufacturers with an advisory committee that includes a teratologist; an infectious disease specialist; an epidemiologist; a biostatistician; and a group of obstetric, maternal–fetal medicine, and pediatric providers. This prospective 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
301 Government Center Drive
Wilmington, NC 28403
Telephone: 1-800-258-4263
Fax: 1-800-800-1052
Email: SM_APR@APRegistry.com

Antiretroviral Drugs and Birth Defects

The potential harm to the fetus from birthing parent's 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 birthing parent and fetus. Information regarding the safety of using certain drugs during pregnancy is derived from multiple sources, including animal reproductive/developmental toxicity data, anecdotal experience, registry data, randomized clinical trials, and observational studies.

Drug choice should be individualized and discussed with people who are pregnant or are trying to conceive 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. When considering whether a pregnant person should continue an effective antiretroviral regimen when they present 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.[1] For additional information, see People with HIV Who Are Taking Antiretroviral Therapy When they Become Pregnant.

Data continue to be collected on the placental passage, pharmacokinetics, and safety of U.S. 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 Appendix B: Supplement: Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy). The Antiretroviral Pregnancy Registry has predefined analytical methods and criteria for recognizing a potential signal. When analyzing registry data, data on birth outcomes from 200 infants who were exposed to an ARV drug during the first trimester are viewed as sufficient to detect a doubling of 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 overall birth defects. The general U.S. population birth defect prevalence is 2.72% as determined by the Metropolitan Atlanta Congenital Defect Program, the Centers for Disease Control and Prevention's population-based surveillance system for birth defects.[2] Table 8 below summarizes Antiretroviral Pregnancy Registry risk assessment for individual ARV drugs and points out that risk assessment is not available when pregnancy exposures are not reported. Detailed information about Antiretroviral Pregnancy Registry data for individual drugs is available in Appendix B: Supplement: Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy.

Table 8. Drug-Specific Risk Assessment by the Antiretroviral Pregnancy Registry

ARV Drug	Level of Risk Assessment	Risk Assessment Outcome
BIC, COBI, DRV, d4T, ddI, DTG, EVG, IDV, RAL, RPV, and TAF	Sufficient numbers of first-trimester exposures have been monitored to detect at least a 2-fold increase in the risk of overall birth defects.	No such increases detected.
3TC, ABC, ATV, EFV, FTC, LPV/r, NFV, NVP, 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 detected.
CAB, DOR, ETR, FTR, LEN, and T-20	Insufficient numbers of exposures reported to assess the level of risk.	Not available.

Key: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; ATV = atazanavir; BIC = bictegravir; CAB = cabotegravir; COBI = cobicistat; d4T = stavudine; ddI = didanosine; DOR = doravirine; DRV = darunavir; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG = elvitegravir; FTC = emtricitabine; FTR = fostemsavir; IDV = indinavir; LEN = lenacapavir; LPV/r = lopinavir/ritonavir; NFV = nelfinavir; NVP = nevirapine; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; T-20 = enfuvirtide; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; ZDV = zidovudine

For individual birth defects, the power of the Antiretroviral Pregnancy Registry to find an increased risk will vary depending upon the frequency of the defect in the population. 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. Thus, large numbers of cases are required to detect increased risk of rare but serious defects, underscoring the need for providers to report all ARV exposures prospectively to the Antiretroviral Pregnancy Registry.[3]

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),[4] nutritional and folate status,[5] and tobacco and alcohol use.[6] 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. Additionally, clinicians should consider all medications used in early pregnancy. According to a 2018 study involving 9,546 pregnant people, 97.1% reported taking at least one medication during their pregnancy.[7] In the last decade, 89.3% of the 290 therapeutics submitted to the FDA between 2010 and 2019 lacked human data related to pregnancy.[8] Thus, it is important to know of any and all medication exposures in pregnancy when evaluating risk of birth defects in relation to ARV drugs.

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.[9-13] The Antiretroviral Pregnancy Registry conducts a primary analysis of prospective cases of ARV drug exposure during pregnancy provided by health care providers. In the current analysis through January 31, 2023, the prevalence of birth defects was 3.0 per 100 live births among women with a first-trimester exposure to any ARV drug (348 of 11,767 exposures; 95% confidence interval [CI], 2.7–3.3). 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 1.04; 95% CI, 0.89–1.21).[2] Although these

data 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.

Experience with efavirenz (EFV) and dolutegravir (DTG) highlights the importance of obtaining sufficient data about the use of ARV drugs in pregnancy. Although early data from animal studies of EFV and retrospective case reports in humans[14,15] raised concerns about the potential for congenital nervous system abnormalities and neural tube defects (NTDs) when EFV was taken around the time of conception and in early pregnancy, later data have shown EFV is not associated with NTDs.[16,17] Similarly, early data from an active surveillance study of birth defects in Botswana, including 426 preconception DTG exposures, suggested a possible association between NTDs and DTG use at conception[18]; however, data from expanded and ongoing surveillance of DTG use in Botswana found there was no detectable increase in NTDs or major external structural abnormalities among more than 11,000 exposures to DTG at conception captured in the Tsepamo Study from 2014 to 2022.[19] A similar study in Eswatini also found no increase in NTDs with preconception DTG exposure.[20] In the United States, a cohort study using health care claims data did not find an increased risk of NTDs with use of DTG.[21] As reported perinatal DTG exposures in the United States have increased, the latest interim Antiretroviral Pregnancy Registry report included sufficient data to state that DTG is not associated with NTDs.[2] This change over time demonstrates the importance of reporting perinatal ARV exposures to the Antiretroviral Pregnancy Registry so that data are sufficient to draw conclusions. Drug-specific teratogenicity data are summarized in Appendix B: Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy. Additional data and further studies are needed to assess and understand the risks associated with newer ARV drugs and drugs with more limited use.

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Antiretroviral Drug Regimens and Pregnancy Outcomes

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Panel's Recommendations
• Clinicians should be aware of a possible increased risk of adverse neonatal outcomes (e.g., preterm birth [PTB]) in pregnant people who are receiving antiretroviral therapy (ART). However, given the clear benefits of ART for the health of the pregnant person and the prevention of perinatal transmission, HIV treatment should not be withheld due to concern for adverse pregnancy outcomes (AII). • Use of ART for the prevention of perinatal HIV transmission, especially preconception or in the first trimester, may be associated with an increased risk of PTB. However, the Panel does not recommend that people with HIV stop ART before conception or in early pregnancy for the purpose of preventing PTB (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*

In this section, the Panel on Treatment of HIV During Pregnancy and Prevention of Perinatal Transmission (the Panel) provides a summary of recently published data on antiretroviral therapy (ART) and adverse pregnancy outcomes. Pregnant people with HIV, regardless of antiretroviral (ARV) drug use, may be at increased risk for adverse neonatal outcomes. These outcomes may include preterm birth (PTB) (delivery before 37 weeks of 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 sex), and stillbirth (delivery of a nonviable infant after 20 weeks). The gestational age cutoff 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 complications of pregnancy, such as hypertensive disorders of pregnancy (HDP) (i.e., chronic hypertension, gestational hypertension, preeclampsia, and eclampsia). Some of the data described in this section involve historical 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 drug use and teratogenicity (i.e., their relation to birth defects), please refer to Teratogenicity and the individual drug sections in Appendix B: Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy and Table 14. Antiretroviral Drug Use in Pregnant People with HIV: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy.

Interpretation of Adverse Pregnancy Outcomes Data

Multiple studies have evaluated the potential association between ARV drug use and PTB, LBW, SGA, and stillbirth with conflicting results. These adverse outcomes often occur without an identifiable cause, and it can be difficult to establish a causal link with medication exposure. Adverse pregnancy outcomes are relatively common, so a small increase in risk can have 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 drug 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. People 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 people on ART to pregnant people without HIV is confounded by HIV status. Some evidence suggests that the risk of adverse outcomes varies by ARV drug, even within ARV drug classes. The risk of adverse outcomes also may 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 drug regimens or ARV drug classes are compared with each other. Unfortunately, many studies continue to use comparison groups of women without HIV and women with HIV who are not taking ART or who are taking older regimens that are no longer recommended for treatment of HIV. Studies of the safety of newer ART, specifically integrase strand transfer inhibitors (INSTIs), on pregnancy outcomes are reassuring but limited.[1] 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 ARV drugs, and ART.

Preterm Birth

Multiple meta-analyses and systematic reviews have evaluated the potential association of ARV drug use and PTB. Some large meta-analyses have not demonstrated a significant association between ARV drug use and PTB. The sample sizes pooled for these meta-analyses ranged from 13 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 ARV drugs currently used.[2-6] A large meta-analysis of 61 observational studies (n = 409,781) compared the risk of PTB between HIV negative women and women with HIV who were either not on ART, prescribed zidovudine (ZDV) single-drug therapy, or prescribed ART. Although the risk of any PTB in women with HIV prescribed ART compared with women with HIV not on ART was not significantly different, women prescribed ART were less likely to experience spontaneous PTB than women not on ART (relative risk [RR] 0.46; 95% confidence interval [CI], 0.32–0.67).[5] Another meta-analysis 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 PTB between these two groups.[2] A network meta-analysis of seven randomized controlled trials (RCTs) evaluated seven different ART regimens and their associations with PTB (including spontaneous PTB in three trials). When compared with women prescribed ZDV/lamivudine (3TC)/abacavir, women prescribed ZDV/3TC/lopinavir (LPV)/ritonavir (r) had an increased risk of spontaneous PTB (n = 991; RR 1.81; 95% CI, 1.21–2.71).[7] ART that contains LPV/r may be associated with a greater risk of PTB than other protease inhibitor (PI)–based regimens.

Multiple observational studies describe an association between the use of ARV drugs during pregnancy and an increased risk of PTB.[4,8-19] In general, the observational studies reviewed in this section have not controlled comprehensively for all factors that may be associated with PTB. A recent observational study that evaluated ARV drug use among women with HIV in British Columbia reduced confounding variables by excluding multiple gestation pregnancies and antiquated ARV drug regimens (i.e., single-drug therapy, two-drug therapy, and triple nucleoside reverse transcriptase inhibitor [NRTI] regimens). The authors concluded that women with HIV were twice as likely to experience PTB as the general population. Compared with women with HIV who were not

on ART during pregnancy, women who were on any ART were less likely to have spontaneous PTB (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 or first-trimester ARV drug use nor PI-based ART was associated with PTB.[20]

Antiretroviral Therapy and Preterm Birth

Protease Inhibitor–Based Regimens

The association between the use of PI-based ART and PTB has been investigated in multiple studies across Europe, North America, and Africa.[7,8,10,12,13,15,21-24] Not all the studies reviewed for this section have identified an association between PI use and an increased risk of PTB.[10,20,21,25,26]

A meta-analysis of 10 studies (eight prospective cohort studies, one RCT, and one surveillance study) demonstrated that the use of PI-based ART is associated with an increased risk of PTB, 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.[27] Another meta-analysis using data from 34 observational studies (n = 57,546) evaluated differences in infant outcomes between pregnant women with HIV prescribed PI-based and non-PI ART.[28] PI-based ART was not associated with an increased risk of PTB. In subanalyses, the authors compared individual PI ARV drugs and determined that women prescribed LPV/r were more likely to experience PTB than women prescribed nelfinavir (RR 1.33; 95% CI, 1.03–1.72; I^2=0%; four studies; n = 1,937 women). Compared with women prescribed nonboosted PI-based ART, women prescribed boosted PIs were more likely to experience PTB (RR 1.36; 95% CI, 1.12–1.65; I^2=0%; five studies; n = 3,333).[28] ART that includes PIs boosted with ritonavir may be associated with an increased risk of PTB compared with nonboosted PI regimens.[29] Despite this potential association between the use of PI-based ART and PTB, some pregnant people may require PI-based regimens. In these cases, the Panel recommends the use of darunavir/ritonavir (DRV/r) over LPV/r.[30]

Nucleoside Reverse Transcriptase Inhibitor–Based Regimens and Non-Nucleoside Reverse Transcriptase Inhibitor–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 PTB (RR 0.9; 95% CI, 0.81–0.99; I^2 = 59%).[2] Some observational studies have shown an association between the use of NRTI-based regimens and PTB. When compared with women without HIV, South African women with HIV who were taking nevirapine (NVP)/emtricitabine (FTC)/TDF had higher rates of PTB (aOR 1.2; 95% CI, 1.0–1.5).[14] When compared with women without HIV, women who were taking efavirenz (EFV)/FTC/TDF were at increased risk of PTB (aOR 1.98; 95% CI, 1.12–3.53).[17] Another study of South African women who received EFV/FTC/TDF did not show an increased risk of PTB when compared with women who were on NVP-based ART or other multidrug regimens.[31]

Integrase Strand Transfer Inhibitor–Based Regimens

INSTIs are a preferred class of ARV drug for HIV treatment in pregnancy. As INSTI use increases among people with HIV, INSTI exposure during pregnancy is observed more often.[20,23,32,33] In the VESTED International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) RCT

comparing pregnant participants receiving EFV/TDF/FTC (n = 207), dolutegravir (DTG)/TDF/FTC (n = 202), and DTG/tenofovir alafenamide (TAF)/FTC (n = 208), women taking ART with EFV were more likely to experience PTB than women taking ART with DTG/TAF/FTC (12% vs. 6%; 95% CI, -11.8% to -0.9%; *P* = 0.02). The percentage of PTB was similar between DTG ART groups.[34]

Observational studies of INSTI use during pregnancy have not reported an association with an increased risk of PTB when compared with non-INSTI ART. Additionally, when compared with one another, individual INSTIs have not been associated with an increased risk of PTB. In the Tsepamo study, women who initiated EFV/FTC/TDF or DTG/FTC/TDF during pregnancy were at increased risk of PTB (aOR 1.2; 95% CI, 1.1–1.3) compared with women without HIV. However, when these regimens were compared with one another, there was no significant difference in the risk of PTB. A total of 845 women who received DTG/FTC/TDF were compared with 4,593 historical controls who received EFV/FTC/TDF, and there was no difference in the risk of PTB between these groups. Some of the historical controls were from a systematic review of six sources (two cohort studies, three databases, and one report).[16]

A large observational study of preconception ART containing DTG (n = 384) or EFV (n = 1,045) in Brazilian women did not demonstrate a difference in gestational ages at delivery; of note, 57 women in the DTG group included exposures to EFV.[35] A French case-control observational study comparing women with HIV prescribed INSTI ART (n = 246) and DRV/r ART matched by ARV backbone (n = 246) did not demonstrate any differences in PTB when ART was initiated before (16.8% vs. 16.1%) and during pregnancy (12.8% vs. 11.2%).[36] A retrospective cohort of 813 women with HIV during pregnancy did not find a significant difference in PTB between INSTI and non-INSTI groups (21% vs 16%, *P* = 0.3).[37] Another cohort study compared ART containing DTG (n = 120) to other INSTI-based regimens with either elvitegravir (EVG) (n = 159) or raltegravir (RAL) (n = 86), and the percentage of pregnant people with PTB was similar when comparing regimens (16.7% vs. 17.6% vs. 15.1%, respectively).[38] Very limited data suggest no association between the use of long-acting injectable cabotegravir in combination with rilpivirine during pregnancy and PTB.[39]

Preterm Birth and Antiretroviral Therapy Exposure Before Pregnancy

A meta-analysis of 24 observational studies (n = 38,293 pregnancies) in 15 countries reported that women initiating ART before pregnancy were at increased risk of PTB compared with women initiating ART during pregnancy (RR 1.16; 95% CI, 1.03–1.31; $I^2 = 81\%$).[6] Additional observational studies have described an association between initiating ART before pregnancy and an increased risk of PTB.[13-15,18,23,24,31,40,41] 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). A secondary analysis of 2,217 women with HIV enrolled in a RCT in Tanzania (99% were prescribed TDF/3TC/EFV) reported that women initiating ART before 20 weeks of gestation were 30% more likely to experience PTB than women initiating ART after 20 weeks of gestation (adjusted risk ratio [aRR] 1.3; 95% CI, 1.03–1.67).[42] The association between PTB and ARV drug use prior to conception is attenuated in some multivariate analyses.[9,13,23,43-45] An observational study of >2,000 women on ART did not show an association between initiation before pregnancy and PTB.[31] ART should not be withheld prior to conception or in the first trimester for the prevention of PTB.

Birth Weight

For the purpose of this section, abnormalities of birth weight related to ARV drug use are commonly reported as LBW infants or SGA infants. LBW may reflect constitutionally small infants, growth restriction, and/or preterm birth; SGA may reflect 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

In a meta-analysis of 12 studies (n = 40,495), women with HIV on ART were not more likely to deliver LBW infants than women with HIV not on ART.[5] In a systematic review of 13 studies (nine observational studies and four RCTs) that compared ZDV single-drug therapy with other ART combinations, the non-nucleoside reverse transcriptase inhibitor (NNRTI)– and PI-based regimens were more likely to be associated with an increased risk of LBW infants than a regimen of ZDV alone.[4] In a single RCT of women prescribed DTG/TAF/FTC, DTG/TDF/FTC, or EFV/TDF/FTC, 12% of infants in the EFV group were LBW compared with 10% (DTG/TDF) and 6% (DTG/TAF) of infants exposed to DTG. These percentages mirror those reported for PTB in the previous section.[34] A secondary analysis of the MOTIVATE study (a behavioral intervention study in Kenya) reported that among 1,275 women with HIV prescribed ART (74% EFV/TDF/3TC and 4% a PI-based regimen), the percentage of LBW infants was similar between women starting ART before conception and after conception (3.3% and 4.4%, respectively).[45] 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).[13] Although multiple observational studies have reported associations between *in utero* ARV drug exposure and LBW, these studies are heterogeneous in population, design, and comparison groups.[3,9,11,13,14,16,21,22,24,26,43,46-51] Given this potential association between ARV drug use and LBW, providers may consider additional monitoring for fetal growth abnormalities during pregnancy.

Small for Gestational Age

Infants exposed to HIV *in utero* may be at risk for SGA.[9,11,14-17,25,26,31,34,43,50,52,53] In a meta-analysis of five studies (n = 6,818), women prescribed ART were more likely to deliver SGA infants than women with HIV not on ART (RR 1.38; 95% CI, 1.09–1.75).[5] Another meta-analysis (34 studies), reported that women with HIV prescribed PI-based ART are more likely to deliver SGA infants than women with HIV prescribed non-PI ART (RR 1.24; 95% CI, 1.08–1.43; I^2 = 67%; 11 studies; n = 25,893).[28] In an RCT, the percentage of SGA infants was similar among women with HIV randomized to DTG-based ART (TAF or TDF/FTC) or EFV-based ART (16%, 23%, and 21%, respectively).[34]

In an observational study of birth outcomes in Botswana, Zash et al. reported a positive association between ARV drug use (for both PI-based and PI-sparing regimens) and SGA among women with HIV.[24] When compared with FTC/TDF/EFV, both NVP-based and LPV/r-based ART were associated with an increased incidence of SGA infants born to women with HIV.[24] In another observational study, women prescribed TDF/3TC/EFV before 20 weeks of gestation were less likely to deliver SGA infants than women initiating after 20 weeks of gestation (aRR 0.71; 95% CI, 0.55–0.3).[54] An observational cohort study of French women with HIV reported similar percentages

of SGA infants born to women initiating ART containing RAL before and during pregnancy (3.7% as first-line ART and 6.2% as second-line ART).[36]

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

Stillbirth

Stillbirth is a relatively rare outcome in resource-rich settings, and data related to stillbirth and ARV drug use are limited. Some studies have reported an association between HIV infection and stillbirth.[9,16,21,24,40,41,46,48,50,55,56] 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] In a meta-analysis evaluating the difference in stillbirth between PI-based and non-PI ART, data from a single study (n = 6,952) reported that PI-based ART was not associated with an increased risk of stillbirth (RR 1.04; 95% CI, 0.06–1.79).[28] In a single RCT, the percentage of stillborn infants was not significantly higher among pregnant women randomized to DTG-based ART (3.7% DTG/TAF and 5.2% DTG/TDF) than to EFV-based ART (1.9%).[34] An observational study of Brazilian women with HIV reported similar percentages of stillborn infants in women prescribed ART with DTG compared with EFV (1% in both groups).[35] A secondary analysis of data collected from Kenyan women with HIV enrolled in an RCT reported that 4.4% (34 of 774) experienced a stillbirth. Most women on ART (n = 723) were prescribed TDF+3TC/FTC+EFV (535 or 74%). The differences in the percentages of stillbirths were not statistically significant between TDF-based (2.3%) and ZDV-based (0%) ART nor between EFV-based (2.8%) and NVP-based (0%) ART.[57]

Data regarding the timing of ART initiation and stillbirth are mixed, but timing of ART initiation is likely not a factor associated with an increased risk of stillbirth. Among women with HIV who delivered in the United Kingdom and Ireland between 2007 and 2015 (n = 10,434), preconception ARV drug use was not associated with an increased risk of stillbirth.[56] Women with HIV who delivered in Malawi from 2012 to 2015, 71% of whom were on ART preconception or during the first trimester, did not experience higher rates of stillbirth than the general population (2.5%, n = 8,380).[58] An observational study of 1,275 pregnant women with HIV in Kenya (2015–2019) demonstrated that women taking ART before conception had a similar incidence of stillbirth (2.7%) when compared with women taking ART after conception (2%). Most women in this cohort were prescribed TDF/3TC/EFV (71%), and only 4% were prescribed PI-based ART.[45] Another study of Kenyan women (n = 724), most of whom were prescribed TDF+3TC/FTC+EFV, reported that preconception ART use was not associated with an increased risk of stillbirth (1.3%, n = 425) compared with women starting ART after conception (2.9%, n = 346).[57] In contrast, an observational study 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).[24] In a case-control study of a longitudinal cohort of French women with HIV (n = 808), the incidence of stillbirth was not significantly different between pregnant women receiving INSTI-based ART with RAL, EVG, or DTG and those receiving DRV-based ART. In women receiving a RAL-based regimen, stillbirths did not differ based on timing of ART exposure (2.3% at conception vs. 1.1% during pregnancy).[36]

Outcomes During Pregnancy

Hypertensive Disorders of Pregnancy

Limited data suggest that women with HIV may have an increased risk of HDP. A meta-analysis did not reveal a clear association between HIV and HDP.[59] Observational data evaluating differences in HDP among people with and without HIV are conflicting. An observational Italian study reported that women with HIV were more likely than women without HIV to be diagnosed with early-onset (before 34 weeks of gestation) and late-onset (after 34 weeks of gestation) preeclampsia (aOR 2.50; 95% CI, 1.51–4.15 and aOR 2.64; 95% CI, 1.82–3.85, respectively), as well as preeclampsia with severe features (aOR 2.03; 95% CI, 1.26–3.28).[60] A secondary analysis of observational data from South Africa reported that women with HIV with low CD4 counts (<200 cells/mm^3) on ART had an increased risk of maternal death from HDP compared with women with HIV and low CD4 counts who were not on ART during pregnancy (RR 1.15; 95% CI, 1.02–1.29).[61] Among these women, those on ART before pregnancy and those who were not on ART before pregnancy had similar rates of HDP (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).[40] In a South African observational cohort study (2013–2015) of women with and without HIV (n = 1,116), women with HIV were more likely to have hypertension at the first antenatal visit (adjusted relative risk 2.37; 95% CI, 1.29–4.35). Nearly half of all women in this cohort were obese (44% without HIV and 36% with HIV).[62] Most women with HIV initiated ART at the first antenatal visit (73%), and the ART prescribed was TDF/3TC/EFV or TDF/FTC/EFV. Hypertension at the initial antenatal visit did not indicate increased risk of adverse pregnancy outcomes, regardless of HIV status.[63] A subsequent large South African cohort (2018–2019) compared people without HIV (n = 146,575) and with HIV (n = 33,978), as well as those with HIV taking ART (n = 30,151) and not taking ART (n = 3,827). ART use initiated before or during pregnancy was not associated with an increased risk of HDP.[64] A small U.S. observational study demonstrated that women with HIV (n = 85) were not more likely to experience HDP than women without HIV (n = 3,556). The authors observed higher rates of HDP among women on INSTIs (25%, n = 23) and NNRTIs (24%, n = 7) than among women on PI-based ART (10%, n = 55). Preconception ARV drug use was associated with an increased risk of HDP.[33] In another retrospective study from the same academic center, INSTI use during pregnancy was associated with an increased risk of HDP compared with non-INSTI regimens (INSTI/TAF, 21%, n = 38; INSTI/TDF, 20%, n = 39; non-INSTI regimens, 7%, n = 214; TDF-exposed, 11%, n = 149).[65]

Although these limited data may suggest an association between HDP and HIV, and data varies regarding the association between ART and HDP, no known interventions reduce this risk. Providers should not withhold ART in the setting of HDP. Some pregnant people may benefit from low-dose aspirin to prevent or delay the onset of preeclampsia. For more information, please refer to U.S. Preventive Services Task Force recommendations.[66,67]

Summary

Clinicians should be aware of a possible increased risk of adverse outcomes for the birthing parent and neonate with the use of ARV drugs during pregnancy for prevention of perinatal HIV infection. Given that ART has clear benefits for the health of pregnant people and reduces the risk of perinatal HIV transmission, these agents should not be withheld because of concern for increased risk of adverse neonatal outcomes. Clinicians should monitor pregnant people with HIV for potential pregnancy complications, including PTB, LBW infants, and SGA infants.

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Special Populations: Hepatitis B Virus/HIV Coinfection

Updated: January 31, 2024
Reviewed: January 31, 2024

Panel's Recommendations
• All pregnant people with HIV should be screened during each pregnancy for hepatitis B virus (HBV) infection unless they are already known to have HBV/HIV coinfection or have serologic documentation of HBV immunity (AIII). • All pregnant people 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). • All pregnant people 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 immunoglobulin G [IgG] or total antibody [IgG and immunoglobulin M]), they should receive the HAV vaccine series (AIII). • After delivery, people with HBV/HIV coinfection should continue antiretroviral regimens that include drugs with anti-HBV activity: tenofovir disoproxil fumarate or tenofovir alafenamide plus lamivudine or emtricitabine (AII). • Pregnant people with HBV/HIV coinfection who are receiving antiretroviral therapy (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). • For pregnant people with HBV/HIV coinfection who discontinue medications with anti-HBV activity, frequent monitoring of liver function tests for potential exacerbation of HBV infection is recommended, with prompt reinitiation of treatment for HBV when a flare is suspected (BIII). • HBV/HIV coinfection is not an independent indication for cesarean delivery (see Intrapartum Care for People with HIV) (AIII). • Infants born to people with HBV should receive hepatitis B immune globulin and the first dose of the HBV vaccine series as soon as possible and within 12 hours of birth (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*

The management of hepatitis B virus (HBV)/HIV coinfection in pregnancy is complex, and consultation with an expert in HIV and HBV coinfection is strongly recommended. For additional information on HBV and HIV, see Hepatitis B Virus/HIV Coinfection in the Adult and Adolescent Antiretroviral Guidelines, Hepatitis B Virus Infection in the Adult and Adolescent Opportunistic Infection Guidelines, and Hepatitis B Virus in Guidelines for the Prevention and Treatment of Opportunistic Infections in Children with and Exposed to HIV.

Screening and Vaccination

Everyone with HIV should be screened for HBV at entry into general HIV care. For guidance on screening for hepatitis C virus (HCV), see Hepatitis C Virus/HIV Coinfection. All pregnant people with HIV should be screened for HBV during each pregnancy unless they are known to have HBV/HIV coinfection or to have serologic documentation of HBV immunity. Screening for HBV should include hepatitis B surface antigen (HBsAg), hepatitis B core antibody (anti-HBc or HBcAb), and hepatitis B surface antibody (anti-HBs or HBsAb). People who test positive for HBsAg should

have follow-up testing to evaluate liver function; prothrombin time; and levels of HBV DNA, hepatitis B e antigen (HBeAg), and hepatitis B e antibody (HBeAb).[1]

To prevent transmission of HIV and HBV from people 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 sex partner with undetectable HIV (Undetectable = Untransmittable or U=U) in preventing HIV transmission. For information on testing and prevention of HIV transmission to sex partners, see Reproductive Options for Couples When One or Both Partners Have HIV and the Let's Stop HIV Together resources from the Centers for Disease Control and Prevention (CDC).[2,3] For more information specifically about preventing HIV and 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 people 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.[4] People with HIV who have remote HBV infection and who have only 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] Assessment of anti-HBs titers 1 to 2 months after the vaccine series and management of nonresponders should be conducted in pregnant people with HIV/HBV coinfection in the same way as recommended for nonpregnant people with HIV/HBV coinfection; see Hepatitis B Virus Infection in the Adult and Adolescent Opportunistic Infection Guidelines.[1] 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 people with HIV.[4-6] Although the two-dose Heplisav-B is an alternative vaccine for nonpregnant people to prevent HBV, available data on its use in pregnancy are insufficient to inform vaccine-associated risks in pregnancy.[7,8]

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) (see the Hepatitis B Virus Infection section of the Adult and Adolescent Opportunistic Infection Guidelines).[9,10] Incidence of HBV viremia with the isolated anti-HBc pattern ranges from 1% to 36% in patients with HIV, depending on the population sampled.[1,11,12] The clinical significance of isolated anti-HBc is unknown. Most people with HIV with isolated anti-HBc are HBV DNA–negative and not immune to HBV infection; therefore, they would benefit from HBV vaccination (see below). While routinely checking HBV DNA is currently not recommended in non-pregnant adults with isolated anti-HBc (see the Hepatitis B Virus Infection section of the Adult and Adolescent Opportunistic Infection Guidelines), it may be considered in pregnancy.[13] If pregnant people with isolated anti-HBc are found to have HBV viremia, their ART should be adjusted to assure control of both HBV and HIV. Pregnant people 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] However, people with isolated anti-HBc and negative or unknown HBV DNA 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[14] (See the Hepatitis B Virus Infection section of the Adult and Adolescent Opportunistic Infection Guidelines).[1]

Pregnant people 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. Pregnant people 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 persons with HIV who have CD4 T lymphocyte (CD4) cell counts <200 cells/mm^3. Antibody response should be assessed in such persons 1 month after the HAV vaccine series is complete. If HAV antibody immunoglobulin (HAV Ab IgG) is negative,[1] these persons should be revaccinated when the CD4 count is >200 cells/mm^3. Pregnant people who received the HAV vaccine series when their CD4 count was ≥200 cells/mm^3 do not need to be revaccinated for HAV because they are likely protected (even if their HAV IgG levels are undetectable using commercially available assays). Although the safety of HAV vaccination during pregnancy has not been directly evaluated, the HAV vaccine contains inactivated HAV, and the theoretical risk to the developing fetus is expected to be low.[16]

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.[17] HBV/HIV coinfection was not associated with preterm delivery, lower CD4 counts, or detectable HIV viral load in this cohort.[17] In a retrospective multivariable analysis of response to antiretroviral therapy (ART) in 1,462 pregnancies among Italian women with HIV in which 12% of the women had HBV/HIV coinfection, women with only HIV had better CD4 responses on ART during pregnancy than women with HBV/HIV coinfection.[18] However, no differences in maternal and infant outcomes were observed between women with HBV/HIV coinfection and women with only HIV.

Therapy for HIV and HBV in Pregnancy

An antiretroviral (ARV) regimen that includes drugs that are active against both HIV and HBV is recommended and should be offered to all individuals with HBV/HIV coinfection, including all pregnant people (see Hepatitis B Virus Infection in the Adult and Adolescent Opportunistic Infection Guidelines). Initiation of ART may be associated with activation of HBV and development of immune reconstitution inflammatory syndrome, particularly in persons with high HBV DNA levels and severe liver disease.[1,19]

The use of an ART regimen with anti-HBV activity during pregnancy in people with HBV mono-infection lowers HBV viremia and lowers the risk of HBV transmission to the infant. All pregnant people with HIV/HBV coinfection should be receiving an ART regimen that includes tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF), and either lamivudine (3TC) or emtricitabine (FTC), which will reduce HBV viremia and thus lower the risk of HBV transmission to the infant.[1,20] All these drugs are *Preferred* nucleoside and nucleotide reverse transcriptase inhibitors for use during pregnancy (see Table 6. What to Start: Initial Antiretroviral Regimens During Pregnancy for People Who Are Antiretroviral-Naive). Please see individual drug sections for TDF, TAF, FTC, and 3TC for detailed reviews of safety, pharmacologic properties, and other clinical data informing use in pregnancy.

In addition to treatment with an ART regimen containing two ARVs that have anti-HBV activity, treatment of symptomatic acute HBV infection during pregnancy should be supportive, with special attention given to maintaining blood glucose levels and normal clotting status. Risk of preterm labor and delivery may increase with acute HBV infection. High maternal HBV DNA levels are strongly correlated with perinatal HBV transmission and with failures of HBV passive-active immunoprophylaxis.[1,21-24]

Consultation with an expert in HIV and HBV is strongly recommended when providing care for pregnant people with HBV/HIV coinfection who continue to have detectable HBV DNA viremia despite receiving an ARV regimen that includes two anti-HBV nucleotide or nucleoside analogues.

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 people with HBV/HIV coinfection.[25]

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 pregnancy because of their direct antigrowth and antiproliferative effects.[26]

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 People 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 pregnant people 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. Pregnant people with HBV/HIV coinfection should be counseled about the 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.

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, and then every 3 to 6 months thereafter, with prompt reinitiation of HBV treatment if a flare is suspected.[1]

Mode of Delivery

Decisions concerning mode of delivery of the infant in a pregnant person with HBV/HIV coinfection should be based on standard obstetric and HIV-related indications alone (see Intrapartum Care for People with HIV). Currently, the guidelines for management of pregnancy with HBV mono-infection do not recommend performing a cesarean delivery to prevent perinatal transmission of HBV.[27-29]

Evaluating and Managing Infants Who Were Exposed to HBV

All infants born to people with HBV infection, including those with HBV/HIV coinfection, should receive hepatitis B immune globulin (HBIG) and the first dose of the HBV vaccination series to prevent perinatal transmission of HBV as soon as possible and within 12 hours of birth. For infants weighing ≥2 kg at birth, the second and final doses of the vaccine series should be administered at age 1 to 2 months and 6 months, respectively. For infants with birth weights <2 kg, 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.[30,31] This regimen is >95% effective in preventing HBV infection in these infants. Maternal ART that includes nucleoside analogues 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 people with HBV/HIV coinfection.[32,33]

Infant post-vaccination 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 revaccination should receive two additional doses of HBV vaccine to complete the second series, followed by postvaccination serologic testing at 1 to 2 months after the final dose.[34]

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Special Populations: Hepatitis C Virus/HIV Coinfection

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Panel's Recommendations

• All pregnant people with HIV should be screened during the current pregnancy for hepatitis C virus (HCV) infection, ideally at the initial prenatal visit (AIII).
  o HCV antibody testing, with confirmatory HCV RNA polymerase chain reaction testing if the antibody test is positive, is recommended for screening (AI).
  o HCV screening could be repeated later in pregnancy in people 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).
• For people who are known to be HCV antibody-positive, HCV RNA and liver function tests should be checked at initiation of prenatal care to assess risk of HCV perinatal transmission and severity of liver disease (AIII).
• Pregnant people, including those with HIV/HCV coinfection, should be tested for hepatitis B surface antigen during each pregnancy, preferably in the first trimester, even if vaccinated or tested previously. If they are negative and lack evidence of immunity, they should receive the hepatitis B virus vaccine series (see Hepatitis B Virus/HIV Coinfection) (AIII).
• Pregnant people 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 immunoglobulin G [IgG] or total antibody [IgG and immunoglobulin M]), they should receive the HAV vaccine series (AIII).
• 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 agents in people who are pregnant. If considering initiating HCV treatment in a pregnant person with HCV/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 pregnant people with HIV, including those who have HCV coinfection (AIII).
• Pregnant people 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).
• HCV treatment with direct-acting antiviral agents should be recommended and offered for people with HCV postpartum (AI).
• In people with HCV infection, 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).
• HCV/HIV coinfection is not an independent indication for cesarean delivery (see Intrapartum Care for People with HIV) (AIII).
• Infants born to people 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 hepatitis C virus (HCV)/HIV coinfection in pregnancy is complex, and none of the approved HCV direct-acting antivirals (DAAs) have been evaluated fully for use in people who are pregnant; thus, consultation with an expert in HIV and HCV infection **is strongly recommended** when managing HCV during pregnancy.

For additional information on 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 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

All pregnant people with HIV should be screened for HCV infection at entry into general HIV care and during each pregnancy, ideally at initiation of prenatal care. For individuals who are known to be HCV antibody–positive, HCV RNA and liver function tests should be checked at initiation of prenatal care to assess risk of perinatal transmission of HCV and severity of liver disease. Consultation with an expert is recommended for follow-up testing and/or referral for treatment postpartum, as appropriate.

The primary reasons for HCV testing during pregnancy are—

- To identify pregnant people 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). (If a trial of HCV treatment during pregnancy is available, voluntary enrollment should be offered.)
- To monitor for HCV-related hepatotoxicity, which has been associated with the use of antiretroviral (ARV) drugs in women with HCV/HIV coinfection.[1]
- To monitor for preterm birth, which has been associated with HCV/HIV coinfection in pregnant women.[2-5]
- To ensure appropriate follow-up and evaluation of infants who were exposed to HCV.

The observed prevalence for HCV infection was 2% to 12% in European cohorts of pregnant women with HIV[4] and 3.8% among women with HIV in New York State.[6] 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.[5,7-14]

The Society for Maternal-Fetal Medicine and the American College of Obstetricians and Gynecologists recommend repeating HCV testing later in pregnancy for individuals 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).[15] The partners of all people 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 transmitted infrequently 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 Prepregnancy Counseling and Care for Persons of Childbearing Age with HIV).

Available DAAs have improved HCV therapy dramatically; it is now possible to cure HCV infection in most patients.[16] Current HCV treatment guidelines recommend therapy for nearly all patients with HCV infection. However, the management of HCV/HIV coinfection during pregnancy is complex. A Phase 1 study evaluated the safety and pharmacokinetics (PKs) of sofosbuvir/ledipasvir in pregnancy.[17] Safety data of DAAs in pregnancy are still limited. Ribavirin, although it is no longer commonly used for the treatment of HCV, is contraindicated in pregnancy.[18] If considering HCV treatment for a pregnant person, consultation with an expert in HIV and HCV is strongly recommended.

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 people in the United States should be screened for HCV at each pregnancy, except in settings where the prevalence of HCV infection is <0.1%.[19,20] 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.[21,22] Individuals who have a positive HCV antibody test should undergo confirmatory testing with a quantitative plasma HCV RNA assay. Many laboratories now perform reflex RNA testing for individuals who test positive for HCV antibodies. Pregnant people also should 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).[23] At the initial prenatal visit, pregnant people who are known to be HCV antibody–positive should have a quantitative plasma HCV RNA assay and liver function tests performed to assess the risk of transmission of HCV to the infant and severity of liver disease.[16]

Because of the added risk of hepatic decompensation from acute infection with any viral hepatitis, people with HCV infection also should be screened for both hepatitis A virus (HAV) and hepatitis B virus (HBV). People with chronic HCV infection who have not already received the HAV vaccine series should be screened for immunity to HAV (either immunoglobulin G [IgG] alone or IgG and immunoglobulin M together). If they screen negative for HAV antibodies, they should receive the HAV vaccine series. Antibody responses to the HAV vaccine should be assessed 1 month after vaccination is complete. If anti-HAV IgG is negative, people should be revaccinated[24] when the CD4 T lymphocyte (CD4) cell count is >200 cells/mm^3. People with HCV/HIV coinfection who screen negative for HBV and lack HBV immunity (i.e., they are hepatitis B surface antigen negative, hepatitis B core antibody negative, and hepatitis B surface antibody [HBsAb] negative) should receive the appropriate HBV vaccine series. People with HCV/HIV coinfection who are HBsAb negative despite receiving the HBV vaccine series may benefit from revaccination (see Hepatitis B Virus/HIV Coinfection).[25]

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

Although the HCV viral load tends to rise in the third trimester, pregnancy does not appear to influence the course of HCV infection clinically. People with chronic HCV generally do well during pregnancy, provided that they have not progressed to decompensated cirrhosis.[26,27]

HCV Transmission to the Infant

About 6% of infants born to women with HCV acquire HCV infection.[22] 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 (7% to 20% transmission risk) than among women with HCV mono-infection.[28-32] The 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.[3,33,34] Early and sustained control of HIV viremia with antiretroviral therapy (ART), however, could reduce the risk of HCV transmission to infants.[27,35-37] A European study of perinatal HCV transmission found that the use of effective ART for HIV was associated with a trend toward reduced rates of HCV transmission (odds ratio [OR] 0.26; 95% confidence interval [CI], 0.07–1.01).[35] In an Italian cohort, [3] 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. In a re-analysis of data from three prospective European cohorts conducted between 1994 and 2004, HCV transmission rates were estimated as about 24% higher than previously thought, but rates of spontaneous HCV clearance in the children were also higher, resulting in clearance–net transmission rates of 2.4% (1.1% to 4.1%) in women with HCV mono-infection and 4.1% (1.7% to 7.3%) in women with HIV/HCV coinfection.[38]

HIV Transmission to the Infant

In the absence of ART, maternal HCV/HIV coinfection can increase the risk of perinatal HIV transmission.[39,40] The risk of perinatal HIV transmission can be reduced in pregnant people with HCV/HIV coinfection by following the standard recommendations for ART that are in place for all people with HIV.

Impact of HCV on HIV Management

Data are limited on the optimal management of pregnant people with HCV/HIV coinfection. Recommendations on the use of ART during pregnancy for treating HIV and preventing perinatal HIV transmission are the same for people with HCV/HIV coinfection as for those with HIV mono-infection (see Antepartum Care of Individuals with HIV). In one Canadian study, HCV/HIV coinfection was associated with an increased risk of HIV viral load increases near delivery among women who were on previously effective ART. Although the authors suggest that additional factors (e.g., adherence) may have played a role, these findings support the need to follow recommendations for HIV RNA monitoring during pregnancy.[41]

HCV-Specific Therapy in Pregnancy

Several DAA regimens have been approved for the treatment of HCV. At present, all currently available DAAs lack sufficient safety data to be recommended for use during pregnancy, but general considerations for treatment are presented in this section.

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:

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

In the past, most anti-HCV therapy regimens 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.[42] Pegylated interferon is now used rarely for treatment of HCV. DAA regimens with ribavirin are indicated for certain patient populations. Any treatment regimens that include ribavirin are **contraindicated** for use during pregnancy 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 also applies to pregnancies of partners of men taking ribavirin.[16]

DAAs are not yet recommended for use in pregnancy because of the lack of PK and safety data; one small PK study investigating the use of sofosbuvir/ledipasvir in eight pregnant women with HCV alone demonstrated 100% virologic suppression and no safety concerns.[17] This open-label, Phase 1 study of sofosbuvir/ledipasvir started between 23 and 24 weeks' gestation in eight women with genotype 1 HCV infection showed that ledipasvir and sofosbuvir exposures were similar in the pregnant women and the nonpregnant reference group and the drug combination was safe.[17] Similarly, a small case series of 15 pregnant women treated with sofosbuvir/ledipasvir reported 100% virologic suppression at 12 weeks and no early safety concerns in the women or their infants.[43] An open-label, Phase 1 study of the pharmacokinetics of sofosbuvir/velpatasvir started between 23 and 25 weeks' gestation reported results in 11 HIV-negative pregnant women with chronic HCV infection. All 10 participants that completed treatment had undetectable HCV RNA at delivery, and all the infants that followed up (n = 7) had undetectable HCV RNA. Nine mothers experienced adverse events related to sofosbuvir/velpatasvir; however, only one adverse event was greater than grade 2 (vomiting) and resulted in discontinuation of sofosbuvir/velpatasvir.[44] A multicenter study (NCT05140941) to evaluate sofosbuvir/velpatasvir safety and efficacy in pregnancy is underway. Another small case series reported results of two pregnant women and one child with severe chronic HCV started on a 12-week course of sofosbuvir/ledipasvir initiated at 31 weeks' gestation, sofosbuvir/velpatasvir initiated at 26 weeks' gestation, and sofosbuvir/ledipasvir initiated at 1.2 years of life, respectively. All three patients were safely cured of HCV with favorable tolerance, and the two newborns were breastfeeding and consistently negative for anti-HCV antibody during the 1-year follow-up after birth.[45]

Pregnant people with HCV/HIV coinfection should be started on HCV treatment with DAAs postpartum.[16] Drug interactions exist between the DAA 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 People with HCV/HIV Coinfection During Pregnancy

Hepatic enzyme levels can increase after ART is initiated in people 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 mono-infection may increase the risk of intrahepatic cholestasis of pregnancy[46]; this risk also is higher among people with HCV/HIV coinfection than among individuals with HIV infection alone.[4] Pregnant patients 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.[47] Spontaneous clearance of HCV can occur postpartum.[47-50] As a result, the AASLD and the IDSA recommend that women have their HCV RNA reevaluated after delivery, particularly if they are being assessed for initiation of therapy with DAA.[16]

Rates of preterm delivery are high among individuals 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). However, women with preterm delivery had significantly higher levels of HCV RNA than those who delivered at term.[3] 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.[4] A study of 339 HIV/HCV coinfected pregnant women from Spain demonstrated a 50% rate of preterm delivery.[32]

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%, $P < 0.01$).[5]

HCV infection in pregnancy may be associated with increased risks for gestational diabetes, small-for-gestational-age infants, and low birth weight infants.[9,51] Although no obstetric guidelines currently suggest that persons with HCV infection should be monitored more frequently for diabetes, preterm birth, or fetal growth during pregnancy,[52] knowledge of these increased risks may inform clinical care.[15]

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.[35,53-55] Thus, the general recommendations for mode of delivery are the same for people with HCV/HIV coinfection as for those with HIV infection alone (see Intrapartum Care for People with HIV).

Evaluation of Infants Exposed to HCV

Infants born to people 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.[56] Sensitivity of HCV RNA testing is low at birth, and viremia can be intermittent or

infection may resolve spontaneously[9,38,57,58]; 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.[59] Rate of HCV testing is very low for infants who were exposed to HCV[60]; therefore, it is important for providers to counsel patients about the need for pediatric follow-up and testing during the first few years of life.[5,61-64] The Pediatric Opportunistic Infection Guidelines and these new CDC Guidelines provide further details about the diagnostic evaluation of infants who were exposed to HCV.

Transmission of HCV to the infant is not increased with breastfeeding.[65] For guidance about infant feeding for people with HIV, see Infant Feeding for Individuals with HIV in the United States.

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HIV-2 Infection and Pregnancy

Updated: January 31, 2024
Reviewed: January 31, 2024

Panel's Recommendations
• HIV-2 infection should be considered in pregnant people 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 people with HIV-2 infection should be treated based on the guidelines for HIV-1 infection but using antiretroviral (ARV) drugs that are active against HIV-2. Non-nucleoside reverse transcriptase inhibitors, enfuvirtide, and fostemsavir 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 people with HIV-2 infection (AIII).
• Dolutegravir, bictegravir, raltegravir, or darunavir/ritonavir plus a dual-NRTI backbone of abacavir plus lamivudine (3TC), or tenofovir disoproxil fumarate or tenofovir alafenamide plus emtricitabine or 3TC, are recommended for treating HIV-2 - infection alone in pregnant people and in people who are trying to conceive (AIII). Zidovudine (ZDV) plus 3TC can be used as an alternative dual-NRTI backbone. See Recommendations for Use of Antiretroviral Drugs During Pregnancy and Appendix C: Antiretroviral Counseling Guide for Health Care Providers.
• If a pregnant individual is already receiving antiretroviral therapy with drugs that are active against HIV-2, treatment should be continued (AIII).
• 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 people with HIV-2 infection (without HIV-1 infection) should receive a 4-week ZDV prophylactic regimen (BIII) (see Table 10. Neonatal Antiretroviral Management According to Risk of HIV Infection in the Newborn and Table 11. Antiretroviral Drug Dosing Recommendations for Newborns).
• People with HIV-2 infection should receive patient-centered, evidence-based counseling to support shared decision-making about infant feeding options prior to and during pregnancy; counseling and plans for infant feeding should be reviewed again after delivery (AIII) (see Infant Feeding for Individuals with HIV in the United States).
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 Burkina Faso, Cape Verde, The Gambia, Ghana, Guinea, Guinea-Bissau, Ivory Coast, Liberia, Mali, Mauritania, Niger, Nigeria, Sao Tome, Senegal, Sierra Leone, and Togo. It is also endemic in Angola, Mozambique, and parts of India.[1-4] It also occurs in countries that have large numbers of immigrants from these regions, such as France and Portugal.[5]

HIV-2 remains rare in the United States. According to the National HIV Surveillance System, 327,700 diagnoses of HIV were recorded in the United States from 2010 to 2017, of which 198 (0.06%) met the criteria for HIV-2 (HIV-2 infection alone, 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 9 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 people 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 person 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 this 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, Bio-Rad 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 U.S. 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. Drug resistance against HIV-2 can be determined using the HIV-2 EU resistance tool, and another French resistance tool.[11,12]

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.[13] The most common mode of HIV-2 transmission is through sex. HIV-2 is less infectious than HIV-1, with a fivefold lower rate of sexual transmission and 20-fold to 30-fold lower rate of perinatal transmission.[3,14,15] 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, higher CD4 T lymphocyte (CD4) cell counts, and less cervical viral shedding in women with HIV-2 infection than in women with HIV-1 infection.[16-19] In a meta-analysis comparing perinatal transmission of HIV-1 and HIV-2, the pooled incidence of HIV-2 perinatal transmission was 0.2% (95% confidence interval [CI], 0.03% to 1.47%) among antiretroviral-naive pregnant women.[20]

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 infection alone—can occur.[21]

Recommended Antiretroviral Therapy for Pregnant People with HIV-2 Infection

Pregnant people with HIV-2 infection should be treated according to the guidelines for patients with HIV-1 infection alone, although 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.[22] Non-nucleoside reverse transcriptase inhibitors (NNRTIs), enfuvirtide, and fostemsavir are not active against HIV-2 and **should not be used** for treatment or prophylaxis.[23,24] The integrase strand transfer inhibitors (INSTIs) raltegravir (RAL), elvitegravir, dolutegravir (DTG), bictegravir (BIC), and cabotegravir (CAB) are effective against HIV-2.[25,26] Although DTG may be able to rescue a failing RAL-based regimen in a person with HIV-2 infection, a study has reported the emergence of DTG-resistance mutations in people with HIV-2 infection.[27] The CCR5 antagonist maraviroc appears to be active against some strains of HIV-2, although no approved assays exist to determine HIV-2 co-receptor tropism.[28,29] HIV-2 drug resistance has been documented with various ARV drugs.[30,31] Among 47 ART-naive people 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% CI, 0.0% to 16.5%). No RAM above the 20% detection threshold was found for protease inhibitors (PIs) or INSTIs.[32] For patients with multidrug-resistant virus, ibalizumab and lenacapavir demonstrate *in vitro* potency against HIV-2 and may be considered; these drugs are not recommended except in special circumstances for use in pregnancy.

HIV-2 has variable susceptibility to PIs, with lopinavir (LPV) and darunavir (DRV) having the most activity.[33]

The care of pregnant people with HIV-2 infection alone 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 people with HIV-2 infection. 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 people with HIV-1 infection:

- DTG, BIC, RAL, or darunavir/ritonavir plus a dual-NRTI backbone of abacavir plus lamivudine (3TC), or tenofovir disoproxil fumarate or tenofovir alafenamide plus emtricitabine or 3TC are the recommended regimens for treating HIV-2 infection alone in pregnant people and people who are trying to conceive. See Recommendations for the Use of Antiretroviral Drugs During Pregnancy: Overview, Table 6. What to Start: Initial Antiretroviral Regimens During Pregnancy for People Who Are Antiretroviral-Naive, Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs in Pregnant People and Nonpregnant People Who Are Trying to Conceive, and Appendix C: Antiretroviral Counseling Guide for Health Care Providers.[34]
- 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.

If a pregnant individual is already receiving ART with drugs that are active against HIV-2, treatment should be continued.

When monitoring the plasma viral loads and CD4 counts in pregnant people with HIV-2 infection, clinicians should follow the guidelines outlined for people with HIV-1 infection (see Initial Evaluation and Continued Monitoring of HIV-Related Assessments 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).

No data are available to address whether treatment should be continued after pregnancy in people with HIV-2 infection alone. To date, no randomized trials have addressed the question of an optimal treatment strategy for HIV-2 infection. The Adult and Adolescent Antiretroviral Guidelines recommend that all patients with HIV-2 infection should be treated using the guidelines provided for patients with HIV-1 infection, see HIV-2 Infection.

All infants born to people with HIV-2 who do not have HIV-1 should receive a 4-week ZDV prophylaxis regimen (see Table 10. Neonatal Antiretroviral Management According to Risk of HIV Infection in the Newborn and Table 11. Antiretroviral Drug Dosing Recommendations for Newborns). The possible risks and benefits of ARV prophylaxis should be discussed with the birthing parents. As noted above, rates of perinatal transmission of HIV-2 are low with and without interventions, and it is unclear whether infants born to people with undetectable HIV-2 viral loads will benefit from ARV prophylaxis. However, monitoring HIV-2 plasma viral loads in birthing parents and receiving the results in a timely manner can be difficult because plasma samples must be sent to the University of Washington or the New York State Department of Health. Therefore, the Panel on Treatment of HIV During Pregnancy and Interventions to Prevent Perinatal HIV Transmission recommends that all infants born to pregnant people with HIV-2 receive prophylaxis. ZDV prophylaxis is recommended in this clinical situation because nevirapine lacks activity against HIV-2. Guidance on ARV prophylaxis for infants born to individuals with HIV-1 and HIV-2 infection is available in Table 10. Neonatal Antiretroviral Management According to Risk of HIV Infection in the Newborn and Table 11. Antiretroviral Drug Dosing Recommendations for Newborns.

No data exist 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 the risk is not zero.[17] Individuals with HIV-2 infection should receive patient-centered, evidence-based counseling to support shared decision-making about infant feeding. Counseling about infant feeding should begin prior to conception or as early as possible in pregnancy; information about and plans for infant feeding should be reviewed throughout pregnancy and again after delivery (see Infant Feeding for Individuals with HIV in the United States).

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.[35] 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) also can 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 People with Perinatally Acquired HIV Infection

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Panel's Recommendations
• The management of prenatal care and general principles of antiretroviral therapy (ART) and HIV management do not differ between pregnant people with perinatally acquired HIV (PHIV) and those with non–perinatally acquired HIV (AII). • People with PHIV are likely to have extensive ART experience and may have multidrug antiretroviral (ARV) resistance when entering pregnancy because of their lifelong duration of HIV and prior issues with ART adherence. Consultation with experts in HIV and pregnancy is recommended when the presence of extensive drug resistance warrants the use of ARV drugs for which there is limited experience in pregnancy (AIII). • Pregnant people 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 people with HIV, including those with perinatally acquired HIV (PHIV). Most people with PHIV in the United States 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 people with PHIV and those with non–perinatally acquired HIV (NPHIV), who acquired HIV through other routes of transmission. However, the prevention of perinatal transmission can pose unique challenges for people with PHIV related to their experiences living with HIV and using antiretrovirals (ARVs) since birth. Adherence to ART is often a major challenge for people with PHIV.

Considering most people with PHIV have extensive ART experience, optimal ARV regimens should be selected using the same guiding principles as for ART-experienced adults. In particular, the ARV regimen should be selected on the basis of resistance testing, pill burden, and the patient's specific ART history and preferences. Because people who acquired HIV perinatally may be more likely to have developed complex drug-resistance mutation patterns, clinicians may consider performing phenotypic resistance testing, in addition to genotypic resistance testing, when resistance testing is indicated during pregnancy. Regimens that can be given once daily and that minimize pill burden are preferred. Regimens should be constructed using ARV drugs that are recommended for use in pregnancy whenever possible (see Recommendations for the Use of Antiretroviral Drugs During Pregnancy: Overview and Table 7: Situation-Specific Recommendations for Use of Antiretroviral Drugs in Pregnant People and Nonpregnant People Who Are Trying to Conceive. 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.

People with PHIV experience lifelong HIV infection, have received multiple ARV regimens, 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.[4-7] 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.[5,7-12] 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%); however, this higher rate was associated with a greater likelihood of detectable maternal viral load at delivery.[13] Historically, women with PHIV have been more likely to have detectable viral loads at delivery, lower CD4 T lymphocyte cell counts, and genotypic drug resistance than women with NPHIV; these factors can have implications during labor and delivery.[7,13-16] Several studies have suggested that pregnant women with PHIV are more likely to have a cesarean delivery to prevent HIV transmission; cesarean deliveries are most commonly indicated in these women due to a lack of viral load suppression.[4,10] Cesarean delivery in people with PHIV raises concerns for increased risk of adverse obstetric outcomes if repeated cesarean deliveries are required for future pregnancies.

Evidence is conflicting as to whether women with PHIV have higher rates of preterm birth and small-for-gestational-age (SGA) infants than women with NPHIV.[17,18] In one cohort, there was a fourfold increased risk for SGA births among women with PHIV, compared with those with NPHIV.[19] In another study, infants born to women with PHIV were born at an earlier gestational age and had lower average birth weights, compared with infants born to women with NPHIV.[10] In contrast, other studies have demonstrated no associations between maternal PHIV and preterm birth, SGA infants, or low birth weight.[18,20]

A retrospective cohort study reported poor rates of retention in care and low rates of viral suppression for up to 2 years postpartum among 22 pregnant women with PHIV.[21] In a retrospective analysis[10] 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 of women with NPHIV. 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.[10] Although genotypic drug-resistance 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 related to lifelong HIV may be magnified by high rates of depression and, frequently, the loss of one or both parents.[22] Attention to developmentally appropriate adherence counseling is critical. A systematic review and meta-analysis of 50 eligible studies on ART adherence in young people with HIV who were aged 12 to 24 years reported 62.3% adherence overall. Youth from U.S. studies had the lowest average rate of adherence at 53%.[23] 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.[24] A history of depression also has been associated with nonadherence to ART among pregnant women with PHIV.[25,26] Attention to 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.[27]

Rates of retention in care and viral suppression are lower among pediatric and adolescent patients with HIV who are transitioning to adult health care than in adults with HIV who are already in

care.[28,29] Among adolescents with PHIV, pregnancy may create additional complications in the transition from pediatric and adolescent HIV care to adult care due to the complexity of navigating an adult health care system with multiple providers. However, pregnancy also may be an opportune time for a young person to transition to adult care. There is a need to identify, develop or adapt, and implement culturally sensitive and women-centered interventions for improving HIV care continuum outcomes of pregnant and postpartum people with HIV.[30] Coordination of care across multiple disciplines—including HIV primary care, obstetric/gynecologic care, 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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Perinatal HIV Prevention for Transgender and Gender-Diverse People Assigned Female at Birth

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Panel's Recommendations
• The Panel on Treatment of HIV During Pregnancy and Prevention of Perinatal Transmission has determined that, in most cases, it is appropriate to extrapolate its recommendations based on data in cisgender women to all people assigned female at birth, including transgender and gender-diverse people, with modification when indicated (e.g., drug interactions with gender-affirming hormones) (AIII). • Patient-centered HIV and perinatal services should be provided using gender-affirming and shared decision-making approaches and models of care that address the unique and varied needs of transgender and gender-diverse people and reduce barriers to ongoing engagement in care that can affect adherence to antiretroviral therapy and the likelihood of viral suppression during prepregnancy, antepartum, and postpartum periods (AII). o Patients should be asked about their gender identity, including the pronouns they use, how they want to be referred to as a parent (e.g., birth parent, mother, father, or another name), and terms they prefer to use for sexual and reproductive anatomy and examinations (e.g., breast exams, pelvic exams) (AIII). • Health care providers should assess reproductive and parenting intentions and support access to appropriate fertility preservation and reproductive health care services for transgender and gender-diverse people (AIII). • Prepregnancy care for transgender and gender-diverse people should incorporate shared decision-making that addresses needs related to gender identity, with consideration of the potential risks and benefits of gender-affirming pharmacologic treatment in relation to pregnancy (AIII). See Prepregnancy Counseling and Care for Persons of Childbearing Age with HIV for more information. • Some transgender and gender-diverse patients may experience the onset or worsening of gender dysphoria and associated symptoms—such as depression—during prepregnancy, antepartum, and postpartum periods; health care providers should regularly assess patients' comfort with their care and provide referrals for mental health or other support services as needed (AIII). For additional information, see Transgender People with HIV in the Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV.
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*

It is important for health care providers to be aware that not all people who become pregnant identify as women or female. Because many transgender and gender-diverse people assigned female at birth retain their reproductive organs, pregnancy can occur, and many desire and/or experience pregnancy in their lifetime.[1-7] This section provides an overview of recommendations from the Panel on Treatment of HIV During Pregnancy and Prevention of Perinatal Transmission (the Panel) regarding perinatal HIV prevention and treatment of HIV in pregnancy for transgender and gender-diverse people assigned female at birth. The Panel uses the terms transgender and gender-diverse people assigned female at birth to include people who do not identify as cisgender women while acknowledging individual preferences and ongoing changes in the terminology used to describe this population. The Panel aims to make the guidelines inclusive of transgender and gender-diverse

people by incorporating inclusive language, considering the appropriateness of existing Panel recommendations for the care of transgender and gender-diverse individuals assigned female at birth, and adding relevant recommendations and content. Additional information is available in the Adult and Adolescent Antiretroviral Guidelines (see Transgender People with HIV), guidance from the American College of Obstetricians and Gynecologists about health care for transgender and gender-diverse individuals,[8] standards of care developed by the World Professional Association for Transgender Health,[6] and guidelines for primary and gender-affirming care developed by the Center of Excellence for Transgender Health at the University of California, San Francisco.[9]

Perinatal HIV Prevention and Care of Transgender and Gender-Diverse People During Prepregnancy, Antepartum, and Postpartum Periods

Research into the fertility, pregnancy-related, and perinatal HIV prevention needs of transgender and gender-diverse people is in early stages, and descriptions of pregnancy-related care are limited. After careful consideration, the Panel has decided it is often appropriate to extrapolate existing recommendations to transgender and gender-diverse people assigned female at birth and to provide additional content and recommendations, when data are available, to address the unique and varied needs of this population if indicated. This approach is consistent with other guidelines for primary care, family planning,[10] and HIV care[11] for transgender and gender-diverse people.

Health care providers should periodically assess the reproductive and parenting desires and intentions of transgender and gender-diverse patients and support access to fertility preservation and reproductive health care services.[12] Transgender and gender-diverse people experience multiple barriers to accessing health care, particularly sexual and reproductive health care, which is often delivered in gender-segregated spaces.[13,14]

Some transgender and gender-diverse people assigned female at birth take testosterone to achieve gender-affirming bodily changes. While testosterone may lead to amenorrhea, it does not reliably suppress ovulation. Individuals having condomless sex that can lead to pregnancy and who want to avoid pregnancy should be counseled on the need for contraception. Testosterone is not recommended during pregnancy due to possible irreversible fetal androgenic effects.[14-17] Experts recommend that patients who are pregnant or are trying to conceive should stop taking testosterone.[6,18-20] Persons taking testosterone who desire pregnancy but have concerns about stopping testosterone should consult with their gender-affirming hormone prescriber or another transgender care expert about risks and benefits.[21] The optimal time period for stopping testosterone prior to conception is unknown.[2,21] For people wanting to conceive, prepregnancy planning and care provide an opportunity to address HIV prevention—including HIV testing and pre-exposure prophylaxis—for those who are HIV negative. For people with HIV, it provides an opportunity to optimize antiretroviral therapy (ART) and viral suppression before pregnancy. It also enables providers to identify and address transgender and gender-diverse people's concerns about the relationships between pregnancy or parenthood and their gender identity and gender-affirming medical interventions, such as hormones or surgeries. For additional information, see Pre-Exposure Prophylaxis (PrEP) to Prevent HIV During Periconception, Antepartum, and Postpartum Periods; Prepregnancy Counseling and Care for Persons of Childbearing Age with HIV; and Reproductive Options When One or Both Partners Have HIV.

Selection and management of ART for transgender and gender-diverse people with HIV should follow Recommendations for Use of Antiretroviral Drugs During Pregnancy: Overview, Table 6: What to Start: Initial Antiretroviral Regimens During Pregnancy for People Who Antiretroviral-

Naive, and Table 7: Situation-Specific Recommendations for Use of Antiretroviral Drugs in Pregnant People and Nonpregnant People Who Are Trying to Conceive. The potential for drug interactions should be considered and discussed with patients who plan to start or resume hormonal therapy postpartum (see Table 17. Potential Interactions Between the Drugs Used in Gender-Affirming Hormone Therapy and Antiretroviral Drugs in Transgender People with HIV).

Gender-Affirming Care

Health care providers should work to develop patient-centered approaches that assess and address the gender affirmation needs of transgender and gender-diverse individuals in all health care settings.[12,19,21,22] Gender affirmation encompasses processes and interventions that recognize and support a person's gender identity and expression.[23] Gender-affirming care may include psychosocial support, hormone therapy, surgery, and other interventions.[19] Gender affirmation—including such medical interventions as hormonal therapy—has been shown to improve mental health outcomes and quality of life in transgender individuals.[6] Rates of viral suppression have been shown to be higher among transgender people with HIV who are receiving gender-affirming hormone therapy.[24,25] A national needs assessment found that transgender and gender-diverse people with HIV were more likely to be virally suppressed when they worked with HIV care providers who affirmed their gender (e.g., providers who use their chosen name and pronoun[s]).[11,26] Language is important for inclusivity and for providing respectful, affirming health care.[12,27] Many transgender and gender-diverse people use terms unique to them and their anatomy; therefore, providers should never assume that a patient prefers a certain term and should respect the patient's expressed preferences.[27,28] All patients should be asked about their gender identity, including the pronouns they use and how they (and their partners) want to be referred to as parents (i.e., birth parent, father, mother, or another name). Clinicians should also ask patients about desired terminology for sexual and reproductive anatomy and be aware that terminology is rapidly changing.[28]

Health care providers should be aware that although transgender and gender-diverse patients may adjust well to pregnancy, some patients may experience and require support for the onset or worsening of gender dysphoria and associated symptoms during prepregnancy, antepartum, and postpartum periods. Gender dysphoria and associated symptoms may be precipitated or exacerbated by the body changes that occur in pregnancy and the harmful practices of misgendering pregnant transgender and gender-diverse people in prenatal, labor and delivery, and postpartum care settings.[18,19,21,29] Gender dysphoria refers to the distress that results from incongruence between a person's sex assigned at birth and their gender identity[30] and is manifested by a range of symptoms, such as depression, anxiety, and a sense of unease.[31] Gender dysphoria can be reduced when a person receives affirmation for their gender identity through various interventions that include interpersonal approaches, such as adaptations made in gender-specific clinic environments and procedures, and medical interventions, such as hormones.[19,31] Health care providers should have individualized discussions with their patients regarding starting or restarting testosterone therapy in the postpartum period, including referral to and/or coordination with a gender-affirming care specialist as needed.

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Early (Acute and Recent) HIV Infection

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Panel's Recommendations

- When early[a] (acute and recent) HIV infection is suspected during pregnancy, the postpartum period, or breastfeeding, a plasma HIV RNA test should be obtained in conjunction with an antigen/antibody immunoassay test (AII). See Early (Acute and Recent) HIV Infection in the Adult and Adolescent Antiretroviral Guidelines and the Centers for Disease Control and Prevention (CDC) HIV testing algorithm for more information.
- Repeat HIV testing in the third trimester is recommended for pregnant people with initial negative HIV test results 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 (states or counties) with elevated HIV incidence among females aged 15 to 45 years (>17 per 100,000 females aged 15–45 years), or those who reside in states or territories that require third-trimester testing (see Pregnancy and Postpartum HIV Testing and Identification of Perinatal and Postnatal HIV Exposure) (AII). Annual state- and county-level HIV incidence among females is available at CDC's National Center for HIV, Viral Hepatitis, STD, and TB Prevention AtlasPlus webpage.
- All pregnant and breastfeeding people with early HIV infection should start antiretroviral therapy (ART) as soon as possible for their own health and to reduce the risk of perinatal and horizontal HIV transmission, with the goal of rapidly suppressing plasma HIV RNA below detectable levels (AI).
- In people with early HIV infection, baseline genotypic resistance testing should be performed simultaneously with initiation of ART, and the regimen should be adjusted, if necessary, to optimize virologic response (AII).
- One of the following regimens is recommended for pregnant people with early infection without a history of prior use of long-acting cabotegravir (CAB-LA) as pre-exposure prophylaxis (PrEP):
  - Dolutegravir (DTG) plus tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF) with emtricitabine (FTC) or lamivudine (3TC) is the *Preferred* ART irrespective of trimester (AII).
  - Bictegravir (BIC) plus TAF plus FTC is an *Alternative* ART regimen (AII).
  - Ritonavir-boosted darunavir (DRV/r) plus (TDF or TAF) with (FTC or 3TC) is an *Alternative* ART regimen (AIII).
  - See Table 6. What to Start: Initial Antiretroviral Regimens During Pregnancy for People Who Are Antiretroviral-Naive, Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs in Pregnant People and Nonpregnant People Who Are Trying to Conceive, Recommendations for Use of Antiretroviral Drugs During Pregnancy, Appendix C: Antiretroviral Counseling Guide for Health Care Providers, and Early (Acute and Recent) HIV Infection in the Adult and Adolescent Antiretroviral Guidelines for more information.
- For pregnant people with early infection with a history of prior use of CAB-LA as PrEP, genotype testing done before the start of ART should include screening for integrase strand transfer inhibitor–resistance mutations.
  - A regimen of DRV/r with (TDF or TAF) plus (FTC or 3TC) is the *Preferred* ART regimen pending results of genotype testing (AIII). See Early (Acute and Recent) HIV Infection in the Adult and Adolescent Antiretroviral Guidelines for more information.
- One of the following regimens is recommended for people diagnosed with early HIV infection during the postpartum period: BIC/TAF/FTC; DTG with (TAF or TDF) plus (FTC or 3TC); or DRV/r with (TAF or TDF) plus (FTC or 3TC) (AIII). See Early (Acute and Recent) HIV Infection in the Adult and Adolescent Antiretroviral Guidelines for more information.
- The Panel on Treatment of HIV During Pregnancy 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).

- People who receive a diagnosis of HIV infection when they are breastfeeding should be counseled to discontinue breastfeeding immediately to reduce the risk of postnatal HIV transmission to the infant (AII).
- Infants born to people who received a diagnosis of early HIV infection during pregnancy or breastfeeding are at high risk of acquiring HIV infection and should receive presumptive HIV therapy (see Table 10. Neonatal Antiretroviral Management According to Risk of HIV Infection in the Newborn and Table 12. Antiretroviral Management of Infants with Exposure to HIV During Breastfeeding 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.

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

[a] Early HIV infection represents either acute or recent HIV infection.

Women may have an increased risk of HIV infection during pregnancy or breastfeeding.[1-3] People 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 or long-acting injectable antiretroviral (ARV) formulations for pre-exposure prophylaxis (PrEP).[4] For more information, see Pre-exposure Prophylaxis (PrEP) to Prevent HIV During Periconception, Antepartum, and Postpartum Periods.

Risk of Perinatal Transmission After Early HIV Infection in the Birthing Parent

Early HIV infection is a term that encompasses acute or recent infection. During pregnancy or breastfeeding, early infection is associated with an increased risk of perinatal HIV transmission, and a significant proportion of pediatric infections can be attributed to maternal acute infection.[5] 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 before pregnancy (1.6%) ($P < 0.0001$).[6] Similarly, among 108 new perinatal HIV infections that were identified between 2006 and 2013 in the United Kingdom, 23 (21.3%) were associated with a concurrent maternal seroconversion.[7] The high rate of transmission in people with acute infection likely is related to the high viral loads in plasma, breast milk, and the genital tract that are present during acute infection.[8] Acute HIV infection can be asymptomatic or symptoms can be nonspecific, which results in missed opportunities to diagnose and implement interventions that can reduce the risk of perinatal transmission.

Diagnosis of Early (Acute or Recent) HIV Infection During Pregnancy, Postpartum, or Breastfeeding

Acute HIV infection occurs immediately after acquisition and is typically characterized by high viremia detected by the presence of HIV RNA or p24 antigen. Anti-HIV antibodies are not detectable early during this phase of HIV infection (see Early [Acute and Recent] HIV Infection section of the Adult and Adolescent Antiretroviral Guideline). Recent HIV infection generally is considered the phase of HIV disease ≤6 months after infection, during which anti-HIV antibodies develop and become detectable.[9-14] Health care providers should maintain a high level of awareness of possible HIV infection in patients who are pregnant or breastfeeding and have clinical signs and symptoms that are compatible with acute infection. Even when patients do not report high-risk behaviors, it is

still possible that their sexual partners are practicing high-risk behaviors without their knowledge or that they do not recognize that such behaviors put them at risk for HIV acquisition. 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.[15-19] Providers often do not recognize acute HIV infection because the symptoms are similar to those of other common illnesses, and some individuals with acute HIV infection may be asymptomatic.

When early HIV infection is suspected during pregnancy or breastfeeding, a quantitative or qualitative plasma HIV RNA test should be obtained in conjunction with an antigen/antibody immunoassay test. Guidance for HIV testing recommends using a U.S. Food and Drug Administration–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 early HIV-1 infection. More specific guidance on HIV testing can be found in the Early (Acute and Recent) 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 section. People who acquire HIV while taking PrEP may sometimes have ambiguous HIV test results that may require additional testing. See Early (Acute and Recent) HIV Infection in the Adult and Adolescent Antiretroviral Guidelines and Pre-exposure Prophylaxis (PrEP) to Prevent HIV During Periconception, Antepartum, and Postpartum Periods for more information on diagnosing acute HIV infection in people taking PrEP.

Repeat HIV testing in the third trimester is recommended for pregnant people 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 persons per year, those who reside in jurisdictions (states or counties) with elevated HIV incidence among females aged 15 to 45 years (>17 per 100,000 females aged 15–45 years), and those who reside in states or territories that require third-trimester testing.[20,21] Annual state- and county-level HIV incidence among females is available at CDC's National Center for HIV, Viral Hepatitis, STD, and TB Prevention AtlasPlus webpage (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). 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 in Maryland reported that repeat prenatal HIV testing was performed in only 28.4% of women.[22] In states with mandated late-trimester HIV testing, reported rates of retesting are substantially higher. At a large, urban tertiary hospital in Florida, 82% of women were retested in the third trimester.[23] Similarly, a single high-volume birthing center in Illinois reported an increase in repeat testing from 80% to 98% after implementing measures to comply with the state's third-trimester testing mandate.[24]

Antiretroviral Therapy for People with Acute or Recent HIV Infection During Pregnancy or the Postpartum Period

Acute or recent HIV infection during pregnancy, postpartum, or breastfeeding is associated with a high risk of vertical transmission of HIV.[1,5] Therefore, all pregnant people with acute or recent HIV infection should start antiretroviral therapy (ART) as soon as possible to rapidly achieve and sustain plasma viral suppression, for their own health and to prevent perinatal and horizontal transmission. Baseline genotypic resistance testing should be performed to guide adjustment of an optimal ARV

drug regimen. Data from the United States and Europe demonstrate that in 6% to 19% of patients, transmitted virus may be resistant to ≥1 ARV drugs.[25-27] 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. The Panel on Antiretroviral Guidelines for Adults and Adolescents does not currently recommend routine genotype testing for integrase strand transfer inhibitor (INSTI) resistance in treatment-naive individuals, with the exception of individuals who acquire HIV infection during or after the use of long-acting cabotegravir (CAB-LA) as PrEP (see Early [Acute and Recent] HIV Infection in the Adult and Adolescent Antiretroviral Guidelines for more information). Some panel members also recommend genotypic testing for INSTI resistance in pregnant people with early infection who have sexual partners on INSTI-based ART with unsuppressed or unknown viral loads.

In pregnant people who have not received CAB-LA prior to diagnosis of acute/recent HIV infection, a regimen that includes dolutegravir (DTG) plus tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF) plus emtricitabine (FTC) or lamivudine (3TC) should be initiated (see Table 6. What to Start: Initial Antiretroviral Regimens During Pregnancy for People Who Are Antiretroviral-Naive, Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs in Pregnant People and Nonpregnant People Who Are Trying to Conceive, Appendix C: Antiretroviral Counseling Guide for Health Care Providers, and Early [Acute and Recent] HIV Infection in the Adult and Adolescent Antiretroviral Guidelines for more information). DTG is associated with high rates of viral suppression, fast rates of viral load decline, and a high genetic barrier to drug resistance. DTG plus TDF (or TAF) plus FTC (or 3TC) is one of the recommended ARV regimens for treatment of acute and early infection in nonpregnant adults and a *Preferred* regimen for treatment during pregnancy. Bictegravir (BIC) plus TAF plus FTC is now recommended as an *Alternative* regimen for ART treatment in pregnancy and can also be considered for treatment of early infection. For pregnant people with early infection and a history of prior use of CAB-LA as PrEP, genotype testing done before the start of ART should include screening for INSTI-resistance mutations, and a regimen of ritonavir-boosted darunavir (DRV/r) (administered twice daily during pregnancy) plus (TDF or TAF) plus (FTC or 3TC) (see Table 6. What to Start: Initial Antiretroviral Regimens During Pregnancy for People Who Are Antiretroviral-Naive, and Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs in Pregnant People and Nonpregnant People Who Are Trying to Conceive) should be initiated. The regimen can be adjusted once drug resistance results are available. In the case that the pregnant person cannot receive an INSTI-based regimen (e.g., intolerance, potential transmitted resistance), DRV/r plus (TDF or TAF) plus (FTC or 3TC) should be administered. TDF (or TAF) plus (FTC or 3TC) are *Preferred* nucleoside reverse transcriptase inhibitor (NRTI) backbones for treatment of early infection. The efficacy and toxicity of TDF and TAF in pregnant patients are similar. In the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) 2010 trial, no differences were observed in viral suppression, Grade 3 or higher adverse events, or estimated creatinine clearance among people randomized to initiate TDF/FTC (n = 215) versus TAF/FTC (n = 217) with DTG at >14 weeks gestational age.[28] Abacavir (ABC) **is not recommended** for empiric treatment of acute infection unless the patient previously tested negative for the HLA-B*5701 gene variant; using TDF or TAF rather than ABC will avoid delays in ART initiation while awaiting HLA-B*5701 test results.

Several studies have demonstrated that the use of INSTI-based regimens is associated with shorter time to viral suppression compared with other ARV regimens.[28-33] Although no data are available to inform the treatment of early HIV during pregnancy, two studies in pregnant women demonstrated more rapid viral decline on DTG-based regimens than on efavirenz (EFV)-based ART. In the DolPHIN 2 study (dolutegravir in pregnant HIV mothers and their neonates), 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% confidence interval, 1.3–2.1]; $P < 0.0001$).[32] In the IMPAACT 2010 trial, 643 pregnant women, 14 to 28 weeks gestation, were assigned randomly to receive DTG plus FTC and TDF, DTG plus FTC and TAF, or EFV plus FTC and TDF. At delivery, 395 (98%) of 405 participants in the combined DTG-containing groups had viral suppression (HIV-1 RNA <200 copies per mL) compared with 182 (91%) of 200 participants in the EFV plus FTC and TDF group. Furthermore, participants assigned to a DTG-containing group had a significantly shorter time to viral suppression than those in the EFV-containing group.[28]

People who are diagnosed with acute or recent HIV postpartum should start ART as soon as possible. ART options and management should follow guidance outlined in Early (Acute and Recent) HIV in the Adult and Adolescent Antiretroviral Guidelines. One of the following ART regimens is recommended: BIC/TAF/FTC; DTG with (TAF or TDF) plus (FTC or 3TC); or boosted DRV with (TAF or TDF) plus (FTC or 3TC).

Obstetrical and Neonatal Considerations

When early 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 (see Intrapartum Care for People with HIV). Infants born to people who received a diagnosis of early HIV infection during pregnancy or breastfeeding are at high risk of acquiring HIV infection and should receive presumptive HIV therapy (see Table 10. Neonatal Antiretroviral Management According to Risk of HIV Infection in the Newborn and Table 12. Antiretroviral Management of Infants with Exposure to HIV During Breastfeeding in Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection). The infant also should receive immediate diagnostic testing (see Diagnosis of HIV Infection in Infants and Children). Consulting a pediatric HIV specialist regarding appropriate infant management is strongly recommended.

When HIV infection is diagnosed during breastfeeding, breastfeeding should be discontinued immediately. In nursing people with suspected seroconversion, breastfeeding should be interrupted immediately, and it should not resume if infection is confirmed (see Situations to Consider Stopping or Modifying Breastfeeding in Infant Feeding for Individuals with HIV in the United States). Patients can continue to express and store breast milk while awaiting confirmation of infection status. Due to the high risk of postnatal transmission associated with early infection in pregnancy and during breastfeeding, this guidance is more directive than the shared decision-making recommended for individuals on suppressive ART.

All people who receive a diagnosis of infection should be asked whether they know the HIV status of their partners. HIV testing of the sexual partners of all pregnant people 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 People with HIV

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Panel's Recommendations

HIV Testing for Pregnant People with Unknown HIV Status in Labor

- Pregnant people who present in labor with unknown HIV status and people with increased risk of HIV infection who were not retested in the third trimester should undergo expedited antigen/antibody HIV testing (AII). See Pregnancy and Postpartum HIV Testing and Identification of Perinatal and Postnatal 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 or recent HIV infection is suspected or if a person has had recent HIV exposure, an HIV RNA assay also should be done at the time of expedited antigen/antibody testing (AII). See Early (Acute and Recent) HIV Infection.

Intrapartum Antiretroviral Therapy, Zidovudine Prophylaxis, and Mode of Delivery for Pregnant People with HIV

- See Table 9: Intrapartum Care and Recommended Interventions to Prevent Perinatal HIV Transmission for Pregnant People with HIV Based on HIV RNA Levels at the Time of Delivery below.
- Patients should continue taking their antepartum antiretroviral therapy (ART) on schedule during labor and before scheduled cesarean delivery (AIII).
- For individuals with HIV RNA >1,000 copies/mL or unknown HIV RNA near the time of delivery (within 4 weeks of 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) known or 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 patients 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 patients 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 individuals receiving ART with HIV RNA ≤1,000 copies/mL near the time of delivery (within 4 weeks of delivery):
  - IV ZDV is **not required** for people who meet ALL of the following criteria: (1) are receiving ART, (2) have HIV RNA <50 copies/mL within 4 weeks of delivery, and (3) are adherent to their ARV regimen (BII).
  - IV ZDV may be considered for people with HIV RNA ≥50 copies/mL and ≤1,000 copies/mL within 4 weeks of delivery (BII). Data are insufficient to determine whether administration of IV ZDV to people 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 their recent ART adherence and preferences, and involving expert consultation if needed (CII).
  - Scheduled cesarean delivery performed solely for prevention of perinatal HIV transmission in those 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 pregnant people 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 pregnant people 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 9 below)

- Fetal scalp electrodes for fetal monitoring should be avoided, particularly when the HIV RNA level of the birthing parent is not suppressed (≥50 copies/mL) or is unknown, because of the potential risk of HIV transmission (BIII).
- Artificial rupture of membranes and operative vaginal delivery with forceps or a vacuum extractor should follow standard obstetric indications but should be avoided, if possible, in those with HIV RNA ≥50 copies/mL (BIII).
- The ARV regimen a patient is receiving should be taken into consideration when using methergine to treat excessive postpartum bleeding caused by uterine atony.
  - In patients 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 patients 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 Pregnant People with HIV

Pregnant people with HIV require specialized care during labor and delivery to optimize their health outcomes and to prevent perinatal HIV transmission. Documentation of HIV status should be assessed in all people 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 Pregnancy and Postpartum HIV Testing and Identification of Perinatal and Postnatal HIV Exposure and Early [Acute and Recent] HIV Infection). Because maternal HIV RNA level is linked directly to the risk of perinatal HIV transmission,[1] the Panel on Treatment of HIV During Pregnancy and Prevention of Perinatal Transmission (the Panel) recommends viral load testing throughout pregnancy, and specifically at approximately 36 weeks gestation (or within 4 weeks of anticipated delivery), to inform decisions about intrapartum care. The risk of perinatal HIV transmission is reduced to very low levels (1% or less) in pregnant people receiving antiretroviral therapy (ART) who have documented viral suppression (<50 copies/mL) near delivery.[1-3] The Panel's recommendations about intrapartum care to prevent HIV transmission are based on HIV RNA levels in the birthing parent and encompass continuation of ART during pregnancy, intrapartum intravenous (IV) zidovudine (ZDV) during labor and delivery, scheduled cesarean delivery, and other intrapartum management considerations. Table 9 provides an overview of the Panel's recommendations for intrapartum care based on HIV RNA in the birthing parent. These recommendations are discussed in the following sections.

Pregnant People Who Present in Labor without Documentation of HIV Status

All pregnant people 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 Pregnancy and Postpartum HIV Testing and Identification of Perinatal and Postnatal HIV Exposure for details about testing procedures). Expedited repeat HIV testing also is recommended for those who present in labor and tested negative for HIV in early pregnancy but are at increased risk of HIV infection and were not retested in the third trimester.[4,5] Factors that may increase the risk of HIV infection include having a sexually transmitted infection diagnosis, having a substance use disorder, exchanging sex for money or drugs, having multiple sexual partners during pregnancy, having a sexual partner who is at risk of HIV infection or who is known to have HIV, having signs or symptoms of acute HIV infection, or living in a region with an elevated incidence of HIV in women of childbearing age.[4] **Those who test positive on the initial HIV test during labor should be presumed to have HIV until follow-up testing clarifies their HIV status.** Expert consultation should be obtained regarding starting patients on combination oral ART during labor and is available through the National Perinatal HIV/AIDS Clinical Consultation Center at 1-888-448-8765. To prevent perinatal HIV transmission, intrapartum IV ZDV should be started immediately, as discussed below, and patients should not initiate breastfeeding until HIV infection is ruled out definitively (see Infant Feeding for Individuals with HIV in the United States). For additional information, see Postpartum Follow-up of People with HIV, Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection, and Table 11. No further testing is required for specimens that are nonreactive on the initial immunoassay, unless the patient has had recent HIV exposure or acute infection is suspected, in which case an HIV RNA assay should be obtained. For additional information regarding HIV testing during labor and delivery, please see the HIV Testing During Labor in People with Unknown HIV Status section of Pregnancy and Postpartum HIV Testing and Identification of Perinatal and Postnatal HIV Exposure.

Expedited HIV testing should be available on a 24-hour basis, and results should be available within 1 hour 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 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 people with HIV, regardless of CD4 T lymphocyte cell count and HIV RNA (viral load). Pregnant people should continue their antepartum antiretroviral (ARV) regimen on schedule 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 anesthesiologist during the preoperative period. If the birthing parent's ARV drug regimen must be interrupted temporarily (i.e., 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 ARV pre-exposure prophylaxis at a time when infants are at increased risk of exposure to the blood and body fluids of their birthing parent.

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 the birthing parent's ART, HIV RNA level, and adherence considerations (see Table 9). IV ZDV also is recommended for those with an initial diagnosis of HIV during labor and pregnant people with HIV whose HIV RNA level is unknown.

Current evidence indicates that intrapartum IV ZDV reduces perinatal HIV transmission for people with HIV RNA >1,000 copies/mL who are on ART, but the benefits for those 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 received triple-ARV regimens). The majority (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 [OR] 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 pregnant people with HIV RNA >1,000 copies/mL within 4 weeks of delivery (or to people with HIV who have unknown HIV RNA levels within 4 weeks of delivery), regardless of their antepartum ARV regimen. Although not required, administration of intrapartum IV ZDV may be considered for individuals with HIV RNA levels ≥50 copies/mL and ≤1,000 copies/mL or in people for whom there are concerns about adherence to or tolerance of their ARV regimens in late pregnancy. Specifically, patients who have not maintained an undetectable viral load consistently throughout the third trimester, patients who have had challenges consistently participating in prenatal care, and patients with ongoing psychosocial factors that raise additional concerns about adherence should be considered potential candidates for intrapartum IV ZDV despite a viral load <1,000 copies/mL. Many experts think the data are insufficient to determine whether administration of intrapartum IV ZDV to pregnant people 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%).[1,6,9,10]

IV ZDV is **not required** for individuals who meet ALL of the following criteria: (1) are receiving ART, (2) have HIV RNA <50 copies/mL within 4 weeks of delivery, and (3) are adherent to their ARV regimen. However, a study showing that 6% of women with suppressed HIV RNA levels during pregnancy had viral load rebound near delivery[11] 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 pregnant individuals 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 still is recommended in patients with HIV RNA >1,000 copies/mL near delivery unless a documented history of hypersensitivity exists. This intrapartum use of IV ZDV is recommended because of its proven record in reducing the risk of perinatal HIV transmission, even when the birthing parent has resistance to the drug (see Antiretroviral Drug Resistance and Resistance Testing in Pregnancy).

Administration of Intrapartum IV ZDV

Intrapartum IV ZDV is recommended for individuals with HIV RNA >1,000 copies/mL or unknown HIV RNA near the time of delivery or when they present in labor. In those 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; pregnant people **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.[12] 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 the pregnant person's viral load is ≤1,000 copies/mL near the time of delivery, administering IV ZDV is not required.

When an urgent unscheduled cesarean delivery is indicated in a patient 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.

When IV ZDV is not available, substitution of single-agent oral ZDV for IV ZDV is not recommended. In some international studies, oral (rather than IV) ZDV has been administered during labor. Data are limited on the PK 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.[13,14] Therefore, IV administration is recommended over oral administration in the United States for individuals with HIV RNA >1,000 copies/mL near delivery. Prompt administration of combination ART to the pregnant patient is preferred to single therapy with oral ZDV. Consultation with a person experienced in HIV management during labor and delivery is recommended and is available through the National Perinatal HIV/AIDS Clinical Consultation Center at 1-888-448-8765.

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 (ROM), is recommended at 38 weeks gestation for prevention of

perinatal HIV transmission in individuals with HIV RNA levels >1,000 copies/mL near delivery and for those 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 recommends viral load testing at approximately 36 weeks gestation or within 4 weeks of anticipated delivery to inform decisions about mode of delivery and optimal treatment of the newborn. The American College of Obstetricians and Gynecologists (ACOG) recommends that pregnant people with HIV RNA >1,000 copies/mL be counseled regarding the potential benefits of scheduled cesarean delivery.[15]

Recommendations for cesarean delivery to prevent perinatal HIV transmission were based initially on findings from a multicenter, randomized clinical trial[16] and a large individual patient data meta-analysis[17] that were conducted before the availability of viral load information, when most pregnant people 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.[18] Results of studies conducted since then have been extrapolated to make current recommendations about the mode of delivery in an era when ART is recommended for all pregnant people 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 women; 0.3%) were not significantly different from those who had a planned vaginal delivery (6 of 2,238 women; 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).[19] Among 290 deliveries in women with HIV in Finland from 1993 to 2013, 75.4% of women delivered vaginally, 12.5% delivered by elective cesarean, and 12.5% delivered by emergency cesarean; 80% had HIV RNA <50 copies/mL. No perinatal HIV transmissions occurred across the delivery methods.[20] 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.[19]

Given the low perinatal HIV transmission rates that can be achieved when the pregnant person uses ART, the benefit of scheduled cesarean delivery is difficult to evaluate for people who are virally suppressed. It is unclear whether scheduled cesarean delivery confers any additional benefit in reducing transmission, and there are harms associated with unindicated cesarean delivery. No evidence to date suggests any benefit from scheduled cesarean delivery in people 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.[21] Therefore, decisions about mode of delivery for pregnant people receiving ART with HIV RNA levels ≤1,000 copies/mL should be individualized based on discussion between an obstetrician and a pregnant person. Pregnant people 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 people receiving ART with HIV RNA ≤1,000 copies/mL and, therefore, **is not routinely recommended** in these situations.

Timing of Delivery

ACOG recommends against nonmedically indicated cesarean delivery prior to 39 0/7 weeks gestation because of the risk of iatrogenic prematurity.[22,23] However, when the birthing parent's viral load is >1,000 copies/mL, earlier delivery is indicated. When cesarean delivery is indicated to prevent transmission of HIV, ACOG recommends scheduling cesarean delivery at 38 0/7 weeks gestation to decrease the likelihood of onset of labor or ROM before delivery.[5] Gestational age should be determined by best obstetrical dating criteria, including last menstrual period and early ultrasound for dating purposes. Consistent with ACOG guidelines for management of individuals with suboptimal pregnancy dating, amniocentesis to document lung maturity should be avoided in pregnant people with HIV. See Managing Individuals Who Present in Early Labor or with Ruptured Membranes below for management in the setting of early labor or ruptured membranes.

Among 1,194 infants born to mothers with HIV, 9 (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.[24] Although newborn complications may be increased with planned cesarean delivery at <39 weeks gestation, the benefits of planned cesarean delivery at 38 weeks generally are thought to outweigh the risks if the procedure is performed to prevent HIV transmission.

In pregnant people with HIV RNA ≤1,000 copies/mL, cesarean delivery is not recommended to prevent perinatal HIV transmission. The Panel recommends that pregnant people 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 pregnant people 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 pregnant people 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 significant difference (0.3% vs. 0.5%) in perinatal HIV transmission by estimated gestational age at delivery, which suggests that individuals without an indication for scheduled cesarean delivery for prevention of perinatal HIV transmission should be delivered according to standard obstetric indications.[25]

Cesarean Delivery for People Presenting Late in Pregnancy

People 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 for the Use of Antiretroviral Drugs During Pregnancy: Overview and Pregnant People Who Have Not Achieved Viral Suppression on Antiretroviral Therapy).[26-30] 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 for a person 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 person's plasma HIV RNA level was <1,000 copies/mL by the day of delivery. In these situations, patient-centered counseling and shared decision-making should be used in planning for delivery.

Regardless of mode of delivery, presumptive HIV therapy should be considered for the neonate in these circumstances (see Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection). 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, administering IV ZDV and supporting vaginal delivery would be reasonable **(CIII).**

Risk of Complications with Cesarean Delivery

Administration of perioperative antimicrobial prophylaxis is recommended for all pregnant people to decrease 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 those without HIV and that their risk of complications is related to degree of immunosuppression and the receipt of suppressive ART.[31-36] 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.[37,38] Complication rates in women with HIV in most studies[16,39-43] 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 those without HIV.[21] The rate of any complication associated with cesarean delivery was 117 per 1,000 deliveries among women with HIV and 67 per 1,000 deliveries among women without HIV. A meta-analysis of primarily observational studies in women with HIV also reported higher morbidity with elective cesarean delivery than with vaginal delivery (OR: 3.12) and no reduction in perinatal HIV transmission among the mothers on ART.[44] Therefore, pregnant people 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 people who are likely to have additional pregnancies and perhaps multiple cesarean deliveries. The risks of abnormal placentation (e.g., placenta previa, placenta accreta spectrum), bowel and bladder injury, and intrapartum hemorrhage increase as the number of cesarean deliveries a person has increases. These risks should be considered and discussed with the pregnant person before proceeding with a cesarean delivery.[45,46]

Managing Individuals 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,[47] it is not clear how soon after the onset of labor or the ROM that the benefit of cesarean delivery is lost for women with HIV RNA >1,000 copies/mL.[48] Later data on the

association between the duration of 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 during 2007 to 2012, no difference was observed 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: 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% 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.[49]

Because it is not clear whether cesarean delivery after onset of labor reduces the risk of perinatal HIV transmission in individuals with HIV RNA >1,000 copies/mL, management of patients originally scheduled for cesarean delivery who present in labor or with ruptured membranes must be individualized at the time of presentation.

If spontaneous ROM occurs at >34 weeks gestation before labor or early in labor in individuals 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. Antibiotics to prolong the time from membrane rupture to onset of labor (the latency period), magnesium sulfate for fetal neuroprotection, and antenatal corticosteroids should be given in accordance with usual obstetric guidelines because no data exist to suggest that these recommendations need to be altered for pregnant people with HIV.

In these circumstances, where there is a paucity of data, 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 at 1-888-448-8765) may provide assistance in rapidly developing an individualized plan.

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.[50-53] 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 potential source of perinatal HIV exposure for the infant and, when possible, should be avoided if the birthing parent has HIV. 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 birthing parent is virally suppressed (HIV RNA <50 copies/mL). See Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection.

Based on data discussed in the previous section (see Managing Individuals Who Present in Early Labor or with Ruptured Membranes, above), artificial ROM can be performed for standard obstetric indications in people with HIV RNA <50 copies/mL who are on ART and are virally suppressed. Artificial ROM should be avoided in people 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.[54-56] In the setting of HIV infection, a 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, no HIV transmissions were reported and the risk of jaundice or polycythemia in infants with delayed cord clamping did not increase.[57]

Intrapartum Epidural Use and Pharmacologic Interactions with ARV Drugs

Ritonavir (RTV) inhibition of cytochrome P450 (CYP) 3A4 decreases the elimination of fentanyl by 67%. This raises concerns about a possible increased risk of respiratory depression, particularly with patient-controlled analgesia during labor, in patients 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.[58] 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 were available, HIV was considered a relative contraindication to operative vaginal delivery with forceps or vacuum device. In a review of 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% for the deliveries from 2007 through 2011 and 90% 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, one case of HIV transmission with multiple possible causes was reported and not enough evidence existed to confirm intrapartum transmission. The study authors concluded that operative delivery is a safe option for women who are virally suppressed.[59] 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 pregnant people without HIV (e.g., a need for expedited vaginal delivery, shoulder dystocia).

Postpartum Hemorrhage, ARV Drugs, and Methergine Use

Oral or parenteral methergine or other ergot alkaloids often are 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, including acute ischemia of the lower extremities.[60,61] When uterine atony results in excessive postpartum bleeding in people 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 9. Intrapartum Care and Recommended Interventions to Prevent Perinatal HIV Transmission for Pregnant People with HIV Based on HIV RNA Levels at the Time of Delivery

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

HIV RNA at Time of Delivery Assessed at 36 Weeks Gestation or within 4 Weeks of Delivery				
	<50 copies/mL and on ART with No Concerns About Adherence[a]	**≥50** to **≤1,000** copies/mL	**>1,000 copies/mL**	Unknown HIV RNA ART Adherence Concerns[a] Not Receiving ART HIV Diagnosis in Labor
Intrapartum ART	Pregnant people should take their prescribed ART on schedule during labor and before scheduled cesarean delivery (CIII). In general, ARV regimens are initiated postpartum for people 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 gestation[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 people with detectable or unknown viral load who are not receiving a cesarean delivery (BIII)
Induction of Labor	Per standard obstetric indications, including use of oxytocin. Pregnant people with HIV RNA ≤1,000 copies/mL should NOT be routinely induced at 38 weeks gestation.		Not applicable; scheduled cesarean delivery recommended	Avoid if possible (BIII)
IUPC	Data not available for pregnant people with HIV; use IUPC with caution and only if clear obstetric indications exist.			
Fetal Scalp Electrodes for Fetal Monitoring	Avoid—particularly when the birthing parent's 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 HIV Infection.			
Operative Delivery with Forceps or a Vacuum Extractor	Per standard obstetric indications (BIII)	Avoid for pregnant people in the setting of viremia if possible (BIII)		
Delayed Cord Clamping	Per standard obstetric indications and care			

Table 9. Intrapartum Care and Recommended Interventions to Prevent Perinatal HIV Transmission for Pregnant People with HIV Based on HIV RNA Levels at the Time of Delivery

HIV RNA at Time of Delivery Assessed at 36 Weeks Gestation or within 4 Weeks of Delivery				
	<50 copies/mL and on ART with No Concerns About Adherence[a]	**≥50** to **≤1,000** copies/mL	**>1,000 copies/mL**	Unknown HIV RNA ART Adherence Concerns[a] Not Receiving ART HIV Diagnosis in Labor
Use of Methergine for Postpartum Hemorrhage	Due to potential drug interactions with some ARV drugs, consider a patient'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 HIV Infection, Table 10, Table 11, Postpartum Follow-Up of People with HIV, and Infant Feeding for Individuals with HIV in the United States.			

Key: ART = antiretroviral therapy; ARV = antiretroviral; IUPC = intrauterine pressure catheter; IV = intravenous; ZDV = zidovudine

[a] Assess ART adherence at every visit and upon presentation for delivery.

[b] Begin IV ZDV when patients 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 people receiving ART with HIV RNA ≤1,000 copies/mL is not recommended given the low rate of perinatal transmission in this group (AII). In people 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 people who present in spontaneous labor or with ruptured membranes. Management of people 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 pregnant people 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 people who are receiving a cytochrome P450 3A4 (CYP3A4) 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 people 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

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Postpartum Follow-Up of People with HIV

Updated: January 31, 2024
Reviewed: January 31, 2024

Panel's Recommendations
• Continuous antiretroviral therapy (ART) currently is recommended for all individuals with HIV to reduce the risk of disease progression and 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 individual and their 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 and retention in HIV care, arrangements for new or continued supportive services should be made throughout pregnancy and before postpartum hospital discharge (AII). • People with a positive HIV test during labor should receive confirmatory testing; see Pregnancy and Postpartum HIV Testing and Identification of Perinatal and Postnatal HIV Exposure. If testing confirms HIV infection, ART should be offered, and the person should be given a supply of ART before postpartum hospital discharge to prevent treatment interruption (AII). Immediate linkage to HIV care and comprehensive follow-up also is needed (AII). • Infants of people who have HIV newly diagnosed in the intrapartum period should begin presumptive HIV therapy, and a supply of ART for their infants should be provided before postpartum hospital discharge (AII) (see Antiretroviral Management of Infants with Perinatal HIV Exposure or HIV Infection). • People with HIV should receive evidence-based counseling to support shared decision-making about infant feeding options prior to and during pregnancy; counseling and plans for infant feeding should be reviewed again after delivery (AIII) (see Infant Feeding for Individuals with HIV in the United States). • Clinicians should discuss future reproductive plans and timing, as well as the risks and benefits of conceiving while on specific antiretroviral (ARV) medications (AII). The use of appropriate contraceptive options to prevent unintended pregnancy and optimal interpregnancy intervals should also be discussed (AII) (see Prepregnancy Counseling and Care for Persons of Childbearing Age with HIV). • Contraceptive counseling should involve shared decision-making and should start during the prenatal period; a contraceptive plan should be developed before postpartum hospital discharge, as desired by the patient (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*

The postpartum period provides an opportunity to review and optimize a patient's health care. Comprehensive medical care and supportive services are particularly important for people 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;
- Pediatric and pediatric HIV specialty care for the infant;
- Sexual and reproductive health services, including contraception;
- Mental health services;

- Substance use prevention and treatment;
- Supportive services;
- Coordination of care through case management for the patient, their 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 with HIV (i.e., treatment as prevention), and the potential use of pre-exposure prophylaxis (PrEP) by the partner without HIV (see Pre-exposure Prophylaxis [PrEP] to Prevent HIV During Periconception, Antepartum, and Postpartum Periods).

Supportive services should be tailored to the individual's needs and can include screening for intimate partner violence; case management; childcare; 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.

During the postpartum period, immediate linkage to care, comprehensive medical assessment, counseling, and follow-up are required for all people with HIV and particularly for those who have a new positive HIV test during labor or at delivery. This is important because intrapartum diagnosis of HIV has been negatively associated with HIV care outcomes in the postpartum period.[1,2] The American College of Obstetricians and Gynecologists recommends that all people have contact with their obstetrician-gynecologists within 3 weeks postpartum and that postpartum care be provided as an ongoing process based on an individual's needs rather than as a single postpartum visit.[3] People 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 of postpartum hospital discharge. People who have difficulty attending in-person appointments should consider telemedicine visits.[4]

When care is not co-located or not within the same health care system, a case manager's role for care coordination becomes even more crucial. People who are receiving case management are more likely to have viral suppression and be retained in care.[5] Alternative models of HIV care delivery—such as HIV-adapted group prenatal care—have been associated with higher retention in HIV care for women in the postpartum period.[6] Ensuring continuity of ART between the antepartum and postpartum periods is especially critical. People with HIV newly diagnosed in the intrapartum period should receive ART, and presumptive HIV therapy should be initiated immediately for the newborn before hospital discharge. Special hospital programs may need to be established to support dispensing ART to birthing parents before discharge.

Transgender and gender-diverse people who were assigned female sex at birth may require additional support and linkage to care during the postpartum period (see Perinatal HIV Prevention for Transgender and Gender-Diverse People Assigned Female at Birth).[7-9]

Postpartum Antiretroviral Therapy

ART should be continued postpartum. Decisions about changes to an ART regimen after delivery should be made after discussion between the individual and their HIV care provider, ideally before delivery. When providing counseling about postpartum ART, health care providers should consider

the person's desire for future planned pregnancies or the potential for unplanned pregnancies in the context of the person'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 Prepregnancy Counseling and Care for Persons of Childbearing Age with HIV and Appendix C: Antiretroviral Counseling Guide for Health Care Providers). Some ART regimens that are recommended for nonpregnant adults may not be recommended for use during pregnancy or for people who are trying to conceive (see the Adult and Adolescent Antiretroviral Guidelines). See Recommendations for Use of Antiretroviral Drugs During Pregnancy, Table 4. Antepartum Screenings and Assessments for Pregnant People with HIV, Table 5. HIV-Related Laboratory Monitoring Schedule for Pregnant People with HIV, Teratogenicity, and Antiretroviral Drug Regimens and Pregnancy Outcomes for additional information and specific recommendations regarding regimens for use during pregnancy and when 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.[10] The Strategic Timing of AntiRetroviral Treatment (START)[11] and TEMPRANO trials[12] 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 HIV Prevention Trials Network (HPTN) 052 randomized clinical trial demonstrated that effective ART can reduce the risk of sexual transmission of HIV to a partner without HIV by 100%.[13] 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).[14]

Helping people with HIV understand the need for lifelong ART is a priority during postpartum care. Several studies have demonstrated significant decreases in ART adherence postpartum.[15-19] During the postpartum period, people 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 during the postpartum period.

Adherence to ART and Postpartum Depression

Symptoms of depression have been associated with lower ART adherence and viral suppression during pregnancy and the postpartum period.[20] Furthermore, postpartum depression is common among people with HIV.[2,21-24] The U.S. Preventive Services Task Force recommends screening all postpartum people for postpartum depression[25] using a validated tool (e.g., the Edinburgh Postnatal Depression Scale); such screening is especially important for people with HIV who appear to be at increased risk for postpartum depression and poor ART adherence during the postpartum period. Enquiring about intimate partner violence, food or housing insecurity, and substance use is also important, as these factors have been associated with worsening depressive symptoms.[26] People 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.[5,27-30]

Poor adherence has been shown to be associated with virologic failure, development of antiretroviral (ARV) drug resistance, and decreased long-term effectiveness of ART.[31-33] In people who achieve viral suppression by the time of delivery, postpartum ART simplification to once-daily, coformulated regimens—which are often the preferred initial regimens for nonpregnant adults—could promote adherence during this challenging time. Efforts to maintain adequate adherence during

the postpartum period may ensure effectiveness of therapy (see Adherence to the Continuum of Care in the Adult and Adolescent Antiretroviral Guidelines). For people who are continuing ART and who received increased protease inhibitor doses during pregnancy, available data suggest that doses can be reduced to standard doses immediately after delivery. In addition, such behavioral interventions as peer support and text messaging may help improve retention in HIV care postpartum.[34]

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,[35] 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 without HIV. With full, sustained viral suppression (undetectable viral load) in the person with HIV—with or without reliable PrEP use by the partner—there is no risk of sexual transmission (see Reproductive Options for Couples When One or Both Partners Have HIV and National Institutes of Health's Treatment as Prevention guidance for more information).

Comprehensive prepregnancy counseling and contraception should be integrated into all health care visits, with special attention given to these topics during 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 people—even before resumption of menses—putting them at risk of pregnancy soon after delivery.[36] HIV does not preclude the use of any contraceptive method (see Table 3. Drug Interactions Between Antiretroviral Agents and Hormonal Contraceptives). The contraceptive plans for people with HIV should not differ from those for people without HIV; however, because of the significantly higher prevalence of unplanned pregnancy in people with HIV,[37] establishing contraceptive plans early, using shared decision-making, is important. 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 before postpartum hospital discharge or during the routine postpartum visit. If LARC insertion is planned for the postpartum visit and the patient desires a contraceptive method in the interim, intramuscular depot medroxyprogesterone acetate is an option that can be given before postpartum hospital discharge. People should be advised to avoid interpregnancy intervals shorter than 6 months.[3,38,39]

The potential for drug–drug interactions between several ARV drugs and hormonal contraceptives is discussed in Prepregnancy Counseling and Care for Persons of Childbearing Age with HIV and Table 3. Drug Interactions Between Antiretroviral Agents and Hormonal Contraceptives. 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.[40,41] This is consistent with Centers for Disease Control and Prevention recommendations advocating access to a broad range of effective contraceptive methods, including combined hormonal contraceptives, progestin-only pills, depot medroxyprogesterone acetate, and implants.[42]

Infant Feeding

People with HIV should receive evidence-based counseling to support shared decision-making about infant feeding options prior to and during pregnancy (see Infant Feeding Counseling for Individuals with HIV in the United States. Counseling and plans for infant feeding should be reviewed again after delivery.

Lactation Inhibition

For people who do not breastfeed, 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.[3] Although pharmacologic options for lactation inhibition generally are not used in the United States, recent data suggest cabergoline may be appropriate for some people.[43,44] Cabergoline is a dopamine agonist/ergot derivative that reduces the production of prolactin; however, it is not approved by the U.S. Food and Drug Administration for lactation inhibition.[45,46] Cabergoline is **contraindicated** for women with hypertension—including pregnancy-induced hypertension, preeclampsia, or eclampsia—or liver disease and for women being treated with antipsychotics or those who have a history of puerperal psychosis.[47] Bromocriptine, another dopamine agonist, is no longer used for lactation inhibition because of serious cardiovascular and neurologic complications associated with its use.[48]

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Infant Feeding for Individuals With HIV in the United States

Updated: January 31, 2023
Reviewed: January 31, 2023

Panel's Recommendations
• People with HIV should receive evidence-based, patient-centered counseling to support shared decision-making about infant feeding. Counseling about infant feeding should begin prior to conception or as early as possible in pregnancy; information about and plans for infant feeding should be reviewed throughout pregnancy and again after delivery (AIII). During counseling, people should be informed that— o Replacement feeding with properly prepared formula or pasteurized donor human milk from a milk bank eliminates the risk of postnatal HIV transmission to the infant (AI). o Achieving and maintaining viral suppression through antiretroviral therapy (ART) during pregnancy and postpartum decreases breastfeeding transmission risk to less than 1%, but not zero (AI). • Replacement feeding with formula or banked pasteurized donor human milk is recommended to eliminate the risk of HIV transmission through breastfeeding when people with HIV are not on ART and/or do not have a suppressed viral load during pregnancy (at a minimum throughout the third trimester), as well as at delivery (AI). • Individuals with HIV who are on ART with a sustained undetectable viral load and who choose to breastfeed should be supported in this decision (AIII). • Individuals with HIV who choose to formula feed should be supported in this decision. Providers should ask about potential barriers to formula feeding and explore ways to address them (AIII). • Engaging Child Protective Services or similar agencies is not an appropriate response to the infant feeding choices of an individual with HIV (AIII). • Clinicians are encouraged to consult the national Perinatal HIV/AIDS hotline (1-888-448-8765) with questions about infant feeding by individuals with HIV (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 this document, the term "breastfeeding" is used to describe feeding a child one's own milk (either direct feeding or with expressed milk). When counseling individuals with HIV about infant feeding, it is important to assess and use their preferred terminology; some transgender men and gender-diverse individuals may prefer using the term "chestfeeding" rather than "breastfeeding." We urge providers to consult community-based resources for more information about inclusive, affirming language around gender in health care settings.

Counseling about infant feeding is an integral component of care for pregnant and postpartum people with HIV. Ideally, this counseling should begin before pregnancy, continue during pregnancy, and be reviewed again after delivery. Patient-centered counseling should assess an individual's opinions and plans about infant feeding, engage them in shared decision-making, and assist them in implementing their plans for infant feeding. Replacement feeding with properly prepared formula or banked, pasteurized donor human milk has been recommended for individuals with HIV in the United States because it is generally available and eliminates any risk of HIV transmission through breastfeeding.

However, breastfeeding provides certain benefits to the mother and infant that are not possible with formula feeding. In addition, the risk of transmission through breastfeeding is very low, but not zero, for women on antiretroviral therapy (ART) with an undetectable HIV viral load.[1-3] Multiple experts and community organizations have called for a patient-centered approach to infant feeding decision making and for parents with HIV to have access to the information, support, and tools necessary to make informed infant feeding decisions.[4-12] As part of the shared decision-making process, providers and parents should discuss the possible use of infant antiretroviral (ARV) prophylaxis during breastfeeding in addition to the ARV prophylaxis recommended for all infants with perinatal HIV exposure; these conversations need to take place during pregnancy as well as after delivery (see Antiretroviral Management of Newborns With Perinatal HIV Exposure or HIV Infection and Table 12. Infant Antiretroviral Prophylaxis for Newborns of Mothers With Sustained Viral Suppression Who Breastfeed.)

Most of the data on HIV transmission via breastmilk come from low- and middle-income countries. Interest in and experience with breastfeeding for people with HIV in higher resource settings have been explored in a small number of studies. In a survey of 15 treatment centers in Germany, the number of women with HIV who breastfed increased over time from 0 to 2 women per year in 2009 to 2016 to 9 to 13 women per year in 2017 through 2019.[13]

In five small case series that reported on breastfed infants in higher-resource countries, all mothers were on ART and almost all were virally suppressed. A group in Toronto described three breastfed infants with no transmission via breastfeeding.[14] Nine women with 10 pregnancies successfully breastfed at one site in the United States,[15] and eight women breastfed at a U.S. second site[16]; there were no cases of HIV transmission. Thirteen women, described in a prospective study conducted in Italy, also had no transmissions of HIV through breastfeeding.[17] In Germany, among 30 women with HIV who breastfed, there were no cases of breastfeeding transmission of HIV, although only 25 women had optimal viral suppression. Four of the five women not considered to be optimally suppressed had viral loads of 50 to 70 copies/mL at some point postpartum, and two had had a detectable viral load early in pregnancy and, therefore, did not meet the authors' criteria for optimal suppression.[18] Of note, the approaches to infant prophylaxis ranged from 4 weeks of zidovudine (ZDV) to three-drug ARV regimens using therapeutic doses for the duration of breastfeeding.

The Panel on Treatment of HIV in Pregnancy and Prevention and Perinatal Transmission and the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (Panels) recommend that clinicians engage parents in patient-centered counseling and shared decision-making regarding infant feeding. Among 93 U.S. clinicians who provide specialty care to women with HIV, one-third of the providers were aware that women in their care breastfed their infants after being advised not to do so.[19] Open communication that involves the parent in shared decision-making provides an opportunity for providers to understand their patients' values and infant feeding preferences, thus allowing individuals who choose to breastfeed, and their infants, to receive appropriate care and support.

Clinicians who are caring for people with HIV who have questions about infant feeding or are considering breastfeeding should consult with an expert and/or the national Perinatal HIV/AIDS hotline (1-888-448-8765).

Overview of Counseling and Management

For people with HIV who are not on ART and/or do not have a suppressed viral load at delivery, replacement feeding with formula or banked pasteurized donor human milk is recommended to eliminate the risk of HIV transmission. However, it is important to recognize that accessing an adequate supply of formula may be difficult for some people, and there may be cost and access barriers to obtaining donor milk. For anyone with HIV who chooses replacement feeding, systems of care should ensure supportive access to clean water, safe formula, and banked human milk, if available.

Individuals with HIV on ART with a consistently suppressed viral load during pregnancy (at a minimum during the third trimester) and at the time of delivery should be counseled on the options of formula feeding, banked donor milk, or breastfeeding. Community-based organizations have developed patient-facing materials to assist pregnant individuals in considering their infant feeding options.[20]

- The infant feeding options that eliminate the risk of HIV transmission are formula and pasteurized donor human milk.
- Fully suppressive ART during pregnancy and breastfeeding decreases breastfeeding transmission risk to less than 1%, but not zero.
- If breastfeeding is chosen, exclusive breastfeeding up to 6 months of age is recommended over mixed feeding (i.e., breast milk and formula), acknowledging that there may be intermittent need to give formula (e.g., infant weight loss, milk supply not yet established, mother not having enough stored milk). Solids should be introduced as recommended at 6 months of age, but not before.[21]
- The postpartum period, which can be difficult for all parents, can present several challenges to medication adherence and engagement in care. Ensuring that parents have access to both a supportive clinical team and peer support in the postpartum period is beneficial in promoting medication adherence and viral load monitoring (see Postpartum Follow-up for Individuals With HIV).
- Access to a lactation consultant or lactation support provider with expertise in supporting breastfeeding by individuals with HIV is beneficial.
- As most studies of breastfeeding in mothers with HIV were conducted in resource-limited settings, more information is needed about the risk of HIV transmission through breastfeeding in high-resource settings and when individuals are adherent to ART with sustained viral suppression starting early in pregnancy.
- Breastfeeding provides numerous health benefits to both the infant (e.g., reduction in asthma, gastroenteritis, and otitis media) and the parent (e.g., reduction in hypertension; type 2 diabetes; and breast and ovarian cancers).[21]

Special Concerns

Engaging Child Protective Services or similar agencies is not an appropriate response to the infant feeding choices of an individual with HIV.

Numerous pregnant people with HIV have reported that after expressing their interest/intention to breastfeed, their providers threatened to report them to Child Protective Services or actually did so. Such engagements can be extremely harmful to families; can exacerbate the stigma and discrimination experienced among people with HIV; and are disproportionately applied to minoritized individuals, including Black, Indigenous, and other people of color.[22-24]

Approach to Counseling

Health care providers who care for individuals with HIV who are pregnant or planning a pregnancy should initiate conversations about infant feeding early in pregnancy, or even prior to the pregnancy, and the discussion should continue during the pregnancy.

One approach is to say, "Have you thought about how you would like to feed your baby? Formula feeding eliminates the risk of HIV transmission through breastmilk. Less than 1 of 100 breastfed infants would be expected to acquire HIV through breastmilk when the breastfeeding parent is taking ART and has an undetectable viral load, but the risk is not zero. What information can I provide to help you decide?"

For individuals with HIV who are considering breastfeeding, providers should engage them in patient-centered, evidence-based counseling about infant feeding, allowing for shared decision-making. It should be a private, nonjudgmental conversation to understand the motivations for breastfeeding (e.g., bonding, health benefits for lactating parents and their infants) and potential barriers to formula feeding (e.g., concern about formula feeding, inadvertently disclosing HIV status, barriers to accessing formula, cultural concerns). Factors such as resource accessibility, the need for informed lactation support, and history of medication adherence should be considered when making these decisions. The conversation should also include information about the risks of HIV transmission during breastfeeding, the importance of sustained viral suppression, and common challenges to ART adherence during the postpartum period.

Transgender and Gender-Diverse People Who Desire to Chestfeed

Transgender and gender-diverse people may desire to feed their infants their own milk (e.g., breastfeeding, chestfeeding, or body feeding), although some may find it dysphoric.[25] All pregnant individuals with HIV, regardless of gender identity, should be counseled about infant feeding options, as discussed in this section. There are no evidence-based guidelines on timing of restarting testosterone after giving birth or while breast/chestfeeding. In one published case report of restarting testosterone 13 months postpartum while still lactating, the calculated milk-to-plasma ratio was under 1.0, and the calculated relative infant dose was under 1%, the infant had no observable side effects, and the infant serum testosterone concentrations remained undetectable.[26]

Approach to Management

If a parent decides to breastfeed, several measures should be taken to reduce the possibility of HIV transmission. Care of the parent and infant should be coordinated prior to delivery among the

maternity care provider, HIV provider, infant provider, lactation consultant, and social worker, all of whom may need education about new approaches to infant feeding among people with HIV. Counseling should include the importance of adherence to ART, viral suppression during pregnancy and breastfeeding, and engagement in postpartum care for both the lactating parent and infant. Some providers and/or institutions have chosen to have individuals sign a written agreement acknowledging the risks of HIV transmission via breastfeeding; others have felt this practice is too stigmatizing. Recommendations include the following:

- Support the parent's ART adherence and engagement in care throughout pregnancy and breastfeeding.
  - Provide case management and/or social work support from individual(s) with perinatal support experience.
  - Provide early active referral to a supportive lactation consultant knowledgeable in concerns regarding HIV transmission and the situations in which to consider stopping or temporarily interrupting breastfeeding. (Refer to the next section on Situations in which to Consider Stopping or Modifying Breastfeeding.)
  - Screen and provide support for postpartum depression and other mental health conditions that are highly prevalent among new parents and may affect ART adherence. Postpartum depression occurs more frequently in individuals with HIV compared to those without HIV.[27]
- Document sustained viral suppression before delivery and throughout breastfeeding.
  - No data exist to inform the appropriate frequency of viral load testing for the breastfeeding parent. One approach is to monitor the plasma viral load of the parent every 1 to 2 months during breastfeeding.[15,16]
  - Decide which clinician (e.g., prenatal care provider or primary care HIV clinician) is responsible for following viral loads of the parent postpartum and continuing counseling/education around breastfeeding.
  - If the parent's viral load becomes detectable, consult an expert in breastfeeding and HIV immediately and consider the options provided in the section Situations to Consider Stopping or Modifying Breastfeeding below.
  - Recommend exclusive breastfeeding in the first 6 months of life, followed by the introduction of complementary foods with continued breastfeeding, if desired.[21] Some people may choose to breastfeed for fewer than 6 months.
  - In pre-ART studies, exclusive breastfeeding was associated with lower rates of HIV transmission compared to mixed feeding (a term used to describe infants fed breast milk plus other liquid or solid foods, including formula).[28,29] The highest risk in these studies was from very early introduction of solids (before 2 months of age).[30,31]
  - In the context of parental ART and viral suppression, it is not known whether formula supplementation increases the risk of HIV acquisition in the breastfed infant.
- Administer appropriate ARV prophylaxis starting at birth as described in Antiretroviral Management of Newborns With Perinatal HIV Exposure or HIV Infection.
- Provide guidance on good breast care, including strategies to avoid and promptly resolve over-production of breastmilk, milk stasis, and breast engorgement, which can lead to sore nipples, mastitis, or breast abscess. Promptly identify and treat mastitis, thrush, and cracked or bleeding

nipples. These conditions may increase the risk of HIV transmission through breastfeeding, although the impact of these conditions in the context of ART and viral suppression is unknown.

- Develop a joint plan for weaning with family and providers. Since very rapid weaning was associated with increased risk of HIV shedding into breast milk and risk of transmission in the pre-ART era,[32-34] weaning over a 2- to 4-week period might be safer, paying special attention to good breast care and avoidance of breast engorgement and milk stasis.
- There is little evidence to guide the infant HIV testing schedule during breastfeeding, and there have been transmissions detected many weeks or even months after reported cessation of breastfeeding.[35] Information about HIV testing for infants who are being breastfed is available in Diagnosis of HIV Infection in Infants and Children, see Table 13. Recommended Virologic Testing Schedules for Infants Who Were Exposed to HIV According to Risk of Perinatal HIV Acquisition at and After Birth.

Situations to Consider Stopping or Modifying Breastfeeding

Situations may arise in which there is a need to stop or modify breastfeeding, such as the breastfeeding parent having a detectable viral load or developing mastitis or bleeding nipples. If the situation is temporary, some options to consider until the condition has resolved or viral load becomes undetectable include: (1) giving previously stored expressed milk from a date when person was virally suppressed while encouraging pumping and discarding breastmilk to ensure that breastfeeding can resume; (2) pumping and flash heating breastmilk before feeding it to the baby; (3) providing replacement feeding with formula or pasteurized donor human milk; or (4) permanent cessation of breastfeeding. Flash heating, which has been documented to eliminate HIV from breastmilk, involves placing a sample of milk in a glass container within a small pot of water, heating the water to a boil, and immediately removing the milk from the heated water when the water has boiled.[36,37] Once cooled to room temperature, milk can be given to the baby via bottle or cup.

In the case of mastitis or bleeding nipples, pump and either flash heat or discard milk from the affected breast while continuing to feed or pump from the unaffected breast.

In the case of a detectable viral load in a breastfeeding parent, the Panels recommend that breastfeeding be temporarily stopped, using one of the above options, while the viral load is repeated. If the repeat viral load is undetectable, breastfeeding may resume. This is also an opportunity to provide positive feedback and review the risks and benefits of continued breastfeeding, adherence strategies, and other considerations. If the repeat viral load remains detectable, providers should urgently discuss and counsel about the significant elevation in risk of vertical transmission conferred by ongoing breastfeeding. Due to the high risk of postnatal transmission associated with viremia during breastfeeding, the Panels advise immediate cessation of breastfeeding; this guidance is more directive than counseling for individuals on suppressive ART. In situations where viremia is low and an addressable cause has been identified, the added risk of short term continued breastfeeding would be less. No studies have evaluated different approaches to ARV prophylaxis in this specific clinical scenario, but the Panels recommend that infants with newly identified exposure to breastmilk from a person with viremia be managed using the ARV prophylaxis approach of an infant identified at high risk of transmission (see Breastfeeding in Newborns at High Risk of Perinatal HIV Acquisition in Antiretroviral Management of Newborns With Perinatal HIV Exposure or HIV Infection). Diagnosis of HIV Infection in Infants and Children provides guidance about HIV diagnostic testing for infants who are being breastfed. If after counseling, a breastfeeding parent with viremia chooses to continue to breastfeed, the parent and provider should remain engaged; the provider should offer guidance on

ARV prophylaxis and testing for the infant and assist the parent to rapidly regain and maintain virologic suppression. Consultation with an expert or the National Perinatal HIV/AIDS hotline (1-888-448-8764) is recommended.

Infant HIV Infection

If an infant has a positive NAT result, it should be confirmed with a repeat NAT as soon as possible (see Diagnosis of HIV Infection in Infants and Children). Antigen–antibody combination immunoassays are not recommended for diagnosis in infants because of the transplacental transfer of HIV antibodies during pregnancy.

In the event of HIV transmission via breastfeeding, consult a pediatric HIV specialist and promptly initiate a full ART regimen for the infant (see What to Start: Regimens Recommended for Initial Therapy of Antiretroviral-Naive Children in the Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection). If an infant acquires HIV, breastfeeding may be continued. Drug-resistance testing should be done on the infant's viral isolate. If resistance is identified, the ARV regimen can be adjusted appropriately.

Factors Affecting Decisions About Infant Feeding

Several factors affect parents' decisions about infant feeding. Patient-centered counseling should be conducted in a manner that supports the family by sharing the risks and benefits of feeding options; listening to beliefs, values, and interests of parents; addressing concerns; and engaging in shared decision-making to identify and support each family's infant feeding decision.

Benefits of Breastfeeding

In general, breastfeeding is widely considered to be the healthiest infant feeding option for both parents and infants in the general population (see CDC, Recommendations and Benefits: Breastfeeding). Breastfeeding is associated with improved neonatal immune status and a lower risk of infants developing asthma, obesity, type 1 diabetes, severe lower respiratory disease, otitis media, sudden infant death syndrome, gastrointestinal infections, and necrotizing enterocolitis. In addition to bonding with their infant and avoiding the monetary costs of formula, benefits to the breastfeeding parent include decreased risk of hypertension; type 2 diabetes; and breast, endometrial, and ovarian cancers.[21] An exclusive focus on the risk of perinatal HIV transmission via breastfeeding fails to acknowledge the health benefits to lactating parents and their infants that may be lost by prohibiting breastfeeding for individuals with HIV.

Equity Considerations

Black women are disproportionately affected by HIV. People of color and their infants also experience a greater burden of many health conditions that research has shown may be alleviated by breastfeeding.[38] These inequities are largely driven by the effects of structural racism, poverty, and segregation. Research has also shown that systemic racism contributes to lower uptake and continuation of breastfeeding among Black individuals without HIV.[39] These inequities and health disparities should be considered as part of counseling and support for infant feeding decisions for people with HIV in the United States. It is also important to recognize that, even in the United States, some people have limited access to safe water and/or difficulty obtaining formula. It is estimated that

17% of the U.S. population relied on privately owned wells for water in 2010; these are not regulated and are not subject to Environmental Protection Act standards.[40]

Cultural Considerations

Pregnant individuals may face environmental, social, familial, and personal pressures to consider breastfeeding.[4,11,38,41-46] Qualitative studies 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.[42]

Some women, especially those from a country or cultural background where breastfeeding is the norm, feared that not breastfeeding would lead to disclosure of their HIV status.[4,45,46] Focus groups held in Canada elucidated the importance of discussing infant feeding options and motivations to breastfeed, especially among women who had immigrated from other countries where they had been encouraged to breastfeed.[12]

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- 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 or infant ARV prophylaxis, the risk of an infant acquiring HIV through breastfeeding is 15% to 20% over 2 years.[47,48] The mechanisms of HIV transmission by breastfeeding are not fully understood.[49,50] This lack of current knowledge, and the fact that rare HIV transmissions during breastfeeding have occurred from individuals with undetectable breast milk and/or plasma HIV viral load, complicate decision-making.[51,52]

Studies have shown that maternal ART throughout pregnancy and breastfeeding or infant ARV prophylaxis during breastfeeding can reduce, but not eliminate, the risk of breast milk–associated HIV transmission.[53-57] However, in most of these studies, ART was initiated late in pregnancy, and ARV medications for women or infants were only provided for 6 months after birth, with 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 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.[58] 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.[59]

In a secondary analysis of the Breastfeeding, Antiretrovirals, and Nutrition (BAN) study, increased maternal ART adherence was associated with lower breast milk and plasma viral loads. Higher breast milk and plasma viral loads were associated with increased breast milk transmission. Where maternal plasma viral load remained <100 copies/mL during breastfeeding, there were no occurrences of infant HIV acquisition.[52]

The PROMISE (Promoting Maternal and Infant Survival Everywhere Study) trial, which included more than 2,400 women with CD4 T lymphocyte cell counts ≥350 cells/mm^3, compared the efficacy of prolonged infant ARV prophylaxis with NVP 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.[1] Both maternal HIV RNA load and maternal HIV drug resistance were independently associated with breastfeeding transmission.[60] A secondary analysis of the PROMISE trial demonstrated an association between maternal viral load and HIV transmission among mother–baby pairs in the maternal ART arm but not in the infant ARV prophylaxis arm. Two infants in the maternal ART arm acquired HIV despite maternal viral load measured as not detected or detected but less than 40 copies/mL on the date that the infants' first samples tested positive for HIV RNA.[51]

In the 72-week analysis of the DolPHIN-2(Dolutegravir in Pregnant HIV Mothers and Their Neonates) study, comparing dolutegravir- and efavirenz-based ART started in the third trimester, there was one breastfeeding HIV transmission reported in the efavirenz group.[2] This infant transmission was diagnosed at 72 weeks of life and occurred despite maternal plasma viral load <50 copies per mL at 12, 24, 48, and 72 weeks postpartum. The infant tested HIV DNA negative at birth and 6 weeks and 12 weeks postpartum. Infant visits at 24 or 48 weeks were missed; however, subsequent analysis of stored specimens was negative. The mother had undetectable viral loads at each visit. The infant was exclusively breastfed until 24 weeks, followed by introduction of complementary foods; breastfeeding stopped at 48 weeks postpartum. No history of maternal mastitis was recorded throughout the postpartum period.

In all these studies, maternal ART was initiated in the second or third trimester or postpartum. No studies have systematically evaluated the risk of HIV transmission through breastfeeding when maternal ART is started before pregnancy or in the first trimester and continued throughout breastfeeding.

In the Tshilo Dikotla Study (Botswana), frequent monitoring of HIV viral load occurred in pregnancy and postpartum while breastfeeding was ongoing, counseling was offered on adherence to ARV medications for both mothers and infants, and infant virologic diagnostic tests were performed routinely. Women were maintained on ART and infants received 4 weeks of prophylactic ZDV or NVP. If a woman had a detectable viral load, she was encouraged to switch to formula feeding but shared decision-making was employed. Among 247 participants, 19 had detectable viral loads at some point during breastfeeding. Twelve chose to stop breastfeeding, and 7 continued to breastfeed with ongoing counseling and frequent viral load checks. There were no cases of HIV transmission via breastfeeding.[61]

Safety of Antiretroviral Drugs During Breastfeeding

Parents are often concerned about infant exposure to ARV drugs through breast milk. The non-nucleoside reverse transcriptase inhibitors (NNRTIs) 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, ritonavir, 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.[62] Nucleoside reverse transcriptase inhibitors (NRTIs) show more variability than PIs and NNRTIs. Tenofovir concentrations from tenofovir disoproxil fumarate (TDF) are very low in breast milk, and the drug is undetectable in the blood of

the breastfed infant.[62-64] 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).[62] A sub-analysis of the BAN study confirmed higher levels of the NRTIs ZDV and 3TC in breast milk than in maternal 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.[65] 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.[66] For more details on the passage of ARV drugs into breast milk, see the individual drug sections in Appendix B: Supplement: Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy.

A systematic data review 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 persisted after discontinuation of breastfeeding was not known.[67] The clinical significance of the reduced bone mineral density is uncertain. Subsequent studies in Africa have shown TDF-based ART to be associated with a decrease in bone mineral density during lactation. In one study, bone mineral density decline through 74 weeks postpartum was greater in breastfeeding women with HIV receiving TDF than in those receiving ZDV-based ART.[68] A second study comparing bone mineral density in women with HIV receiving TDF-based ART to women without HIV showed accelerated loss during lactation, with only partial recovery by 3 months after cessation of lactation.[69]

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 (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.[1,54] An infant who acquires HIV while breastfeeding is at risk for developing ARV drug resistance due to subtherapeutic drug levels in breast milk.[60,70,71]

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.[54] Studies to date have examined only short-term adverse events, and few data are available on whether there might be long-term consequences of these drug exposures.

Clinicians who are caring for people with HIV and who have questions about infant feeding should consult with an expert and/or the national Perinatal HIV/AIDS hotline (1-888-448-8765).

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Antiretroviral Management of Newborns With Perinatal HIV Exposure or HIV Infection

Updated: January 31, 2023
Reviewed: January 31, 2023

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 the following:
  - 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.
  - 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).
- For newborns at low-risk of perinatal HIV acquisition, a 2-week zidovudine (ZDV) ARV regimen is recommended for ARV prophylaxis if the newborn is ≥37 weeks gestation and is born to a person with HIV who—
  - Is currently receiving and has received at least 10 consecutive weeks of ART during pregnancy (BII); *and*
  - Has achieved and maintained *or* maintained viral suppression (defined as at least two consecutive tests with HIV RNA <50 copies/mL obtained at least 4 weeks apart) for the duration of pregnancy (AII); *and*
  - Has a viral load <50 copies/mL at or after 36 weeks (AII); *and*
  - Did not have acute HIV infection during pregnancy (BII); *and*
  - Has reported good ART adherence, and adherence concerns have not been identified (BII).
- Infants born to individuals who do not meet the criteria above but who have a viral load <50 copies/mL at or after 36 weeks gestation should receive ZDV for 4 to 6 weeks (BII).
- Newborns at high risk of perinatal acquisition of HIV should receive presumptive HIV therapy with 3-drug regimens administered from birth for 2 to 6 weeks (see Tables 10 and 11); if the duration of the 3-drug regimen is shorter than 6 weeks, ZDV should be continued alone, to complete total of 6 weeks of prophylaxis. Newborns at high risk of HIV acquisition include those born to people with HIV who—
  - Have not received antepartum 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 at least two consecutive tests with HIV RNA level <50 copies/mL obtained at least 4 weeks apart) within 4 weeks of delivery (AIII), *or*
  - Have primary or acute HIV infection during pregnancy (AI).
- All premature infants <37 weeks gestation who are not at high risk of perinatal acquisition of HIV should receive ZDV for 4 to 6 weeks (BII).

- Infants of people who have primary or acute HIV infection while breastfeeding should be managed like infants at high risk of perinatal transmission with presumptive HIV therapy (see Table 10) (AII).
- 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).
- If an individual 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) (see What to Start in the Pediatric Antiretroviral Guidelines).
- People with HIV should receive patient-centered, evidence-based counseling to support shared decision-making about infant feeding. See Infant Feeding for Individuals With HIV in the United States.
- Providers with questions about ARV management of perinatal HIV exposure should consult an expert in pediatric HIV infection or 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 HIV acquisition 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 viral suppression (defined as at least two consecutive tests with HIV RNA level <50 copies/mL obtained at least 4 weeks apart). 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. Most ARV prophylaxis includes administration of a single agent—usually zidovudine (ZDV). In some situations, combinations of two or three ARV drugs may also be administered as ARV prophylaxis.

- **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.
- **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 10 provides an overview of neonatal ARV management recommendations according to the risk of perinatal HIV transmission to the newborn, and Table 11 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 people with HIV-2 infection is available in HIV-2 Infection and Pregnancy and Table 10. 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 people with HIV and their newborns, and consultants can provide referrals to local or regional pediatric HIV specialists.

Table 10. 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) or from an expert in pediatric HIV infection.

Level of Perinatal HIV Transmission Risk	Description	Neonatal ARV Management
Low Risk of Perinatal HIV Transmission	**Infants ≥37** weeks gestation when the mother— • Is currently receiving and has received at least 10 consecutive weeks of ART during pregnancy, *and* • Has achieved and maintained *or* maintained viral suppression (defined as at least two consecutive tests with HIV RNA levels <50 copies/mL obtained at least 4 weeks apart) for the duration of pregnancy, *and*	ZDV for 2 weeks[a]

Table 10. Neonatal Antiretroviral Management According to Risk of HIV Infection in the Newborn

Level of Perinatal HIV Transmission Risk	Description	Neonatal ARV Management
	• Has HIV RNA <50 copies/mL at or after 36 weeks and within 4 weeks of delivery, *and* • Did not have acute HIV infection during pregnancy, *and* • Has reported good ART adherence, and adherence concerns have not been identified.	
	Infants born to mothers who do not meet the criteria above but who have a HIV RNA <50 copies/mL at or after 36 weeks gestation	ZDV for 4 to 6 weeks[a]
	Premature infants (<37 weeks gestation) who are not at high risk of perinatal acquisition of HIV	ZDV for 4 to 6 weeks[a]
High Risk of Perinatal HIV Transmission[a,b]	Mothers who did not receive antepartum ARV drugs, *or* Mothers who received only intrapartum ARV drugs, *or* Mothers who received antepartum ARV drugs but did not have viral suppression (defined as at least two consecutive tests with HIV RNA level <50 copies/mL obtained at least 4 weeks apart) within 4 weeks prior to delivery, *or* Mothers with acute or primary HIV infection during pregnancy or breastfeeding (in which case, breastfeeding should be immediately discontinued)[c]	Presumptive HIV therapy using either ZDV, 3TC, and NVP (treatment dose) *or* ZDV, 3TC, and RAL administered together from birth for 2 to 6 weeks; if the duration of the 3-drug regimen is shorter than 6 weeks, ZDV should be continued alone, to complete a total of 6 weeks of prophylaxis[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 newborn has a positive HIV antibody test	ARV management as described above for newborns with a high risk of perinatal HIV acquisition 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. Refer to the What to Start: Regimens Recommended for Initial Therapy of Antiretroviral-Naive Children in the Pediatric Antiretroviral Guidelines for specific treatment recommendations.

[a] ZDV prophylaxis 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 for

Table 10. Neonatal Antiretroviral Management According to Risk of HIV Infection in the Newborn

infants at high risk of perinatal HIV-2 acquisition. See text for evidence that supports the use of presumptive HIV therapy and a two-drug ARV prophylaxis regimen.

[b] See Intrapartum Care for People With HIV for guidance on indications for scheduled cesarean delivery and intrapartum intravenous 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 born to mothers with acute HIV infection during pregnancy because of the higher risk for *in utero* transmission. If acute HIV is diagnosed during breastfeeding, the mother should immediately discontinue breastfeeding.

[d] The optimal duration of presumptive HIV therapy in newborns who are at a high risk for HIV acquisition is unknown. Newborns who are at a high risk for HIV acquisition should receive the ZDV component of the three-drug presumptive HIV therapy regimen for 6 weeks. The other two ARVs (3TC and NVP *or* 3TC plus RAL) may be administered for 2 to 6 weeks; the recommended duration for treatment with three ARVs varies depends on infant HIV NAT results, maternal viral load at the time of delivery, and additional risk factors for HIV transmission including breastfeeding (see sections below). 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 infant HIV NAT results.

[e] Infant ART should be initiated without waiting for the results of confirmatory HIV NAT testing, given the low likelihood of a false-positive HIV NAT. However, the specimen for confirmatory HIV testing should be obtained prior to ART initiation.

Note: ARV drugs should be initiated as close to the time of birth as possible, preferably within 6 hours of delivery. See Table 11 for dosing specifics.

Key: 3TC = lamivudine; ART = antiretroviral therapy; ARV =antiretroviral; NAT = nucleic acid test; NVP = nevirapine; Panel = Panel on Treatment of HIV During Pregnancy and Prevention of Perinatal Transmission and Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV; RAL = raltegravir; ZDV = zidovudine

Table 11. Antiretroviral Drug Dosing Recommendations for Newborns[a]

<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 or alternative simplified weight-band dosing (see below)

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>
<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; make this dose increase only 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 to 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>ABC[c]

Note: ABC is not approved by the FDA for use in neonates and infants aged <1 month. However, dosing</td><td>
≥37 Weeks' Gestation at Birth

Birth to 1 Month

• ABC 2 mg/kg per dose orally twice daily

Age 1 Month to <3 Months
</td></tr>
</table>

Table 11. Antiretroviral Drug Dosing Recommendations for Newborns

Drug	Drug Doses by Gestational Age at Birth
recommendations have been modeled using PK simulation. Because of ABC-associated hypersensitivity, negative testing for HLA-B5701 allele should be confirmed prior to administration of ABC.	• ABC 4 mg/kg per dose orally twice daily
3TC	**≥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
NVP[d]	**≥37 Weeks' Gestation at Birth** *Birth to Age 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.
	≥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.
	≥32 to <34 Weeks' Gestation at Birth *Birth to Age 2 Weeks* • NVP 2 mg/kg per dose orally twice daily *Age 2 to 4 Weeks* • NVP 4 mg/kg per dose orally twice daily *Age 4 to 6 Weeks* • NVP 6 mg/kg per dose orally twice daily *Age >6 Weeks* • NVP 200 mg/m^2 BSA per dose orally twice daily; only make this dose increase for infants with confirmed HIV infection.

Table 11. Antiretroviral Drug Dosing Recommendations for Newborns

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

Note: If the mother has taken RAL 2 to 24 hours prior to delivery, the neonate's first dose of RAL should be delayed until 24 to 48 hours after birth; additional ARV drugs should be started as soon as possible.[7]</td><td>≥37 Weeks' Gestation at Birth and Weighing ≥2 kg[e]

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>
<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>
</table>

[a] The optimal duration of presumptive HIV therapy in newborns who are at a high risk for perinatal HIV acquisition is unknown. Newborns who are at a high risk for HIV acquisition should receive the ZDV component of the three-drug presumptive HIV therapy regimen for 6 weeks. The other two ARVs (3TC and NVP *or* 3TC plus RAL) may be administered for 2 to 6 weeks; the recommended duration for these ARVs varies depending on infant 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 infant HIV NAT results.

[b] For ARV management of infants with HIV infection, see the What to Start: Regimens Recommended for Initial Therapy of Antiretroviral-Naive Children section in the Pediatric Antiretroviral Guidelines.

[c] ABC is approved by the FDA for use in children aged ≥3 months when administered as part of an ARV regimen. ABC also has been reported to be safe in infants and children ≥1 month of age. More recently, an ABC dosing recommendation using PK simulation models has been endorsed by the WHO using weight-band dosing for full-term infants from birth to 1 month of age. See Abacavir in Appendix A: Pediatric Antiretroviral Drug Information in the Pediatric Antiretroviral Guidelines for additional information about the use of ABC between birth and 1 month of age. At this time, the Panels do not recommend ABC as part of a presumptive HIV therapy regimen. However, in situations where ZDV is not available or the infant has ZDV-associated toxicity, ABC could be considered an alternative to ZDV. This substitution should be considered in circumstances where increased risk of ZDV toxicity may exist, such as in infants with anemia or neutropenia. Because of ABC-associated hypersensitivity, negative testing for HLA-B5701 allele should be confirmed prior to administration of ABC.

Table 11. Antiretroviral Drug Dosing Recommendations for Newborns

[d] The NVP doses for infants ≥32 to <37 weeks gestation at birth and infants ≥37 weeks gestation at birth are not yet approved by the FDA. The FDA also has not approved a dose of NVP for infants aged <1 month. The doses for infants ≥32 to <34 weeks gestation at birth are based on modeling and might underestimate potential toxicity in infants of 32 to <34 weeks gestational age because the doses used to develop the model were lower than the doses now recommended. See Nevirapine in Appendix A: Pediatric Antiretroviral Drug Information in the Pediatric Antiretroviral Guidelines for additional information about dosing.

[e] RAL dosing is increased at 1 week and 4 weeks of age because metabolism by UGT1A1 is low at birth and increases rapidly during the next 4 to 6 weeks of life. No dosing information is available for preterm infants or infants weighing <2 kg at birth. In infants with HIV infection, twice-daily RAL can be replaced with once-daily DTG at ≥ 4 weeks of age (see Dolutegravir and What to Start: Regimens Recommended for Initial Therapy of Antiretroviral-Naive Children in the Pediatric Antiretroviral Guidelines). The current dosing regimen with two dose changes in the first month of life may be challenging for some families. To minimize dosing changes, some experts increase to the 3 mg/kg twice daily dose upon discharge on day 4 or 5 of life.

Key: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; BSA = body surface area; DTG = dolutegravir; FDA = U.S. Food and Drug Administration; IV = intravenous; NVP = nevirapine; the Panels = the Panel on Treatment of HIV During Pregnancy and Prevention of Perinatal Transmission and the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV; PK = pharmacokinetic; RAL = raltegravir; UGT = uridine diphosphate glucotransferase; WHO = World Health Organization; ZDV = zidovudine

Recommendations for Antiretroviral Drugs in Specific Clinical Situations

In this section and Table 10. Neonatal Antiretroviral Management According to Risk of HIV Infection in the Newborn, the Panel on Treatment of HIV During Pregnancy and Prevention of Perinatal Transmission and the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panels) presents available data and recommendations for management of newborns with documented HIV and newborns born to mothers who—

- Are at low risk for transmitting HIV to their newborns born at ≥37 weeks gestation, including mothers who –
  - Received at least 10 consecutive weeks of antepartum ARV drugs, *and*
  - Achieved and maintained *or* maintained effective viral suppression (defined as at least two HIV RNA level <50 copies/mL obtained at least 4 weeks apart) for the duration of pregnancy, *and*
  - Had a HIV RNA <50 copies/mL at or after 36 weeks, *and*
  - Did not have acute HIV infection during pregnancy, *and*
  - Have reported good ART adherence and adherence concerns have not been identified.
- Are at high risk for transmitting HIV to their newborns, including mothers who—
  - Did not receive antepartum ARV drugs, *or*
  - Received only intrapartum ARV drugs, *or*
  - Received antepartum ARV drugs but do not have effective viral suppression (defined as at least two consecutive tests with HIV RNA level <50 copies/mL obtained at least 4 weeks apart) within 4 weeks prior to 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 and Maintained or *Maintained Viral Suppression on Antepartum Antiretroviral Drugs*

The risk of HIV acquisition in newborns born to people who received ART during pregnancy and labor and who had undetectable viral load near or at the time of delivery is <1%. In the Pediatric AIDS Clinical Trials Group (PACTG) 076 study, ZDV alone reduced the incidence of perinatal HIV transmission by 66%, and ZDV is recommended as prophylaxis for neonates whose mothers received ART that resulted in consistent viral 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, evidence supporting a reduced duration of ZDV prophylaxis in infants born to people who were suppressed virologically during pregnancy and at the 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 people who have a very low risk of HIV transmission. These people have been on ART for longer than 10 weeks **and** have had at least two documented

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 **or** the infant is born prematurely (< 34 weeks gestation) but most recent maternal viral load is <50 copies/mL. 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] The Swiss Federal Office of Public Health does not recommend infant ARV prophylaxis for infants of people with regular follow-up, ART use during pregnancy, and where maternal viral load is <50 copies/mL, ideally sustained throughout pregnancy, but at least at the last two consecutive measurements before delivery where viral load testing is performed at least 4 weeks apart and the last viral load is measured after week 36 of pregnancy.[15] Among 87 infants born to women with HIV RNA levels <50 copies/mL in the last trimester, none acquired HIV infection.[16]

The Panels recommend 2 weeks of ZDV prophylaxis for newborns born at ≥37 weeks gestation if the mother is receiving ART and has received at least 10 consecutive weeks of ART during pregnancy **and** achieved and maintained or maintained viral suppression (defined as at least two consecutive tests with HIV RNA levels <50 copies/mL obtained at least 4 weeks apart) for the duration of pregnancy **and** has HIV RNA <50 copies/mL at or after 36 weeks and within 4 weeks of delivery, **and** did not have acute HIV infection during pregnancy, **and** maternal ART adherence is not of concern (see Table 10). Infants born to individuals who do not meet the criteria above, but who have a viral load <50 copies/mL at or after 36 weeks, should receive ZDV for 4 to 6 weeks. In addition, all premature infants (<37 weeks gestation) should receive 4 to 6 weeks of ZDV unless they are at high risk of HIV acquisition. Dosing recommendations for ZDV are available for premature newborns, and an intravenous preparation of ZDV is available. Table 11. Antiretroviral Drug Dosing Recommendations for Newborns shows recommended neonatal ZDV dosing based on gestational age and birthweight.

ARV Prophylaxis for Newborns at Low Risk of Perinatal HIV Transmission Who Are Breastfed

Increasingly, individuals who have achieved and maintained *or* maintained viral suppression on ART are considering breastfeeding their infants. Individuals with HIV on ART with a consistently suppressed viral load during pregnancy (at a minimum during the third trimester) and at the time of delivery should be counseled on the options of formula feeding, banked donor human milk, or breastfeeding. The Panels recommend patient-centered, evidence-based counseling to support shared decision-making about infant feeding. See Infant Feeding for Individuals With HIV in the United States for more information on counseling, management, and monitoring.

There is no consensus on appropriate management of ARV prophylaxis for infants of individuals with sustained viral suppression who are breastfed. Available data to guide decisions are from studies in sub-Saharan Africa, where breastfeeding is recommended for all birthing parents with HIV infection. It is important to note that the World Health Organization (WHO) recommends six weeks of NVP for all infants who are breastfed by a parent who is receiving ART in resource-limited countries.[49] In the PROMISE study, among 1,219 infants of mothers on ART, there were 7 HIV transmissions reported. Among these, five mothers had documented detectable viral loads immediately prior to first report of the infant's positive HIV nucleic acid test (NAT); the remaining two mothers had elevated viral loads in subsequent testing.[17] Note that these two infants had their first detectable HIV NAT at weeks 13 and 38 of life, beyond 6 weeks of age where infant NVP was administered according to WHO guidelines. In the Breastfeeding, Antiretrovirals, and Nutrition

study, a sub-study of 31 infected infants and 232 uninfected infants and their mothers[18] demonstrated that there were no HIV transmissions when the mother consistently maintained a viral load less than 100 copies/mL. Bispo et al. have reported a meta-analysis of 11 studies of breastfeeding mothers with HIV who started ART before or during pregnancy and continued until at least 6 months postnatally.[19] The included studies were very heterogeneous and did not include viral load measurements or information about adherence. In addition, some studies included infants receiving NVP prophylaxis. Six of these studies provided estimates of postnatal transmission rates, excluding peripartum infections. In these six studies, the postnatal transmission rate was 1.08% (95% confidence interval: 0.32–1.85) at 6 months in infants who tested HIV negative at 4 to 6 weeks of age. In a *post-hoc* analysis of the HIV Prevention Trials Network (HPTN) 046 study, which showed <1% risk of postnatal HIV transmission in both the extended NVP and placebo arms, the addition of infant prophylaxis did not further reduce breastfeeding transmission in mothers who were receiving ART.[20] Taken together, these data support the efficacy of ART with documented sustained viral suppression to prevent postnatal transmission of HIV, suggesting that the recommended management consisting of 2 weeks of infant ZDV prophylaxis is appropriate for breastfed infants when their mothers have sustained viral suppression. This approach is currently recommended by the British HIV Association (BHIVA).[12]

The Panels could not reach a consensus on recommendations for infant prophylaxis while breastfeeding. Most Panel members agree on adopting the BHIVA recommendation of only 2 weeks of infant ZDV in this scenario. However, several Panel members prefer to extend the duration of ZDV prophylaxis to 4 to 6 weeks. Alternatively, some Panel members recommend 6 weeks of NVP, as currently recommended by WHO for breastfeeding infants at low risk of HIV transmission in resource limited countries. Some others opt to continue NVP dosing throughout breastfeeding. In infants who cannot tolerate ZDV or NVP, alternative regimens include daily lamivudine (3TC) or daily lopinavir/ritonavir (LPV/r).[21,22] Dosing recommendations are included in Table 11 should these regimens be preferred.

Table 12. Infant Antiretroviral Prophylaxis for Newborns of Mothers With Sustained Viral Suppression Who Breastfeed

<table>
<tr><th colspan="2">Newborns at Low Risk of HIV Acquisition During Breastfeeding</th></tr>
<tr><th>Recommended Regimen</th><th>Recommended Duration</th></tr>
<tr><td>ZDV</td><td>ZDV administered for 2 weeks (see Table 11 for dosing)</td></tr>
<tr><th colspan="2">Optional Extended Postnatal Prophylaxis for Newborns at Low Risk of HIV Transmission During Breastfeeding</th></tr>
<tr><th>Optional Regimen</th><th>Optional Recommended Duration</th></tr>
<tr><td>ZDV</td><td>ZDV administered for 4 to 6 weeks (see Table11 for dosing)</td></tr>
<tr><td>NVP</td><td>Simplified Age-Based Dosing for Newborns ≥32 Weeks Gestation Receiving Extended NVP Prophylaxis During Breastfeeding[a]
<table>
<tr><th>Age</th><th>Volume of NVP 10 mg/mL Oral Syrup Daily</th></tr>
<tr><td>Birth to 6 weeks</td><td>1.5 mL</td></tr>
</table></td></tr>
</table>

Table 12. Infant Antiretroviral Prophylaxis for Newborns of Mothers With Sustained Viral Suppression Who Breastfed

	6 weeks to 6 months	2.0 mL
	6 months to 9 months	3.0 mL
	9 months to 1 to 4 weeks post-weaning	4.0 mL

[a] Extended NVP prophylaxis during breastfeeding recommendations are adapted from the Consolidated Guidelines on HIV Prevention, Testing, Treatment, Service Delivery and Monitoring: Recommendations for a Public Health Approach. If prescribed, these simplified doses should start following confirmation of a negative infant NAT test and completion of a presumptive HIV therapy regimen in infants at high risk of HIV acquisition. For infants at low risk of transmission, these doses can be given from birth. Geneva: World Health Organization; 2021 Jul. Simplified Age-Based Dosing for Newborns ≥32 Weeks Gestation Receiving Extended NVP Prophylaxis During Breastfeeding in Consolidated Guidelines on HIV Prevention, Testing, Treatment, Service delivery and Monitoring: Recommendations for a Public Health Approach

[b] For breastfeeding parents with viral resistance to NVP, alternative regimens for infant prophylaxis after completion of the 4 to 6 weeks of presumptive HIV therapy include daily 3TC or LPV/r; see Table 11. Antiretroviral Drug Dosing Recommendations for Newborns for dosing information.

Newborns Born to Mothers Who Received No Antepartum 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 Panels recommend that all newborns born to mothers who do not have viral suppression (defined as at least two consecutive tests with HIV RNA level <50 copies/mL obtained at least 4 weeks apart and a HIV RNA <50 copies/mL at or after 36 weeks and within 4 weeks prior to delivery), who received only intrapartum ARV drugs, or who received no ARV drugs during pregnancy are at high risk for HIV acquisition and **should receive presumptive HIV therapy**.[5,23-28] These infants should also have a HIV NAT test performed as soon as possible to determine HIV infection status. Primary or acute HIV infection during pregnancy also is associated with an increased risk of perinatal transmission of HIV. Infants born to people who acquired HIV during pregnancy **should receive presumptive HIV therapy** (see Early (Acute and Recent) HIV Infection).

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.[29-37] Because of these potential benefits of early ART, the Panels recommend a three-drug ARV presumptive HIV therapy regimen consisting of ZDV, 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. In the International Maternal, Pediatric, Adolescent AIDS Clinical Trials (IMPAACT) P1115, 438 neonates who were at least 34 weeks gestational age at birth and enrolled within 48 hours of birth received a presumptive HIV therapy regimen containing two nucleoside reverse transcriptase inhibitors (NRTIs) (97% received ZDV and 3TC) and NVP dosed at 6 mg/kg twice daily for term neonates (≥37 weeks gestational age) or 4 mg/kg twice daily for 1 week and 6 mg/kg twice daily therapy for preterm neonates (34 to <37 weeks gestational age). Among the study participants, 7% reported Division of AIDS Grade 3 or 4 adverse events at least possibly

related to ART. These Grade 3 or 4 events included 6% with neutropenia and 1% with anemia.[28] The Early Infant Treatment Study in Botswana initiated ART consisting of NVP 6 mg/kg twice daily, ZDV, and 3TC at <7 days gestational age in 40 infants who were ≥35 weeks gestational age and ≥2 kg at birth with HIV infection. Eighteen percent of these infants had Grade 3 or 4 hematologic toxicity, mostly neutropenia.[38] Similar findings have been reported from other studies of presumed HIV therapy or early treatment of confirmed HIV infection.[38-40] 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 than 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.[41] In a Madrid, Spain, cohort, 227 infants received prophylaxis containing two or more drugs (64% who received ZDV, 3TC, and NVP) and 1,002 infants received ZDV alone. Although there were more frequent reports of anemia and neutropenia among infants receiving prophylaxis with 2 or more drugs, there were no significant differences in grade 3 or 4 anemia or neutropenia between the two groups.[42] 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%; $P = 0.01$).[40]

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 at least 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.[43-48]

At this time, if a presumptive HIV therapy regimen is required, the Panels recommend using a combination of ZDV, 3TC, and NVP (treatment dose) or ZDV, 3TC, and RAL (see Table 10. Neonatal Antiretroviral Management According to Risk of HIV Infection in the Newborn, and Table 11. Antiretroviral Drug Dosing Recommendations for Newborns). The optimal duration of presumptive HIV therapy in newborns at high risk of perinatal HIV acquisition is unknown. Some Panel members opt to discontinue additional medications if infant birth 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, NVP should be replaced with an integrase strand transfer inhibitor or a boosted protease inhibitor at the appropriate infant age. Information about selecting an agent and recommended dosing can be found in What to Start: Regimens Recommended for Initial Therapy of Antiretroviral-Naive Children and Appendix A: Pediatric Antiretroviral Drug Information in the Pediatric Antiretroviral Guidelines.

New dosing recommendations for abacavir (ABC) in neonates based on the IMPAACT P1106 trial and two observational European and African cohorts are now available from WHO.[49] ABC is not approved by the U.S. Food and Drug Administration (FDA) for use in neonates and infants aged <3 months. However, a 2-mg/kg-per-dose twice-daily dose has been modeled using PK simulation and is endorsed by WHO using weight-band dosing for full-term infants from birth through 1 month of age. Limited observational data suggested safety of ABC when initiated in neonates <1 month of age (see Abacavir in the Pediatric Antiretroviral Guidelines).[50,51] At this time, the Panels do not recommend ABC as part of a presumptive HIV therapy regimen. However, in situations where ZDV

is not available or the infant has ZDV-associated toxicity, ABC could be considered an alternative to ZDV. This substitution should be considered in circumstances where increased risk of ZDV toxicity may exist, such as in infants with anemia or neutropenia. It also is suggested that negative testing for HLA-B5701 allele be confirmed prior to administration of ABC. 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

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development–HIV Prevention Trials Network 040/Pediatric AIDS Clinical Trials Group 1043 (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 NRTI resistance in 3 of 53 participants (5.7%) with *in utero* infection who were treated with ZDV alone and in 6 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% of study participants.[52]

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 11.

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 people who received ARV drugs during pregnancy but who have a detectable viral load within 4 weeks prior to delivery, 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% and 0.3% when the mother had a viral load <50 copies/mL at delivery. Rates of transmission in these studies increased to 1.1% and 1.5 percent when viral load was 50 to 399 copies/mL and 2.8% and 4.1% when viral load was >400 copies/mL.[53,54] Although most Panel members would recommend initiating presumptive HIV therapy with any detectable level of viremia within 4 weeks prior to delivery, others may opt for a two-drug prophylaxis regimen if maternal viral load was less than 200 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 acquisition, 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 this section). 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 Perinatal HIV/AIDS hotline (1-888-448-8765) is recommended when selecting a regimen based on case-specific risk factors.

Breastfeeding in Newborns at High Risk of Perinatal HIV Acquisition

For people with HIV who are not on ART and/or have not achieved sustained viral suppression at the time of delivery, the Panels strongly advise against breastfeeding. Replacement feeding with formula or banked pasteurized donor human milk is recommended given the high risk of postnatal HIV transmission associated with viremia during breastfeeding (see Infant Feeding for Individuals With HIV in the United States).

If after counseling, the breastfeeding parent without a suppressed viral load chooses to continue to breastfeed, the parent and provider should remain engaged; the provider should offer guidance on ARV prophylaxis (see below) and testing for the infant and assist the parent to work with their primary provider to most rapidly regain and maintain virologic suppression. Diagnosis of HIV Infection in Infants and Children provides guidance about HIV diagnostic testing for infants who are being breastfed.

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.[22,55-58] Many of these studies were in mothers who were not receiving ART or, if receiving ART, did not have viral load routinely measured. If, despite the recommendation not to breastfeed, the infant is breastfed by a parent with unsuppressed viral load, the Panels recommend 6 weeks of presumptive HIV therapy followed by daily NVP throughout breastfeeding and for 1 to 4 weeks after weaning to minimize the risk of vertical transmission. Dosing recommendations are shown in Table 11. For breastfeeding parents with viral resistance to NVP, alternative regimens for infant prophylaxis after completion of the 6 weeks of presumptive HIV therapy include daily 3TC or LPV/r. Consultation with an expert in pediatric HIV infection is strongly recommended. Coordination with adult care providers (such as obstetric or infectious disease clinicians) can provide appropriate services to support adherence.

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

HIV testing is recommended during labor for people 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). HIV test results should be available within 60 minutes. If maternal or infant testing is positive, the newborn **should begin presumptive HIV therapy immediately** without waiting for the results of supplemental tests. HIV testing with quick turnaround times 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 infection until supplemental testing clarifies maternal and newborn HIV 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 breastfeeding parent 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 breastmilk can be recommended. If HIV is ruled out, breastfeeding can resume. If HIV is confirmed, breastfeeding should be discontinued permanently.[59]

Newborns Born to Mothers With Antiretroviral Drug-Resistant Virus

The optimal ARV regimen for newborns born to mothers 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,[60] perinatal transmission of multidrug-resistant virus does occur.[61-66] 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).[66] Maraviroc (MVC) was approved recently for infants ≥2 kg and may provide an additional treatment option for newborns of mothers carrying multidrug-resistant HIV-1 that remains CCR5-trophic.[67] However, the lack of data about MVC as prophylaxis or treatment in infants 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, ART initiation should not be delayed while waiting for the results of the confirmatory HIV NAT, given the low likelihood of a false-positive HIV NAT. A confirmatory specimen should be obtained prior to ART initiation. To date, 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 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.[68] 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.[38]

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).

For information about recommended ART regimens for newborns, please see What to Start: Regimens Recommended for Initial Therapy of Antiretroviral-Naive Children in the Pediatric Antiretroviral Guidelines.

Newborns of Mothers Who Receive an HIV Diagnosis While Breastfeeding

People 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 breastfeeding parents 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. Given the high risk of HIV transmission when HIV is acquired or diagnosed during breastfeeding, the Panels advise against breastfeeding and recommend replacement feeding with formula or banked pasteurized donor human milk if HIV infection is confirmed in the breastfeeding parent.[69]

Other than discontinuing breastfeeding, optimal strategies for managing a newborn who was breastfed by a parent with HIV (often because the parent just learned of her own HIV diagnosis) have yet to be defined. Some Panel members would consider the use of post-exposure prophylaxis in newborns for 4 to 6 weeks after cessation of breastfeeding. Post-exposure prophylaxis, however, is less likely to be effective in this circumstance than with other nonoccupational exposures because the exposure to breast milk is likely to have occurred over a prolonged period rather than a single exposure to the virus.[70] 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 person with acute HIV infection who is breastfeeding, 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.[70] 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 Perinatal HIV/AIDS hotline (1-888-448-8765) can provide referrals to local or regional pediatric HIV specialists.

In the event that the parent does not stop breastfeeding, interventions similar to individuals with chronic HIV infection and detectable viral load who breastfeed should be followed. In these scenarios, 6 weeks of a presumptive HIV regimen followed by daily NVP throughout breastfeeding and for 1 to 4 weeks after weaning should be considered to minimize the risk of vertical transmission. See Breastfeeding in Newborns at High Risk of Perinatal HIV Acquisition, above, and Infant Feeding for Individuals with HIV in the United States. Again, consultation with a pediatric HIV specialist or the National Perinatal HIV hotline (1-888-448-8765) is recommended.

Newborns exposed to HIV during breastfeeding should be tested for HIV infection prior to initiating presumptive HIV therapy, as well as at specified time points after diagnosis of HIV infection in the breastfeeding person 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 and Table 13. Recommended Virologic Testing Schedule for Infants Who Were Exposed to HIV According to Risk of Perinatal HIV Acquisition At and After Birth). 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 1 week[26,71,72] 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% of newborns, and neutropenia was reported in 18% of newborns who were exposed to ZDV/3TC, with 2% of newborns requiring blood transfusion and 4% requiring treatment discontinuation for toxicity.[73] 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% and neutropenia seen in 13% of newborns.[74]

Recent data from the IMPAACT P1106 trial and two observational European and African cohorts provided reassuring data on the safety of ABC in infants when initiated at <3 months of age, including in infants with weight <3 kg.[75-77] See the Abacavir section of the Pediatric Antiretroviral Guidelines for additional information. At this time, the Panels suggest using ABC as an alternative to ZDV in certain situations and after negative HLA-B5701 allele testing.

Experience with other NRTI drugs for neonatal prophylaxis is more limited.[78,79] Hematologic and mitochondrial toxicity may be more common with exposure to multiple NRTI drugs than with exposure to a single NRTI.[73,80-83]

In rare cases, chronic multiple-dose NVP prophylaxis in pregnant women has been associated with severe and potentially life-threatening rash and hepatic toxicity.[84] 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.[5,55-58,85]

The FDA 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. PK modeling studies in infants with birthweight <2.5 kg with gestational age at birth ranging from 32.7 to 40 weeks suggests that prematurity reduces RAL clearance, and a modified dosing regimen may be needed to avoid elevated plasma RAL concentrations.[86] 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.[46] 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. Only one episode of Grade 4 neutropenia, possibly related to RAL, was reported. Among infants with RAL exposure (infants whose mothers received RAL within 2 to 24 hours before delivery), the first dose of RAL should be delayed for 24 to 48 hours after birth.[87] See the Raltegravir section of the Pediatric Antiretroviral Guidelines for additional information.

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Diagnosis of HIV Infection in Infants and Children

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Panel's Recommendations

- Virologic assays (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 and HIV antigen/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 maternal antiretroviral therapy (ART), or by antiretroviral (ARV) drugs administered to the infant as prophylaxis or presumptive HIV therapy.
- An assay that detects HIV non-B subtype viruses or Group O infections (e.g., an HIV RNA NAT or a dual-target total DNA/RNA test) is recommended for use in infants and children who were born to mothers with known or suspected non-B subtype virus or Group O infections (AII).
- Virologic diagnostic testing (see Table 13 below) 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 ARV drugs are discontinued (BII).
- For infants with perinatal HIV exposure who are being breastfed, virologic diagnostic testing is recommended at birth, 14 to 21 days, 1 to 2 months, and 4 to 6 months of age (AII). An additional virologic test should be performed between the 1-to-2-month and 4-to-6-month time points if the gap between tests is greater than 3 months. See Infant Feeding for Individuals With HIV in the United States.
  - Virologic diagnostic testing should be performed every 3 months during breastfeeding (BII);
  - After cessation of breastfeeding, irrespective of when breastfeeding ends, virologic diagnostic testing should be performed at 4 to 6 weeks, 3 months, and 6 months after cessation (BII).
- A positive virologic test should be confirmed as soon as possible by a repeat virologic test (AII).
- Definitive exclusion of HIV infection in non-breastfed infants is based on two or more negative virologic tests, with one negative test obtained at age ≥1 month (and at least 2 -6 weeks after discontinuation of multi-drug ARV prophylaxis/presumptive HIV therapy) and one at age ≥4 months, or two negative HIV antibody tests from separate specimens that were obtained at age ≥6 months (AII).
- Additional HIV testing (e.g., HIV RNA or HIV DNA NAT, HIV antibody, HIV antigen/antibody) is not needed routinely for non-breastfed infants who meet the criteria for definitive exclusion of HIV and who have had no known or suspected HIV exposure after birth.
- Infants with potential HIV exposure after birth (e.g., from maternal HIV diagnosis during breastfeeding, premasticated feeding, sexual abuse, contaminated blood products, percutaneous exposure) who are aged <18 months require additional testing using HIV RNA/DNA NAT assays to establish their HIV status. Infants aged ≥18 months who have these potential exposures require HIV antigen/antibody testing.
- Age-appropriate HIV testing also is recommended for infants and children with signs and/or symptoms of HIV, even in the absence of documented or suspected HIV exposure.

- For children aged >24 months and for children aged 18 to ≤ 24 months with non-perinatal HIV exposure only, HIV antibody (or HIV antigen/antibody) tests are recommended for diagnostic testing (AII).
- 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- Perinatal HIV/AIDS provides consultations on issues related to the management of perinatal HIV infection, including diagnostic testing (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 diagnosed definitively by virologic testing in most non-breastfed infants with perinatal HIV exposure by age 1 to 2 months and in almost all perinatally-exposed infants by age 4 to 6 months. Antibody tests, including 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 and HIV DNA NATs are generally equally recommended. However, both tests can be affected by maternal antiretroviral therapy (ART) through transplacental transfer of antiretroviral (ARV) drugs from the pregnant person to the fetus or by ARV drugs administered to the infant as prophylaxis or presumptive HIV therapy. In general, qualitative HIV proviral DNA PCR assays from whole blood detecting cell-associated virus are 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 infections, Group O HIV-1 infections, and HIV-2 infections, see the relevant sections below and the HIV Sequence Database. 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, sometimes called total nucleic acid or TNA test), which also can identify non-subtype B and Group O infections.[10-12]

Antigen/antibody combination immunoassays that detect HIV-1/2 antibodies and 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.[13-15] 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 Diagnostic Testing in Children With Perinatal HIV Exposure in Special Situations below). Diagnosis in children aged >24 months relies primarily on HIV antibody and antigen/antibody tests (see Diagnostic Testing in Children with Non-Perinatal HIV Exposure or Children With Perinatal HIV Exposure Aged >24 Months below).[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 in Timing of Diagnostic Testing in Infants with Perinatal HIV Exposure below,[16] and receive 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 HIV Infection.

Timing of Diagnostic Testing in Infants With Perinatal HIV Exposure

Confirmation of HIV infection is based on the results of positive virologic tests from two separate blood samples in infants and children younger than 18 months. Table 13 below summarizes the timing of recommended virologic diagnostic testing for infants based on HIV transmission risk. Infants at high risk of perinatal HIV transmission, may require additional virologic testing, 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. 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 at age ≥8 weeks at least 2 weeks after discontinuing multi-drug ARV prophylaxis/presumptive therapy, or one negative HIV antibody test at age ≥6 months.[1,16]

Definitive exclusion of HIV infection in non-breastfed infants is based on two or more negative virologic tests, with one negative test obtained at age ≥1 month (and at least 2 -6 weeks after discontinuation of multi-drug ARV prophylaxis/presumptive therapy) and one at age ≥4 months, or two negative HIV antibody tests from separate specimens that were 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 cell count/percentage) or clinical evidence of HIV infection and must not be breastfeeding. No additional HIV testing of any kind (e.g., NAT, antibody, antigen/antibody) is needed routinely for non-breastfed infants who meet the criteria for definitive exclusion of HIV and who have had no known or suspected HIV exposure after birth.

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 infection.[17] 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 *Pneumocystis jirovecii* Pneumonia in the Pediatric Opportunistic Infection Guidelines).

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,[18-23] 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 have specimens obtained for HIV testing 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 non-breastfed 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.[18,19,24] Testing at birth also might 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,[16] 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 3 months is intended to maximize the likelihood of detecting HIV infection in perinatally exposed infants. In the HIV Prevention Trials Network 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.[25] For infants at high risk of perinatal HIV transmission, the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV and the Panel on Treatment of HIV During Pregnancy and Interventions to Reduce 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.[25,26]

In these situations, many experts recommend one test at age 4 to 6 weeks to allow prompt diagnosis of HIV in infants 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 Table 13 below). For infants at low risk of HIV transmission, a single test obtained at 1 to 2 months of age may be timed to occur 2 to 4 weeks after cessation of ARV prophylaxis.

An infant with two negative virologic test results (the first at age ≥14 days and the other at age ≥4 weeks), or one negative test result at age ≥8 weeks at least 2 weeks after discontinuing multi-drug ARV prophylaxis/presumptive therapy, can be viewed as presumptively HIV uninfected, assuming the child has not had a positive prior virologic test result 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 had no positive virologic tests, 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.

Virologic Testing for Infants With Perinatal HIV Exposure Who Are Being Breastfed.

Some individuals with HIV may choose to breastfeed their infants (see Infant Feeding for Individuals With HIV in the United States). Infants with perinatal HIV exposure who are being breastfed should have virologic diagnostic testing at the standard time points: 14 to 21 days, 1 to 2 months, and 4 to 6 months (see Table 13 below). In addition, a virologic test at birth is recommended. In some cases, an additional virologic test should be performed between the 1-to-2 month and 4-to-6-month time points if the gap between tests is greater than 3 months. Infants continuing to be breastfed beyond 6 months of age should have virologic diagnostic testing every 3 months during breastfeeding. At cessation of breastfeeding, virologic diagnostic testing should be performed at 4 to 6 weeks, 3 months, and 6 months after breastfeeding has ended, regardless of the age of the child when breastfeeding is discontinued. If an infant's virologic test result is positive, a repeat test should be performed as soon as possible and ART should be initiated.

Maternal viral load monitoring is recommended every 1 to 2 months during breastfeeding. Additional infant virologic testing, including immediate NAT testing, is indicated if maternal viral load becomes detectable during breastfeeding. If the mother has a detectable viral load and continues breastfeeding, some Panel members would recommend monthly virologic testing of the infant as an approach to early detection of HIV infection during ongoing exposure. After cessation of breastfeeding, virologic testing should be performed at least 2 weeks after cessation of presumptive HIV therapy or ARV prophylaxis (see Antiretroviral Management of Newborns of Newborns With Perinatal HIV Exposure or HIV Infection) and at 4 to 6 weeks, 3 months, and 6 months after cessation of breastfeeding. Consultation with an expert and/or the Perinatal HIV Hotline (888-448-8765) is recommended in these situations and for questions about HIV diagnostic testing for infants with perinatal HIV exposure who are being breastfed. For additional information see Infant Feeding for Individuals With HIV in the United States.

Table 13. Recommended Virologic Testing Schedules for Infants Who Were Exposed to HIV According to Risk of Perinatal HIV Acquisition at and After Birth[a]

Infants at High Risk	
Criteria for Infants at High Risk	**Age at HIV NAT[b] Testing for Infants at 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	Birth 14–21 days 1–2 months 2–3 months[c] 4–6 months All infants at high risk of perinatal HIV transmission should have specimens obtained for HIV testing at birth before initiating an ARV drug regimen; however, presumptive HIV therapy should not be delayed. If an infant's NAT test result is positive, a repeat test should be performed as soon as possible and ART should be initiated.
Infants at Low Risk	
Criteria for Infants at Low Risk	**Age at HIV NAT[b] Testing for Infants at Low Risk**
Infants born to mothers who— • Received ART during pregnancy; • Had sustained viral suppression (usually defined as <50 copies/mL); *and* • Were adherent to their ARV regimens	14–21 days 1–2 months[d] 4–6 months
Infants With Perinatal HIV Exposure Who Are Being Breastfed	
Age at HIV NAT[b] Testing for Infants With Perinatal HIV Exposure Who Are Being Breastfed	
Birth 14–21 days 1–2 months 2–4 months[e] 4–6 months If breastfeeding continues beyond 6 months of age, NAT testing should be performed every 3 months during breastfeeding. In addition to the standard time points after birth, NAT testing also should be performed at 4 to 6 weeks, 3 months, and 6 months after cessation of breastfeeding, regardless of the age at when breastfeeding ends. Consultation with an expert is recommended to determine additional testing time points that may be needed for infants with risk factors for HIV acquisition at birth who are being breastfed. Prompt NAT testing of the infant is indicated if maternal viral load becomes detectable during breastfeeding.	

If the mother has a detectable viral load and continues breastfeeding, some Panel members would recommend monthly virologic testing of the infant as an approach to early detection of HIV infection during ongoing exposure.

See Infant Feeding for Individuals With HIV in the United States. Consultation with an expert and/or the Perinatal HIV Hotline (888-448-8765) is recommended for questions about HIV diagnostic testing for infants with perinatal HIV exposure who are being breastfed.

[a] This table summarizes standard time points for HIV virologic diagnostic testing of infants according to risk of perinatal acquisition.

[b] HIV RNA or HIV DNA NATs that directly detect HIV.

[c] For high-risk infants, virologic diagnostic testing is recommended at birth. For infants treated with multiple ARVs in the first 2 to 4 weeks of life, additional virologic testing is recommended 2 to 6 weeks after ARV drugs are discontinued (i.e., at 8–12 weeks of life).

[d] For low-risk infants, testing may be timed to occur at least 2 weeks after cessation of ARV prophylaxis.

[e] An additional virologic test should be performed at age 2 to 4 months if the gap between the tests at ages 1 to 2 months and 4 to 6 months is greater than 3 months.

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 also can be used to exclude HIV infection definitively in children with no clinical or virologic laboratory-documented evidence of HIV infection.[27,28]

Antibody Testing at Age 18 to 24 Months to Document Seroreversion

In general, no additional HIV testing of any kind (e.g., NAT, antibody, antigen/antibody) is needed routinely for non-breastfed infants who meet the criteria for definitive exclusion of HIV and who have had no known or suspected HIV exposure after birth. However, infants with potential HIV exposure after birth (e.g., maternal diagnosis during breastfeeding, premasticated feeding, sexual abuse, contaminated blood products, percutaneous exposure) who are aged <18 months require additional testing using HIV RNA/DNA NAT assays to establish their HIV status. Infants aged ≥18 months who have these potential exposures require HIV antigen/antibody testing.

In a study from 2012, the median age at seroreversion was 13.9 months.[29] Although the majority of infants who do not have HIV will serorevert by age 15 months to 18 months, late seroreversion after 18 months has been reported (see Diagnostic Testing in Children With Perinatal HIV Exposure in Special Situations below). Factors that might influence the time to seroreversion include maternal disease stage and assay sensitivity.[29-32]

Diagnostic Testing in Children With Perinatal HIV Exposure in Special Situations

Breastfeeding at the Time of New Maternal HIV Diagnosis

Infants may be exposed to HIV through breastfeeding if the mother develops acute or primary HIV infection or when pre-existing maternal HIV infection was not diagnosed during pregnancy or immediately postpartum.[33] People who are diagnosed with HIV during breastfeeding should be counseled to discontinue breastfeeding immediately to reduce the risk of postnatal transmission to the

infant, see Situations to Consider Stopping or Modifying Breastfeeding in Infant Feeding for individuals With HIV in the United States. In these situations, infant virologic diagnostic testing by HIV DNA or RNA PCR is recommended as soon as possible with the schedule for subsequent tests affected by the infant's age when breastfeeding is discontinued. Virologic tests should be conducted at ages 14 to 21 days, 1 to 2 months, and 4 to 6 months. A virologic test also should be performed at least 2 weeks after cessation of ARV prophylaxis or presumptive HIV therapy (see Antiretroviral Management of Newborns With Perinatal HIV Exposure or HIV Infection) and at 4 to 6 weeks, 3 months, and 6 months after cessation of breastfeeding. Duplicate tests are not needed if some of these time points overlap. For additional information, consult the Perinatal HIV Hotline (1-888-448-8765).

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 maternal HIV antibodies up to age 24 months. These children are called late seroreverters.[29-32] In one study, 14% of children with HIV exposure who did not have HIV infection seroreverted after age 18 months.[29] 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 also was 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. In such cases, repeat antibody testing at a later date confirmed seroreversion. Due to the possibility of residual maternal HIV antibodies, virologic testing 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. Age-appropriate HIV testing also is recommended for infants and children with signs and/or symptoms of HIV, even in the absence of documented or suspected HIV exposure.

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 Non-Perinatal HIV Exposure or Children with Perinatal HIV 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.[35-37] The diagnostic approach in these situations is discussed below in Virologic Assays to Diagnose Group M Non-Subtype B and Group O HIV-1 Infections and in 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

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.[38-43] 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 because 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. It may be difficult to obtain a history of HIV exposure. Therefore, age-appropriate HIV testing is recommended for infants and children with signs and/or symptoms of HIV infection, even in the absence of documented or suspected perinatal or non-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.[44]

Diagnostic Testing

Diagnosis of HIV-1 infection in infants and children with non-perinatal HIV exposure only or in children with perinatal HIV exposure who are aged >24 months relies primarily on HIV antibody and antigen/antibody tests.[1,45] U.S. Food and Drug Administration (FDA)-approved diagnostic tests include the following:

- Antigen/antibody combination immunoassays, which detect HIV-1/2 antibodies and 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.[46] 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.[47]
- 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 always is indicated as an additional test to diagnose acute HIV infection.

The diagnosis of HIV-2 in children with non-perinatal exposure only or in children with perinatal exposure aged >24 months relies on the 2014 Centers for Disease Control and Prevention (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.[1,48] 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.[49,50]

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.[26] 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 before 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.[3,26,51]

The sensitivity of HIV RNA assays is affected by maternal antenatal ART or ARV drugs administered to the infant as prophylaxis or presumptive therapy.[52] 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. In contrast, the median HIV RNA levels were high by age 3 months in both groups after stopping prophylaxis.[26] 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 ARV regimens during those years.[53] 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, an HIV RNA measurement assesses baseline viral load. An HIV genotype can be performed on the same sample 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.[24,54-57]

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.[24,26,51]

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. One study noted that among 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.[25] Another 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. 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 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, suggesting that rapid decline of HIV-1 RNA and DNA may complicate definitive diagnosis.[58] 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.[59] A data set of 38,043 infants from the Western Cape province of South Africa who were tested at a median age of 45 days showed that infants who received the World Health Organization Option B+ ARV regimen had fewer indeterminate DNA PCR results than infants who were receiving older ARV regimens.[60] Another group of South African investigators reported similar findings in a study of a cohort of 5,743 neonates from Johannesburg who were exposed to HIV.[61]

The AMPLICOR® HIV-1 DNA test has been used widely 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 early HIV diagnosis in infants, but it is not approved by the FDA.[10,11,61] These considerations underscore the importance of testing with HIV NATs at 4 months—well after neonatal ARV prophylaxis or presumptive HIV therapy has stopped.

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 also are found in the United States.[62] Data from the CDC National HIV Surveillance System (NHSS) showed that the number of non-U.S.-born children with HIV has exceeded the number of U.S.-born children with HIV since 2011, with 65.5% of non-U.S.-born children with HIV born in sub-Saharan Africa and 14.3% in Eastern Europe.[63] 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.[64] 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.[65] 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.[66] 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.[67] Non-subtype B and Group O strains may be seen in countries with links to these geographical regions.[68-72] 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 an 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 rule out HIV infection definitively. 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 HIV testing.

Chimeric Antigen Receptor T-Cell and Lentiviral-Based Gene Therapy May Give Rise to False-Positive HIV NAT Results

Chimeric antigen receptor (CAR) T-cell immunotherapy is a major advancement in cancer therapeutics, including for pediatric B-cell acute lymphoblastic leukemia. Reprogramming of T cells is achieved by using gammaretroviral or lentiviral vectors. Recent reports indicate that these vectors may interfere with long terminal repeat genomes in HIV NAT results 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 results 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 results. Laboratories should, therefore, have appropriate alternate HIV-1 NAT resulting platforms made available for this emerging patient population.[73-77]

Virologic Assays to Diagnose HIV-2 Infections

HIV-2 infection is endemic in Angola; Mozambique; West African countries, including Benin, Burkina Faso, Cape Verde, the Gambia, Ghana, Guinea, Guinea-Bissau, Ivory Coast, Liberia, Mali, Mauritania, Niger, Nigeria, Sao Tome, Senegal, Sierra Leone, and Togo; and parts of India.[78-80]

HIV-2 infection also is well documented in France and Portugal, which have large numbers of immigrants from these regions.[81,82] HIV-1 and HIV-2 coinfection may occur, but this rarely is 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.[83-85] (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 and HIV-1 RNA viral loads that are at or below the limit of detection in the absence of treatment). The current recommendation is to use an HIV-1/HIV-2 antibody differentiation immunoassay for supplemental testing.[1] Between 2010 and 2017, an increase in the number of HIV-1/HIV-2 differentiation test results was reported to the CDC's 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).[86]

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 known or suspected HIV-2 infection. HIV-2 DNA PCR testing can be arranged by the HIV surveillance program of the state or local health department through their public health laboratory, or the CDC, because this assay is not commercially available.[49,50] Clinicians should consult with an expert in pediatric HIV infection when caring for infants with suspected or known exposure to HIV-2.[78,87]

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Initial Postnatal Management of the Neonate Exposed to HIV

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Panel's Recommendations
• All newborns perinatally exposed to HIV should receive appropriate antiretroviral (ARV) drugs as soon as possible, preferably within 6 hours, after delivery (see Antiretroviral Management of Infants with Perinatal HIV Exposure or HIV Infection) (AI). • For infants in whom presumptive HIV therapy is initiated, hemoglobin and neutrophil counts should be obtained at baseline. If combination ARV drugs are continued through 4 weeks, hemoglobin and neutrophil counts should be remeasured at that time (AI). • With 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, other ARV drugs, or certain concomitant medications; and the specific ARV drugs used in the birthing parent's antepartum drug regimen. Infants who are found to have hematologic abnormalities may need to discontinue or switch ARV drugs, and consultation with an expert in pediatric HIV infection is advised (CIII). • Nucleic acid tests (e.g., DNA and RNA polymerase chain reaction [PCR] assays) 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 (PJP), all infants born to persons with HIV should begin PJP prophylaxis at age 4 to 6 weeks, unless adequate test information is available to presumptively exclude HIV infection (see *Pneumocystis jirovecii* Pneumonia in the Pediatric Opportunistic Infections Guidelines) (AII). • Health care providers should inquire routinely about infant feeding plans and/or breastfeeding desires, as well as the use of pre-masticated (pre-chewed or pre-warmed) food. Counseling against pre-mastication and discussion of safe infant feeding options should be provided (see Infant Feeding for Individuals with HIV in the United States) (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 exposed to HIV should have a detailed physical examination, and a thorough birthing parent health history should be obtained. Pregnant people with HIV may have coinfections with other pathogens that can be transmitted during pregnancy and the birthing process, such as cytomegalovirus (CMV), Zika virus, herpes simplex virus, hepatitis B virus (HBV), hepatitis C virus (HCV), syphilis, toxoplasmosis, or tuberculosis. Infants born to a birthing parent with such coinfections should undergo appropriate evaluation to exclude the possibility of transmission of additional infectious agents. The routine primary immunization schedule for children should be followed for infants born to persons with HIV. One study examining humoral response to routine vaccination in infants who were exposed to HIV but uninfected (HEU) demonstrated robust antibody responses to vaccine antigens to support this recommendation.[1] However, the immunization schedule may need to be modified for infants with confirmed HIV infection (see the Pediatric Opportunistic Infections Guidelines for more information).

Infants should be monitored for toxicities associated with antiretroviral (ARV) drugs to which they were exposed *in utero* or the ARV drugs that they are receiving for the prevention of perinatal HIV transmission (see Antiretroviral Management of Infants with Perinatal HIV Exposure or HIV Infection). No evidence is available to enable the Panel on Treatment of HIV During Pregnancy 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

Older studies have shown that anemia is the primary hematologic complication in neonates who received a 6-week postnatal prophylaxis regimen with zidovudine (ZDV).[2] Some experts remeasure hemoglobin and neutrophil counts routinely after ZDV prophylaxis and/or when the results of diagnostic HIV nucleic acid test (NAT) assays 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.[3-7] Although a 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 with low-risk infants who received ZDV alone, these differences did not persist past 2 months of age.[6] In addition, a recent study from the European Pregnancy and Paediatric Infections Cohort Collaboration (EPPICC) evaluated 1,836 infants who were 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, $P = 0.277$).[8] 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, $P = 0.113$).[9] Hemoglobin level and neutrophil count testing should be repeated following the initiation of ARV drugs and/or at the time that a diagnostic HIV NAT is performed in infants who receive regimens that contain ZDV and 3TC.[3,6]

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 birthing parent's history of ARV drugs and viral load near delivery, and mode of delivery). A 4-week ZDV regimen, compared with the 6-week ZDV regimen, has been reported to result in earlier recovery from anemia in infants who are HIV-exposed but otherwise healthy.[10] A 2-week (instead of a 4- or 6-week) ZDV neonatal regimen **is recommended** in situations where there is a low risk of perinatal HIV transmission (see specific criteria in Table 10. Neonatal Antiretroviral Management According to Risk of HIV Infection in the Infant in Antiretroviral Management of Infants with Perinatal HIV Exposure or HIV Infection).[11] The shorter ZDV regimen may mitigate the risk of anemia in infants who are HEU.

Hyperbilirubinemia

Hyperbilirubinemia has been observed in HIV-exposed infants receiving raltegravir (RAL) through 6 weeks of life. The International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Network P1110 study reported Grade 3 to Grade 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.[12] RAL at extremely high levels may displace unconjugated bilirubin from albumin, increasing the potential risk of bilirubin-induced neurologic dysfunction.[13] Because of the possible risk of hyperbilirubinemia, serum total and direct bilirubin measurement may be considered in infants receiving RAL.

Prophylaxis Against *Pneumocystis jirovecii* Pneumonia

To prevent *Pneumocystis jirovecii* pneumonia, all high-risk infants born to people with HIV should begin trimethoprim-sulfamethoxazole prophylaxis at age 4 to 6 weeks, unless adequate virologic test information exists to presumptively exclude HIV infection (see the *Pneumocystis jirovecii* Pneumonia section of the Pediatric Opportunistic Infections Guidelines).[14] 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 postnatal ARV regimen is completed (see Diagnosis of HIV Infection in Infants and Children).

Testing for Viral Coinfections in the Infant

The prevalence of congenital CMV (cCMV) is higher in infants with perinatal exposure to HIV than in the general population. Screening for cCMV is recommended in the first 21 days of life. Early diagnosis allows appropriate monitoring and antiviral intervention with (val)ganciclovir, which improves clinical outcomes for associated comorbidities, including sensorineural hearing loss. The Pediatric Opportunistic Infection Guidelines recommend testing for cCMV in urine and/or saliva using a polymerase chain reaction (PCR) assay, and a routine newborn audiologic evaluation. For infants diagnosed with cCMV, longitudinal audiologic follow-up and neurodevelopmental assessments are recommended (see Cytomegalovirus).[15] In certain states, universal newborn screening for cCMV is recommended using dried blood spots. This test currently serves as an adjunct to urinary and salivary testing for CMV pending further validation.

HCV screening with an anti-HCV antibody test is recommended for all pregnant people during each pregnancy.[16,17] The Centers for Disease Control and Prevention (CDC) recommends HCV testing for all infants and children born to pregnant people with current or probable HCV infection. Infants with perinatal exposure to HCV should receive a NAT for HCV RNA at age 2 to 6 months to identify children in whom chronic HCV infection might develop. Parents or caregivers should receive counseling about the need for testing and follow-up (see Hepatitis C Virus/HIV Coinfection). Infants with detectable HCV RNA should be managed in consultation with a health care provider who has expertise in pediatric HCV management. Infants with an undetectable HCV RNA result do not require further follow-up unless clinically warranted.[18]

It is recommended that HBV screening for hepatitis B surface antigen (HBsAg) for all pregnant people occur during each pregnancy, preferably in the first trimester, regardless of vaccination status or history of testing.[19] The CDC recommends that infants born to people who are HBsAg positive be tested for HBsAg and hepatitis B surface antibody seromarkers. All infants born to people with positive HBsAg screening, including those with perinatal HIV exposure, should receive hepatitis B immune globulin and the first dose of the HBV vaccine series as soon as possible, preferably within 12 hours after birth, followed by the routine HBV vaccine series. See Evaluating and Managing Infants Who Were Exposed to HIV in Hepatitis B Virus/HIV Coinfection for additional information. Infants with detectable HBV DNA should be managed in consultation with a health care provider with expertise in pediatric HBV management.

HIV Testing of the Infant

All infants who are perinatally exposed to HIV require nucleic acid testing (HIV RNA or HIV DNA assays) to diagnose or exclude HIV infection. For a detailed discussion of HIV testing, including types of tests and the recommended HIV testing schedule, see Table 13. Recommended Virologic Testing Schedules for Infants Who Were Exposed to HIV According to Risk of Perinatal HIV Acquisition at and After Birth in Diagnosis of HIV Infection in Infants and Children.

Infant Feeding Practices and Risk of HIV Transmission

People with HIV should receive evidence-based, patient-centered counseling to support shared decision-making about infant feeding prior to conception or as early as possible in pregnancy. Plans for infant feeding should be reviewed throughout pregnancy and again after delivery. At postnatal visits, it is important to discuss infant feeding to assess feeding practices, identify barriers, and provide supports for the appropriate implementation of their chosen method (see Infant Feeding for Individuals with HIV in the United States). For information on ARV prophylaxis duration and HIV screening frequency for breastfeeding infants, see Antiretroviral Management of Infants with Perinatal HIV Exposure or HIV Infection, Pregnancy and Postpartum HIV Testing and Identification of Perinatal and Postnatal HIV Exposure, and Diagnosis of HIV Infection in Infants and Children.

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

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Panel's Recommendations
• Children with perinatal exposure to HIV and antiretroviral (ARV) drugs who develop significant organ system abnormalities of unknown etiology, particularly of the nervous system or heart, should be evaluated for potential metabolic dysfunction (CIII). • It is important that the long-term medical record of a child without HIV includes information about perinatal HIV and 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, long-term monitoring and outcomes studies, as well as ongoing surveillance and research, have been conducted to assess whether *in utero* exposure to HIV and antiretroviral (ARV) drugs may pose later risks to children's health. These studies (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]) include children without HIV infection who are born to mothers with HIV. 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. Furthermore, long-term investigation of potential HIV- and/or ARV-related toxicities is required, especially as antiretroviral therapy (ART) for pregnant people 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 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.[4,5] 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.[6,7] In a meta-analysis, all-cause mortality risk was higher in infants and children who were HEU than in those who were HUU.[8] 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.[9]

Potential Immunologic Dysfunction and Infectious Morbidity

The potential long-term impact of HIV/ARV exposure on the immune system of infants who are HEU is unclear. In a meta-analysis, infants who were HEU had a 50% and 70% increased risk for diarrhea and pneumonia, respectively, in the first 6 months of life compared with infants who were HUU.[10] Studies of infants in Malawi and South Africa who were HEU and HUU found higher rates of lower respiratory tract infections among infants who were HEU,[5,11] although another study in South Africa did not show increased infectious morbidity at 3 to 5 years of life among infants who were HEU.[12] The French Perinatal Cohort Group has observed an increased risk of serious bacterial infections with encapsulated organisms in infants who were HEU born to mothers with HIV with low CD4 T lymphocyte (CD4) cell counts near the time of delivery.[13] A retrospective study of 195,941 infants who were 90 days old or younger in a Spanish cohort from 2008 to 2017 found that infants who were HEU had a sevenfold increased risk of group B streptococcus (GBS) infection and a 29-fold greater risk of GBS meningitis compared to those who were HUU.[14] A Malawian longitudinal cohort study of infants who were HEU and HUU found evidence of dysregulated monocyte and B-cell function, which could partly explain increased rates of invasive bacterial infections and pneumonia in infants who are HEU.[15] In the United States and Canada, rates of hospitalizations early in life have been found to be higher among infants who were HEU than infants who were HUU,[16-18] with respiratory syncytial virus and parainfluenza playing a potential role in these differences.[16,17] In South Africa, studies have reported higher rates of lower respiratory tract and diarrheal illnesses in the first 6 months of life, as well as infectious-cause hospitalizations between 1 month to 12 months of age, in infants who were HEU than infants who were HUU.[19,20] A potential association between maternal viral load at delivery and infant immunity also was documented—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.[21] Immune phenotyping suggests that exposure to HIV *in utero* may be associated with perturbations in infant CD4 and CD8 cell-mediated immune responses, rather than humoral responses, resulting in T-cell dysfunction and altered vaccine responses in infants who were HEU.[17,22,23] These observations have been supported by data showing increased monocyte activation and pro-inflammatory responses with downregulation of genes involved in neutrophil-mediated immunity in infants who were HEU compared with infants who were HUU.[24-30]

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.[31-40] 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, while studies from South Africa, Zambia, Malawi, and Uganda documented persistently lower weight-for-age z-scores (WAZ) and length-for-age z-scores (LAZ) in early childhood, as well as higher rates of stunting (length- or height-for-age z-score <-2) in those who were HEU.[34,37-39,41-44] These changes may reflect disruption to the growth hormone axis in infants who are HEU compared with infants who are HUU.[44] Maternal inflammation and immune activation among pregnant people with HIV may influence child growth.[45] A systematic review of studies investigating children who are HEU found that elevated markers of inflammation (i.e., acute phase reactants, pro-inflammatory cytokines, chemokines) and intestinal microbial translocation are associated with poor growth in infants who are HEU. Elevated markers of inflammation are also associated with adverse neurodevelopment in infants who are HEU.[46] Among studies that included only children who were HEU, a large study in

Ethiopia demonstrated that maternal ART at conception was associated with higher rates of stunting in children who were HEU,[36] but another study in Malawi found no such association.[47] 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 LAZ after 6 months of life were noted between children who were HEU and a matched comparator group of children who were HUU.[48] Furthermore, the PHACS SMARTT study in the United States noted above-average weight in children who were HEU compared with children in the general pediatric population.[32] 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,[49] and obese children and adolescents who were HEU have a greater risk of systolic and diastolic hypertension than obese children and adolescents in the general pediatric population.[50] However, a South African prospective birth cohort study evaluating cardiometabolic outcomes—including body composition and size, glucose metabolism, lipids, and blood pressure—did not find notable differences between children who were HEU and HUU at 5 to 8 years of age.[51,52] 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.[53-55]

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.[56-60] 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.[60-62] However, some studies reported an increased risk for poorer neurodevelopmental outcomes in children who were HEU.[57-59,61-65] A systematic review found in three studies a higher prevalence of psychiatric disorders in children who were HEU compared to children who were HUU, which was linked to socioeconomic status, stigma, and increased psychosocial stress.[66] In a recent study from Nairobi, Kenya, children who were HEU had significantly lower mean z-scores for global cognitive ability than children who were HUU, as well as short-term and delayed memory, attention, and processing speed, even after adjusting for child nutritional status, household food security, and orphanhood.[67] Among a large cohort of 3- to 6-year-old children who were HEU from eastern/southern Africa, group-mean composite neurodevelopmental scores averaged within the low-normal range, with differences noted by country and maternal clinical and socioeconomic factors.[68] These data may reflect recent findings documenting lower caudate and total grey matter volumes in infants who were HEU than infants who were HUU in the first weeks of life. Furthermore, maternal immunosuppression was associated with reduced caudate and grey matter volumes. These findings suggest that antenatal HIV exposure may impact early structural brain development.[69]

Some studies evaluated whether maternal factors or *in utero* ARV drug exposure contributed to adverse neurodevelopmental outcomes among children who were HEU. Although delayed infant neurodevelopment was associated with maternal viremia in one study[70] and with *in utero* efavirenz exposure in another,[71] many studies have not identified associations between maternal ARV use and infant neurodevelopment.[64,70,72-74]

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 Efavirenz). Neurodevelopmental assessments at ages 1 year 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.[75,76] Presently, no definitive evidence shows an association between *in utero* exposure to specific ARV drugs and poorer neurodevelopmental outcomes.[77]

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.[78-80] Aberrant 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 neonates and young children exposed *in utero* to NRTI drugs.[2,81-83] The degree to which these documented mitochondrial abnormalities are clinically relevant is unknown, but they are outweighed significantly by the robust, proven efficacy of maternal and infant ARV prophylaxis in preventing perinatal HIV transmission.[2,84] In addition, newer NRTIs, such as tenofovir, have not been associated with the same degree of mitochondrial toxicity as older NRTIs, such as zidovudine, lamivudine, and abacavir.[79,85,86]

Although early studies from the French Perinatal Study Group cohort noted a significantly increased incidence of clinical effects reflecting either established or possible mitochondrial dysfunction,[87,88] further clinical studies from the United States and Europe did not corroborate findings from the French studies.[89-95] 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.[96-98] Mitochondrial dysfunction may be considered in children without HIV but with perinatal exposure to ARV drugs who present with clinical findings of unknown etiology, particularly metabolic or neurologic findings.

Potential Cancer Risk and Exposure to NRTI 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.[99,100] 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 at least one NRTI drug.[101,102] A U.S. study using state health department records of 13,617 children who were HEU followed for a median of 9.3 years with a maximum of 20 years found a borderline elevated risk for brain cancer, based on six cases, and no significant increase risk for leukemia.[103] Among the NRTIs studied, didanosine **(no longer recommended)** potentially was associated with risk of cancer (See Didanosine in Archived Drugs). 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.[104] 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 people 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: Key to Acronyms

Updated: January 31, 2024
Reviewed: January 31, 2024

Drug Name Abbreviations

Acronym/Abbreviation	Full Name
3TC	lamivudine
ABC	abacavir
ATV	atazanavir
ATV/c	atazanavir/cobicistat
ATV/r	atazanavir/ritonavir
BIC	bictegravir
CAB	cabotegravir
CAB-LA	long-acting cabotegravir; long-acting injectable cabotegravir
COBI, or c	cobicistat
d4T	stavudine
ddC	zalcitabine
ddI	didanosine
DMPA	depot medroxyprogesterone acetate
DOR	doravirine
DRV	darunavir
DRV/c	darunavir/cobicistat
DRV/r	darunavir/ritonavir
DTG	dolutegravir
EFV	efavirenz
ENG	etonogestrel
ETR	etravirine
EVG	elvitegravir
EVG/c	elvitegravir/cobicistat
FPV	fosamprenavir
FPV/r	fosamprenavir/ritonavir

FTC	emtricitabine
FTR	fostemsavir
IBA	ibalizumab-uiyk; ibalizumab
IDV	indinavir
IDV/r	indinavir/ritonavir
INH	isoniazid
LEN	lenacapavir
LNG	levonorgestrel
LPV	lopinavir
LPV/r	lopinavir/ritonavir
MPA	medroxyprogesterone acetate
MVC	maraviroc
NFV	nelfinavir
NVP	nevirapine
RAL	raltegravir
RPV	rilpivirine
RTV, or r	ritonavir
SQV	saquinavir
SQV/r	saquinavir/ritonavir
T-20	enfuvirtide
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil fumarate
TFV	tenofovir
TFV-DP	tenofovir diphosphate
TMP/SMX	trimethoprim/sulfamethoxazole
TPV	tipranavir
TPV/r	tipranavir/ritonavir
ZDV	zidovudine

General Terms

Acronym/Abbreviation	Full Name
AASLD	American Association for the Study of Liver Diseases
ACOG	American College of Obstetricians and Gynecologists
ACTG	AIDS Clinical Trials Group
ALT	alanine aminotransferase
anti-HBc	anti-hepatitis B core antibody
anti-HBs	hepatitis B surface antibody
aOR	adjusted odds ratio
aHR	adjusted hazard ratio
aRR	adjusted risk ratio
ART	antiretroviral therapy
ARV	antiretroviral
AUC	area under the curve
$AUC_{0–24h}$	area under the curve from 0 to 24 hours
BMC	bone mineral content
BMD	bone mineral density
BMI	body mass index
BHIVA	British HIV Association
BSID-III	Bayley Scales of Infant and Toddler Development, Third Edition
C_{12h}	concentration at 12 hours postdose
C_{24h}	concentration at 24 hours postdose
CAR	chimeric antigen receptor
cCMV	congenital cytomegalovirus
CCR5	C-C chemokine receptor type 5
CD4	CD4 T lymphocyte
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CK	creatine kinase
CL/F	apparent clearance

C_{max}	maximum plasma concentration
C_{min}	minimum plasma concentration
CMV	cytomegalovirus
C_{trough}	trough concentration
COC	combined oral contraceptives
COC/P/R	combined oral contraceptives/patch/ring
CrCl	creatinine clearance
C_{trough}	trough concentration
CYP	cytochrome P450
DAA	direct-acting antiviral
DBS	dried blood spot
DMC	Developmental Milestones Checklist
EC	emergency contraception enteric coated
EC_{95}	95% maximal effective concentration
EE	ethinyl estradiol
ePPND	enhanced pre- and postnatal development
FDA	U.S. Food and Drug Administration
FDC	fixed-dose combination
GBS	group B streptococcus
GMC	geometric mean concentration
gp	glycoprotein
HAV	hepatitis A virus
HBIG	hepatitis B immune globulin
HBcAb	hepatitis B core antibody
HBeAb	hepatitis B e antibody
HBeAg	hepatitis B e antigen
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus

HCAZ	head circumference–for-age z-score
HEU	HIV exposed but uninfected
HD	high dose
HDP	hypertensive disorders of pregnancy
HUU	HIV unexposed and uninfected
HR	hazard ratio
HRSA	Health Resources and Services Administration
HSR	hypersensitivity reaction
IC_{50}	inhibitory concentration 50%
IDSA	Infectious Diseases Society of America
IGF	insulin-like growth factor
IgG	immunoglobulin G
IgM	immunoglobulin M
IM	intramuscular
INSTI	integrase strand transfer inhibitor
IPV	intimate partner violence
IQR	interquartile range
IRR	incidence rate ratio
IUD	intrauterine device
IUPC	intrauterine pressure catheter
IV	intravenous/intravenously
LA	long-acting
LARC	long-acting reversible contraceptive
LAZ	length-for-age z-score
LBW	low birth weight
LGBTQIA+	lesbian, gay, bisexual, transgender, queer, intersex, asexual, and gender nonconforming
mtDNA	mitochondrial DNA
NAT	nucleic acid test
NE	norethindrone
NHSS	National HIV Surveillance System

NICHD	*Eunice Kennedy Shriver* National Institute of Child Health and Human Development
NIH	National Institutes of Health
NNRTI	non-nucleoside reverse transcriptase inhibitor
nPEP	non-occupational post-exposure prophylaxis
NPHIV	non–perinatally acquired HIV
NRTI	nucleoside reverse transcriptase inhibitor
NTD	neural tube defect
OARAC	Office of AIDS Research Advisory Council
OI	opportunistic infection
OR	odds ratio
The Panel	The Panel on Treatment of HIV During Pregnancy and Prevention of Perinatal Transmission
PBMC	peripheral blood mononuclear cell
PB	physiologically based
PBPK	physiologically based pharmacokinetic
PJP	*Pneumocystis jirovecii* pneumonia
PCR	polymerase chain reaction
PHIV	perinatally acquired HIV
PI	protease inhibitor
PI/r	ritonavir-boosted protease inhibitor
PK	pharmacokinetic
POC	point of care
POP	progesterone-only oral contraceptive pill
PPI	proton pump inhibitor
PrEP	pre-exposure prophylaxis
PSED	Profile of Social Emotional Development
PTB	preterm birth
RAM	resistance-associated mutation
RCT	randomized controlled trial
RDS	respiratory distress syndrome
ROM	rupture of membranes

RR	relative risk
SGA	small for gestational age
SQ	subcutaneous
STI	sexually transmitted infection
$t_{1/2app}$	terminal-phase half-life
TB	tuberculosis
Tdap	tetanus, diphtheria, and pertussis
UGT	uridine diphosphate glucuronosyltransferase
WAZ	weight-for-age z-score
WHO	World Health Organization
XR	extended release

Study and Trial Names

Acronym/Abbreviation	Full Name
BAN	Breastfeeding, Antiretrovirals, and Nutrition
DolPHIN 2	Dolutegravir in Pregnant HIV Women and Their Neonates
EUROCAT	European Surveillance of Congenital Anomalies and Twins
EPPICC	European Pregnancy Paediatric HIV Cohort Collaboration
HPTN	HIV Prevention Trials Network
IMPAACT	International Maternal Pediatric Adolescent AIDS Clinical Trials
MOTIVATE	Mother–Infant Visit Adherence and Treatment Engagement
PACTG	Pediatric AIDS Clinical Trials Group
PANNA	Pharmacokinetics of newly developed ANtiretroviral agents in HIV-infected pregNAnt women
PARTNER	Partners of People on ART-A New Evaluation of the Risks
PHACS	Pediatric HIV/AIDS Cohort Study
PROMISE	Promoting Maternal and Infant Survival Everywhere
SMARTT	Surveillance and Monitoring for ART Toxicities
START	Strategic Timing of AntiRetroviral Treatment
VESTED	Virologic Efficacy and Safety of ART Combinations with TAF/TDF, EFV, and DTG

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

Updated: January 31, 2024
Reviewed: January 31, 2024

Overview

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 people 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, ZDV)

Didanosine and stavudine are no longer recommended for use in pregnant people. 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 outcomes in the birthing parent and neonate; see Antiretroviral Drug Regimens and Pregnancy 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 people. 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 people. 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)
- Cabotegravir (CAB)
- Dolutegravir (Tivicay, DTG)
- Elvitegravir (EVG)
- Raltegravir (Isentress, RAL)

For information regarding the possible increased risk of neural tube defects in infants born to birthing parents 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)

Capsid Inhibitors

Capsid inhibitors interfere with HIV capsid, a protein shell that protects HIV's genetic materials and the enzymes required for its replication. Capsid inhibitors can disrupt HIV capsid in multiple stages of the viral life.

- Lenacapavir (Sunlenca, LEN)

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

Table 14. Antiretroviral Drug Use in Pregnant People with HIV: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy

Updated: January 31, 2024
Reviewed: January 31, 2024

Note: When using fixed-dose combination (FDC) tablets, refer to other sections in Appendix B and Table 14 in the Perinatal Guidelines 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	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)[c] *Tablet* • 300 mg *Oral Solution* • 20 mg/mL ABC/3TC (Epzicom)[c] • ABC 600-mg/3TC 300-mg tablet ABC/DTG/3TC (Triumeq) • ABC 600-mg/DTG 50-mg/3TC 300-mg tablet	Pregnancy *PK in Pregnancy* • PK not significantly altered in pregnancy *Dosing in Pregnancy* • No change in dose indicated For guidance about use of combination products in pregnancy, please see the specific sections on other components (i.e., 3TC, ZDV, DTG). Standard Adult Doses *ABC (Ziagen)* • ABC 300 mg twice daily or ABC 600 mg once daily, without regard to food *ABC/3TC (Epzicom)*	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.	January 31, 2024

Table 14. Antiretroviral Drug Use in Pregnant People 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
	ABC/3TC/ZDV (Trizivir)[c] • ABC 300-mg/3TC 150-mg/ZDV 300-mg tablet	• 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		
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 (Emtriva) *Capsule*[c] • 200 mg *Oral Solution* • 10 mg/mL FTC/EFV/TDF (Atripla)[c] • FTC 200-mg/ EFV 60-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	Pregnancy *PK in Pregnancy* • PK 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). Standard Adult Doses *FTC (Emtriva)* • Capsule o FTC 200 mg once daily without regard to food • Oral Solution o FTC 240 mg (24 mL) 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.	January 31, 2024

Table 14. Antiretroviral Drug Use in Pregnant People 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
(FTC/TDF) *Truvada* Note: Generic products are available for some formulations.	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 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)[c] • FTC 200-mg/ TDF 300-mg tablet	*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 *FTC/DRV/c/TAF (Symtuza)* • One tablet once daily with food *FTC/TDF (Truvada)* • One tablet once daily without regard to food		

Table 14. Antiretroviral Drug Use in Pregnant People 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) *Symfi* (3TC/EFV/TDF) *Symfi Lo* (3TC/TDF) *Temixys* (3TC/ABC/DTG) *Triumeq* (3TC/ABC/DTG) *Triumeq PD* (3TC/ABC/ZDV) *Trizivir*	3TC (Epivir)[c] *Tablets* • 150 mg • 300 mg *Oral Solution* • 10 mg/mL 3TC/TDF (Cimduo) • 3TC 300-mg/TDF 300-mg tablet 3TC/ZDV (Combivir)[c] • 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)[c] • 3TC 300-mg/ABC 600-mg tablet 3TC/EFV/TDF (Symfi)[c] • 3TC 300-mg/EFV 600-mg/ TDF 300-mg tablet	Pregnancy *PK in Pregnancy* • PK 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). 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	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.	January 31, 2024

Table 14. Antiretroviral Drug Use in Pregnant People 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.	3TC/EFV/TDF (Symfi Lo)[c] • 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/DTG (Triumeq PD) • Pediatric dispersible tablet: 3TC 30-mg/ABC 60-mg/ DTG 5-mg 3TC/ABC/ZDV (Trizivir)[c] • 3TC 150-mg/ABC 300-mg/ ZDV 300-mg tablet	*3TC/EFV/TDF (Symfi or Symfi 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 *3TC/ABC/DTG (Triumeq PD)* • Triumeq PD is a pediatric dispersible tablet not intended for use in adults; it is not recommended for use in patients weighing 25 kg or more. *3TC/ABC/ZDV (Trizivir)* • One tablet twice daily without regard to food		
Tenofovir Alafenamide (TAF) *Vemlidy* (TAF/BIC/FTC) *Biktarvy* (TAF/FTC) *Descovy* (TAF/EVG/c/FTC) *Genvoya*	TAF (Vemlidy) • 25-mg tablet TAF/BIC/FTC (Biktarvy) • TAF 25-mg/ BIC 50-mg/FTC 200-mg tablet TAF/FTC (Descovy) • TAF 25-mg/FTC 200-mg tablet	Pregnancy *PK in Pregnancy* • AUC is lower in pregnancy, depending on the dose and concomitant ARV, but overall exposures are adequate. *Dosing in Pregnancy* • No change in dose indicated.	TAF: low placental transfer to fetus[b] TFV: high placental transfer to fetus; plasma and cord blood concentrations lower than TDF[b] No evidence of human teratogenicity (can rule out twofold increase in overall birth defects) Renal function should be monitored because of the potential for renal toxicity.	January 31, 2024

Table 14. Antiretroviral Drug Use in Pregnant People 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
(TAF/FTC/RPV) *Odefsey* (TAF/DRV/c/FTC) *Symtuza*	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	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). 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		
Tenofovir Disoproxil Fumarate (TDF) *Viread* (TDF/EFV/FTC) *Atripla*	TDF (Viread) *Tablet*[c] • 300 mg	Pregnancy *PK in Pregnancy* • AUC is lower in third trimester than postpartum, but trough levels are adequate.	High placental transfer to fetus[b] No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects)	January 31, 2024

Table 14. Antiretroviral Drug Use in Pregnant People 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
(TDF/3TC) *Cimduo* (TDF/FTC/RPV) *Complera* (TDF/DOR/3TC) *Delstrigo* (TDF/EVG/c/FTC) *Stribild* (TDF/EFV/3TC) *Symfi* (TDF/EFV/3TC) *Symfi Lo* (TDF/3TC) *Temixys* (TDF/FTC) *Truvada* Note: Generic products are available for some formulations.	*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 TDF/EFV/3TC (Symfi Lo) • TDF 300-mg/EFV 400-mg/ 3TC 300-mg tablet	*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, COBI, DOR, EFV, EVG, FTC, RPV). Standard Adult Doses *TDF (Viread)* • Tablet o TDF 300 mg once daily without regard to food • Powder o 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	Human studies demonstrate no consistent link to LBW, but data are conflicting about potential effects on growth outcomes later in infancy. If patient has HBV/HIV coinfection, 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.	

Table 14. Antiretroviral Drug Use in Pregnant People 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
	TDF/3TC (Temixys) • TDF 300-mg/3TC 300-mg tablet TDF/FTC (Truvada) • TDF 300-mg/FTC 200-mg tablet	*TDF/EVG/c/FTC (Stribild)* • One tablet once daily with food *TDF/EFV/3TC (Symfi or Symfi Lo)* • One tablet once daily on an empty stomach and preferably at bedtime *TDF/3TC (Temixys)* • One tablet once daily without regard to food *TDF/FTC (Truvada)* • One tablet once daily without regard to food		
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	Pregnancy *PK in Pregnancy* • PK not significantly altered in pregnancy *Dosing in Pregnancy* • No change in dose indicated • 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. 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)	January 31, 2024

Table 14. Antiretroviral Drug Use in Pregnant People 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
	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 *ZDV/3TC (Combivir)* • One tablet twice daily without regard to food *ZDV/ABC/3TC (Trizivir)* • One tablet twice daily without regard to food		
NNRTIs 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	Pregnancy *PK in Pregnancy* • No PK studies in human pregnancy *Dosing in Pregnancy* • Insufficient data to make dosing recommendations For guidance about the use of combination ARV drug products in pregnancy, please see the specific sections on other drug components (i.e., 3TC, TDF). 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	No human *in vivo* data are available on the placental transfer of DOR, but passage is noted in *ex vivo* models. Insufficient data are available to assess for teratogenicity in humans. No evidence exists of teratogenicity in rats or rabbits.	January 31, 2024

Table 14. Antiretroviral Drug Use in Pregnant People 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
Efavirenz (EFV) *Sustiva* (EFV/FTC/TDF) *Atripla* (EFV/3TC/TDF) *Symfi* (EFV/3TC/TDF) *Symfi Lo* Note: Generic products are available for some formulations.	EFV (Sustiva)[c] *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	Pregnancy *PK in Pregnancy* • AUC is decreased during the third trimester compared with postpartum, but nearly all third-trimester participants exceeded target exposure. *Dosing in Pregnancy* • No change in dose is indicated. For guidance about the use of combination products in pregnancy, please see the specific sections on other components (i.e., 3TC, FTC, TDF). 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. *EFV/3TC/TDF (Symfi or Symfi Lo)* • One tablet once daily on an empty stomach and preferably at bedtime	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 because 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 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 People with HIV Who Are Taking Antiretroviral Therapy When They Become Pregnant).	January 31, 2024

Table 14. Antiretroviral Drug Use in Pregnant People 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*	Tablet • 25 mg • 100 mg • 200 mg For patients who are unable to swallow tablets whole, the tablets may be dissolved in a glass of water.	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 is indicated. Standard Adult Doses • 200 mg twice daily with food	Placental transfer varies; it is usually in the moderate-to-high category, ranging from 0.19 to 4.25.[b] Insufficient data to assess for teratogenicity in humans. No evidence of teratogenicity in rats or rabbits.	January 31, 2024
Nevirapine (NVP) Viramune Viramune XR Note: Generic products are available for some formulations.	NVP (Viramune) *Tablet* • 200 mg[c] *Oral Suspension* • 50 mg/5 mL[c] Viramune XR *Tablets* • 100 mg • 400 mg[c]	Pregnancy *PK in Pregnancy* • PK 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 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 the lead-in period if therapy is discontinued for >7 days.	High placental transfer to fetus[b] No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects and 2-fold increase in cardiovascular and genitourinary defects) An increased risk of symptomatic liver toxicity exists 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 people with CD4 counts ≥250 cells/mm^3 only if benefit clearly outweighs risk. A potential increased risk of life-threatening hepatotoxicity exists in pregnant people with high CD4 counts. Elevated transaminase levels at baseline may increase the risk of NVP toxicity.	January 31, 2024

Table 14. Antiretroviral Drug Use in Pregnant People 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
		• 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.	Patients 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* (CAB and RPV) *Cabenuva* CAB and RPV is a two-drug co-packaged product for IM injection.	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 CAB and RPV (Cabenuva) • CAB 200-mg/mL suspension for IM injection • RPV 300-mg/mL suspension for IM injection	Pregnancy *PK in Pregnancy* • RPV PK 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 people receiving standard dosing should have their viral loads monitored more frequently than people 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., CAB, DT G, FTC, TAF, TDF). Standard Adult Doses *RPV (Edurant)* • RPV 25 mg 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.	January 31, 2024

Table 14. Antiretroviral Drug Use in Pregnant People 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/TDF (Complera) • One tablet once daily with food *RPV/DTG (Juluca)* • One tablet once daily with food *RPV/FTC/TAF (Odefsey)* • One tablet once daily with food *CAB and RPV (Cabenuva)* • Refer to Cabotegravir for dosing and instructions.		
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[c] (generic product only) • 200 mg[c] • 300 mg[c] *Oral Powder* • 50-mg packet ATV/c (Evotaz) • ATV 300-mg/COBI 150-mg tablet	Pregnancy *PK in Pregnancy* • ATV (Reyataz) o ATV concentrations are reduced during pregnancy, and they are further reduced when ATV is given concomitantly with TDF or an H2-receptor antagonist. o Intracellular ATV levels in women taking the standard dose (ATV/r 300 mg/100 mg) without concomitant TDF appear reassuringly stable throughout pregnancy. • ATV/c (Evotaz) o 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.	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.	January 31, 2024

Table 14. Antiretroviral Drug Use in Pregnant People 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 • ATV (Reyataz) o Use of unboosted ATV **is not recommended** during pregnancy. o Use of unboosted ATV **is not recommended** during pregnancy for ARV-experienced patients who are taking TDF and an H2-receptor antagonist. o 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. Increased ATV dosing is recommended for pregnant people in the second and third trimesters who are also receiving either TDF or an H2-receptor antagonist. • ATV/c (Evotaz) o ATV/c should not be used in pregnancy because atazanavir C_{min} is substantially reduced (see COBI). For guidance about the use of combination products in pregnancy, see the specific sections on other components (i.e., COBI). 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.	Use of ATV/c **is not recommended** during pregnancy. See Recommendations for Use of Antiretroviral Drugs During Pregnancy, Table 6, and Table 7 for discussions about avoiding the use of ATV/c during pregnancy.	

Table 14. Antiretroviral Drug Use in Pregnant People 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
		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. *ATV/c (Evotaz)* • One tablet once daily with food		
Darunavir (DRV) *Prezista*	DRV (Prezista) *Tablet* • 75 mg • 150 mg	Pregnancy *PK 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.	January 31, 2024

Table 14. Antiretroviral Drug Use in Pregnant People 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: Must be combined with low-dose RTV or COBI boosting. (DRV/c) *Prezcobix* (DRV/c/FTC/TAF) *Symtuza*	• 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	*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 people. • 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 use of combination products in pregnancy, please see the specific sections on other components (i.e., COBI, FTC, TAF). 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 *ARV-Experienced Patients If Any DRV Resistance Mutations Are Present* • DRV/r 600 mg/100 mg twice daily with food	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.	

Table 14. Antiretroviral Drug Use in Pregnant People 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
		DRV/c (Prezcobix) • One tablet once daily with food *DRV/c/FTC/TAF (Symtuza)* • One tablet once daily with food		
Lopinavir/Ritonavir (LPV/r) *Kaletra* Note: Generic products are available for all formulations.	LPV/r (Kaletra)[c] *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.	Pregnancy *PK 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.	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.	January 31, 2024

Table 14. Antiretroviral Drug Use in Pregnant People 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
		Standard Adult Doses • LPV/r 400 mg/100 mg twice daily, *or* • LPV/r 800 mg/20 mg once daily *Tablets* • Take without regard to food. *Oral Solution* • Take with a 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		
Entry Inhibitors Entry and attachment inhibitors block viral binding or fusion of HIV to host cells.				
Fostemsavir (FTR) *Rukobia*	• Extended-release tablet: 600 mg	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.	January 31, 2024

Table 14. Antiretroviral Drug Use in Pregnant People 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
		Standard Adult Doses *(FTR) Rukobia* • FTR 600 mg twice daily with or without food		
Ibalizumab-uiyk (IBA) *Trogarzo*	IV Solution • 150 mg/mL	Pregnancy *PK in Pregnancy* • No PK studies in human pregnancy *Dosing in Pregnancy* • Insufficient data to make dosing recommendations Standard Adult Doses • IBA 2,000-mg loading dose, followed by IBA 800-mg maintenance doses administered every 2 weeks	No human data are available, but placental transfer of IBA, a monoclonal antibody, is possible and documented in monkeys. Based on data in cynomolgus monkeys with *in utero* exposure, the potential exists for reversible immunosuppression (CD4 T cell and B cell lymphocytopenia) in infants born to mothers exposed to IBA during pregnancy. The FDA requires collection of prospective data in individuals exposed to IBA during pregnancy to monitor maternal and pregnancy outcomes, including adverse effects on the developing fetus, neonate, and infant. Insufficient data to assess for teratogenicity in humans	January 31, 2024
Maraviroc (MVC) *Selzentry*	Tablets • 150 mg • 300 mg	Pregnancy *PK 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.	Moderate placental transfer to fetus[b] No evidence of teratogenicity in rats or rabbits; insufficient data to assess teratogenicity in humans	January 31, 2024

Table 14. Antiretroviral Drug Use in Pregnant People 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 • Adjusting the standard adult MVC dose for concomitant use with ARV drugs seems appropriate. 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 include all PIs except TPV/r and itraconazole		
Capsid Inhibitor Capsid inhibitors are a class of drugs that interfere with HIV capsid, a protein shell that protects HIV's genetic material and enzymes needed for replication. Capsid inhibitors can disrupt HIV capsid during multiple stages of the viral life cycle.				
Lenacapavir (LEN) *Sunlenca*	LEN (Sunlenca) • LEN 300-mg tablets for oral administration • LEN 463.5 mg/1.5 ml for SQ injection	Pregnancy *PK in Pregnancy* • No PK studies in human pregnancy *Dosing in Pregnancy* • Insufficient data to make dosing recommendations	No human data are available regarding placental passage or through breast milk. Data are insufficient to assess for teratogenicity in humans. No evidence of teratogenicity in rats or rabbits.	January 31, 2024

Table 14. Antiretroviral Drug Use in Pregnant People 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
		Standard Adult Doses *Initiation Option 1* • Day 1: 927 mg by SQ injection (2 x 1.5 mL injections) and 600 mg orally (2 x 300-mg tablets) • Day 2: 600 mg orally (2 x 300-mg tablets). *Initiation Option 2* • Day 1: 600 mg orally (2 x 300-mg tablets) • Day 2: 600 mg orally (2 x 300-mg tablets) • Day 8: 300 mg orally (1 x 300-mg tablet) • Day 15: 927 mg by SQ injection (2 x 1.5 mL injections) *Maintenance Dosing* • 927 mg by SQ injection (2 x 1.5 mL injections) every 26 weeks +/- 2 weeks from date of last injection		
INSTIs INSTIs are 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 available only as part of an FDC tablet.	BIC/FTC/TAF (Biktarvy) • BIC 50-mg/FTC 200 mg/ TAF 25-mg tablet • BIC 30-mg/FTC 120-mg/ TAF 15-mg tablet	Pregnancy *PK in Pregnancy* • AUC and C_{24h}/C_{trough} are 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	High placental transfer to fetus[b] No evidence of human teratogenicity (can rule out twofold increase in overall birth defects)	January 31, 2024

Table 14. Antiretroviral Drug Use in Pregnant People 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
		For guidance about use of combination products in pregnancy, please see the specific sections on other components (i.e., FTC, TAF). Standard Adult Doses • One tablet of BIC 50 mg/FTC 200 mg/TAF 25 mg once daily with or without food	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.	
Cabotegravir (CAB) *Vocabria (oral)* *Apretude (injection for HIV pre-exposure prophylaxis)* (CAB) *Cabenuva* Note: CAB and RPV is a two-drug co-packaged product for IM injection.	CAB • CAB 30-mg tablets for oral administration • CAB 200-mg/mL suspension for IM injection CAB and RPV • CAB 200-mg/mL suspension for IM injection • RPV 300-mg/mL suspension for IM injection	Pregnancy *PK in Pregnancy* • No PK studies in human pregnancy *Dosing in Pregnancy* • Insufficient data to make dosing recommendations For guidance about the use of combination products in pregnancy, please see the specific sections on other components (i.e., RPV). Standard Adult Doses *Oral Lead-In Therapy (Optional)* • CAB (Vocabria) o One 30-mg tablet once daily in combination with RPV (Edurant) 25-mg once daily taken with a meal for 4 weeks • CAB (Apretude) o Initiation	No human data are available regarding placental passage. Insufficient data to assess for teratogenicity in humans. No evidence of teratogenicity in rats or rabbits.	January 31, 2024

Table 14. Antiretroviral Drug Use in Pregnant People 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
		▪ CAB 600-mg (3 mL) injections given 1 month apart for 2 consecutive months (on the last day of an oral lead-in, if used, or within 3 days) o Continuation Therapy ▪ CAB 600-mg (3 mL) injections every 2 months thereafter • CAB and RPV (Cabenuva) o Initiation ▪ CAB 600-mg (3 mL) and RPV 900-mg (3 mL), given as two separate injections in separate ventrogluteal sites for 2 consecutive months (on the last day of an oral lead-in if used) o Continuation Therapy ▪ *Monthly:* CAB 400-mg (2 mL) and RPV 600-mg (2 mL), given as two separate injections in separate ventrogluteal sites once a month with allowance for a +/- 7-day administration window ▪ *Every 2 months:* Starting in month 4, CAB 600-mg (2 mL) and RPV 900-mg (2 mL), given as two separate injections in separate ventrogluteal sites once a month with allowance for a +/- 7-day administration window		

Table 14. Antiretroviral Drug Use in Pregnant People 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
		▪ Patients should be monitored for approximately 10 minutes for post-injection reactions. A 23-gauge, 1.5-inch IM needle is recommended for the injection and is provided in the packaging. Longer, 2-inch needles should be used in patients with BMIs >30 kg/m^2. *Changing Dosing Frequency and Managing Missed Doses* • Refer to the package insert for instructions about changing the frequency of continuation doses and managing missed doses (see Apretude and Cabenuva).		
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	Pregnancy *PK 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). Standard Adult Doses *In ARV-Naive or ARV-Experienced (but INSTI-Naive) Patients* • DTG (Tivicay)	High placental transfer to fetus[b] No evidence of teratogenicity in rats or rabbits. The most recent data from Botswana indicate the prevalence of NTDs in infants born to pregnant women with HIV receiving DTG at conception is no longer statistically different than in those receiving other antiretrovirals. DTG is a *Preferred* antiretroviral drug for use during pregnancy, irrespective of trimester, and for people who are trying to conceive (see Recommendations for Use of Antiretroviral Drugs During Pregnancy and Table 7).	January 31, 2024

Table 14. Antiretroviral Drug Use in Pregnant People 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/RPV (Juluca) • DTG 50-mg/RPV 25-mg tablet DTG/ABC/3TC (Triumeq) • DTG 50-mg/ABC 600-mg/ 3TC 300-mg tablet	o One 50-mg tablet once daily, without regard to food • DTG (Tivicay PD) o Six 5-mg tablets (30 mg) dissolved in water once daily, without regard to food • DTG/3TC (Dovato) o One tablet once daily, without regard to food • DTG/RPV (Juluca) o One tablet once daily, with food • DTG/ABC/3TC (Triumeq) o 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) o One 50-mg tablet twice daily, without regard to food • DTG (Tivicay PD) o Six 5-mg tablets (30 mg) dissolved in water twice daily, without regard to food *In INSTI-Experienced Patients* • DTG (Tivicay) o One tablet twice daily, without regard to food	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 14. Antiretroviral Drug Use in Pregnant People 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	Pregnancy *PK 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). Standard Adult Doses *Genvoya and Stribild* • One tablet once daily with food	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 persons who become pregnant while taking EVG/c, consider frequent viral load monitoring or switching to a more effective, recommended regimen. If a pregnant person 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 minerals, such as iron or calcium, including prenatal vitamins.	January 31, 2024
Raltegravir (RAL) *Isentress* *Isentress HD*	RAL (Isentress) *Film-Coated Tablets* • 400 mg *Chewable Tablets* • 25 mg • 100 mg	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.	High placental transfer to fetus[b] No evidence of human teratogenicity (can rule out a 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 reactions and HSRs have been reported in nonpregnant adults.	January 31, 2024

Table 14. Antiretroviral Drug Use in Pregnant People 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
	RAL (Isentress HD) *Film-Coated Tablets* • 600 mg	• Once-daily dosing (i.e., two RAL 600-mg film-coated tablets) **should not be used** in pregnant individuals until more information is available. 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	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.	
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*	COBI (Tybost) *Tablet* • COBI 150 mg ATV/c (Evotaz) • ATV 300-mg/ COBI 50-mg tablet	Pregnancy *PK in Pregnancy* • Based on limited data, COBI exposure and its pharmaco-enhancing effect on ATV, DRV, and EVG are reduced markedly 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.	January 31, 2024

Table 14. Antiretroviral Drug Use in Pregnant People 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
(DRV/c) *Prezcobix* (EVG/c/FTC/TDF) *Stribild* (DRV/c/FTC/TAF) Symtuza	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	*Dosing in Pregnancy* • Although COBI exposure is reduced markedly during pregnancy, higher-than-standard doses have not been studied. The Panel recommends RTV as the preferred pharmaco-enhancer for PIs and INSTIs during pregnancy until more data are available on COBI activity during pregnancy. For guidance about the use of combination products in pregnancy, please see the specific sections on other components (i.e., FTC, TAF, TDF, ATV, DRV, EVG). 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		

Table 14. Antiretroviral Drug Use in Pregnant People 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
		DRV/c/FTC/TAF (Symtuza) • One tablet once daily with food		
Ritonavir (RTV) *Norvir* (LPV/r) *Kaletra*	RTV (Norvir) *Capsule* • RTV 100 mg *Tablet* • 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.	Pregnancy *PK 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 of pregnancy, especially in patients who are PI-experienced and in those 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).	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 a 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.	January 31, 2024

Table 14. Antiretroviral Drug Use in Pregnant People 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
		Standard Adult Dose of RTV (Norvir) When Used as a 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 *Tablet* • 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		

Table 14. Antiretroviral Drug Use in Pregnant People with HIV: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations 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 12).

[b] Placental transfer categories are determined by mean or median cord blood–to–maternal delivery plasma drug ratio:

High: >0.6
Moderate: 0.3–0.6
Low: <0.3

[c] 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; BMI = body mass index; C_{24h} = concentrations at 24 hours postdose; CAB = cabotegravir; 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 = U.S. Food and Drug Administration; FDC = fixed-dose combination; FPV/r = fosamprenavir/ritonavir; FTC = emtricitabine; FTR = fostemsavir; HBV = hepatitis b virus; HSR = hypersensitivity reaction; IBA = ibalizumab; IM = intramuscular; INSTI = integrase strand transfer inhibitor; IV = intravenous; LEN = lenacapavir; 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; SQ = subcutaneous; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TPV = tipranavir; TPV/r = tipranavir/ritonavir; WHO = World Health Organization; ZDV = zidovudine

Abacavir (Ziagen, ABC)

Updated: January 31, 2024
Reviewed: January 31, 2024

Summary

- No dose adjustments are required for abacavir (ABC) during pregnancy.
- First-trimester exposure to ABC is not associated with increased risk of congenital abnormalities.
- HLA-B*5701 screening should be done before initiating ABC. Patients who test positive for HLA-B*5701 are at the highest risk of hypersensitivity reactions and should not receive ABC.

Human Studies in Pregnancy

Pharmacokinetics

In pregnant women, pharmacokinetic (PK) studies of ABC 300 mg twice daily[1] and ABC 600 mg once daily[2] 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.[3] 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.[1,4] In the Mma Bana study,[5] 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. In the Swiss Mother and Child HIV Cohort nested study, ABC was measurable in four breastfeeding infants; the relative infant dose was 0.34%.[6]

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% (47 infants out of 1,455 live births; 95% confidence interval, 2.4% 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 Surveillance Monitoring for Antiretroviral Therapy Toxicities (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 European Pregnancy Paediatric HIV Cohort Collaboration (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 rarely have been fatal; symptoms include fever, skin rash, fatigue, and gastrointestinal symptoms such as nausea, vomiting, diarrhea, and 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 Pediatric HIV/AIDS Cohort Study (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]

Animal Studies

Carcinogenicity

Preputial and clitoral gland tumors and malignant hepatic tumors were seen in rodents at exposures that were 6 to 32 times those observed in humans who received the recommended dose.[16]

Reproduction/Fertility

No effect on reproduction or fertility in rodents was seen at doses that were about eight times the exposures seen in humans who received the recommended dose.[16]

Teratogenicity/Adverse Pregnancy Outcomes

Decreased fetal body weight and reduced crown–rump length were seen in rats treated during organogenesis. An increased number of resorptions and an increased incidence of stillbirths occurred among rats treated from embryo implantation through weaning of the pups. No developmental toxicities and no increases in fetal malformations occurred in pregnant rabbits at up to the highest dose evaluated, resulting in exposures approximately nine times the human exposure at the recommended dose.[16]

Placental and Breast Milk Passage

ABC crosses the placenta and is excreted into the breast milk of lactating rats.[16]

Excerpt from Table 14

Note: When using fixed-dose combination (FDC) tablets, refer to other sections in Appendix B and Table 14 in the Perinatal Guidelines 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)[c] *Tablet* • 300 mg *Oral Solution* • 20 mg/mL ABC/3TC (Epzicom)[c] • 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)[c] • ABC 300-mg/ 3TC 150-mg/ ZDV 300-mg tablet	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). 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	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 12).

[b] Placental transfer categories are determined by mean or median cord blood–to–maternal delivery plasma drug ratio:

High: >0.6
Moderate: 0.3–0.6
Low: <0.3

[c] Generic product available

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

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Emtricitabine (Emtriva, FTC)

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Summary

- No dose adjustments are required for emtricitabine (FTC) during pregnancy.
- First-trimester exposure to FTC is not associated with increased risk of congenital anomalies.
- FTC use during pregnancy has not been associated with adverse maternal, obstetric, or infant outcomes.

Human Studies in Pregnancy

Pharmacokinetics

In the International Maternal, Pediatric, Adolescent AIDS Clinical Trials (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 area under the curve (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 (concentration at 24 hours postdose [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).[1] Similar differences in pharmacokinetic parameters of FTC were found during pregnancy or after delivery in the Pediatric AIDS Clinical Trials Group (PACTG) 394 study[2] and in a European study.[3,4] The increase in FTC clearance during pregnancy correlated with the normal pregnancy-related increase in glomerular filtration rate.[4] These changes are not believed to be large enough to warrant a dose adjustment during pregnancy.

Placental and Breast Milk Passage

FTC has 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).[1] 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).[2]

FTC is excreted into human milk. In a study of women in Uganda and Nigeria who were taking antiretroviral therapy (ART) that contained FTC 200 mg, FTC concentrations in breast milk peaked at 4 to 8 hours compared with 2 to 4 hours in maternal plasma and were threefold higher than maternal plasma concentrations. FTC was detectable in three infants (19%).[5] In a study in 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 for HIV-1.[6] 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.[7]

Teratogenicity/Adverse Pregnancy Outcomes

In pregnancies that occurred in women without HIV in an HIV PrEP trial that randomized participants to receive placebo, TDF, or TDF plus FTC, no increase in the incidence of congenital anomalies was observed in the TDF plus FTC arm.[8] No overall difference was observed 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. Pediatric HIV/AIDS Cohort Study (PHACS) Surveillance Monitoring for ART Toxicities (SMARTT) cohort study, FTC exposure was not associated with an increase in specific or overall birth defect risk.[9] In a large French cohort, FTC exposure in the first trimester was associated with lower risk of birth defects.[10] 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 2.9% (134 of 4,567 live births; 95% CI, 2.5% to 3.5%) compared with a total prevalence of 2.7% in the U.S. population, based on Centers for Disease Control and Prevention surveillance.[11]

Other Safety Information

In the U.S. PHACS/SMARTT cohort study, after adjusting for birth cohort and other factors, maternal use of FTC did not increase the likelihood of adverse metabolic, growth and development, cardiac, neurologic, or neurodevelopmental infant outcomes.[12]

Animal Studies

Carcinogenicity

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.[13]

Reproduction/Fertility

FTC had no observable effect on reproduction or fertility at doses that produced systemic drug exposures (as measured by 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.[13]

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.[13]

Placental and Breast Milk Passage

FTC crosses the placenta in mice and rabbits; the average fetal-to-maternal drug concentration ratio was 0.4 in mice and 0.5 in rabbits.[14]

Excerpt from Table 14

Note: When using fixed-dose combination (FDC) tablets, refer to other sections in Appendix B and Table 14 in the Perinatal Guidelines 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*[c] • 200 mg *Oral Solution* • 10 mg/mL FTC/EFV/TDF (Atripla)[c] • FTC 200-mg/ EFV 60-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	Pregnancy *PK in Pregnancy* • PK 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). Standard Adult Doses *FTC (Emtriva)* • Capsule o FTC 200 mg once daily without regard to food • Oral Solution o 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	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.

Excerpt from Table 14

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)[c] • FTC 200-mg/ TDF 300-mg tablet	*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 *FTC/DRV/c/TAF (Symtuza)* • One tablet once daily with food *FTC/TDF (Truvada)* • One tablet once daily without regard to food	

[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 12).

[b] Placental transfer categories are determined by mean or median cord blood–to–maternal delivery plasma drug ratio:

High: >0.6
Moderate: 0.3–0.6
Low: <0.3

[c] Generic product is available.

Key: ARV = antiretroviral; BIC = bictegravir; COBI = cobicistat; DRV = darunavir; DRV/c = darunavir/cobicistat; EFV = efavirenz; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FTC = emtricitabine; HBV = hepatitis B virus; PK = pharmacokinetics; RPV = rilpivirine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

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Lamivudine (Epivir, 3TC)

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Summary

- No dose adjustments are required for lamivudine (3TC) during pregnancy.
- First-trimester exposure to 3TC is not associated with increased risk of congenital anomalies.
- 3TC use during pregnancy has not been associated with adverse maternal, obstetric, or infant outcomes.

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 adult once-daily or twice-daily 3TC doses,[1] 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.[1] 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.[2] 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,[1] expressed as the amniotic fluid–to–fetal AUC ratio, was 2.9. Urinary excretion of 3TC by the fetus can cause 3TC to accumulate in the amniotic fluid.[3]

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 3TC concentration in plasma[4] was 2.56. 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 evaluations at ages 6 and 12 months, on the other hand, revealed median plasma 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.[5] 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, the U.S. Food and Drug Administration has concluded that no difference exists between the overall risk of birth defects for 3TC and the background birth defect rate in the United States.[6]

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 Antiretroviral Pregnancy Registry, the prevalence of birth defects was 3.1% (173 of 5,613 live births; 95% CI, 2.6% 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 3TC-containing regimens than with use of antiretroviral regimens that do not include 3TC.[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]

Animal Studies

Carcinogenicity

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.[6]

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.[6]

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.[6]

Placental and Breast Milk Passage

In studies of pregnant rats, 3TC was transferred to the fetus through the placenta.[6]

Excerpt from Table 14

Note: When using fixed-dose combination (FDC) tablets, refer to other sections in Appendix B and Table 14 in the Perinatal Guidelines 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) *Symfi* (3TC/EFV/TDF) *Symfi Lo* (3TC/TDF) *Temixys* (3TC/ABC/DTG) *Triumeq* (3TC/ABC/DTG) *Triumeq PD* (3TC/ABC/ZDV) *Trizivir* Note: Generic products are available for some formulations.	3TC (Epivir)[c] *Tablets* • 150 mg • 300 mg *Oral Solution* • 10 mg/mL 3TC/TDF (Cimduo) • 3TC 300-mg/TDF 300-mg tablet 3TC/ZDV (Combivir)[c] • 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)[c] • 3TC 300-mg/ABC 600-mg tablet 3TC/EFV/TDF (Symfi)[c] • 3TC 300-mg/EFV 600-mg/TDF 300-mg tablet 3TC/EFV/TDF (Symfi Lo)[c] • 3TC 300-mg/EFV 400-mg/ TDF 300-mg tablet 3TC/TDF (Temixys) • 3TC 300-mg/TDF 300-mg tablet	Pregnancy *PK in Pregnancy* • PK 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 (ABC, DOR, DTG, EFV, TDF, ZDV). 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	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.

Excerpt from Table 14

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations[a]	Use in Pregnancy
	3TC/ABC/DTG (Triumeq) • 3TC 300-mg/ABC 600-mg/ DTG 50-mg tablet 3TC/ABC/DTG (Triumeq PD) • Pediatric dispersible tablet: 3TC 30-mg/ABC 60-mg/ DTG 5-mg 3TC/ABC/ZDV (Trizivir)[c] • 3TC 150-mg/ABC 300-mg/ ZDV 300-mg tablet	*3TC/ABC (Epzicom)* • One tablet once daily without regard to food *3TC/EFV/TDF (Symfi or Symfi 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 *3TC/ABC/DTG (Triumeq PD)* • Triumeq PD is a pediatric dispersible tablet not intended for use in adults; it is not recommended for use in patients weighing 25 kg or more. *3TC/ABC/ZDV (Trizivir)* • One tablet twice daily without regard to food	

[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 12).

[b] Placental transfer categories are determined by mean or median cord blood–to–maternal delivery plasma drug ratio:

High: >0.6
Moderate: 0.3–0.6
Low: <0.3

[c] Generic formulation available

Key: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; DOR = doravirine; DTG = dolutegravir; EFV = efavirenz; HBV = hepatitis B virus; PK = pharmacokinetics; TDF = tenofovir disoproxil fumarate; ZDV = zidovudine

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Tenofovir Alafenamide (Vemlidy, TAF)

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Tenofovir alafenamide (TAF) is an orally bioavailable prodrug form of tenofovir (TFV). For information about tenofovir disoproxil fumarate (TDF), see the TDF section.

Summary

- No dose adjustments are required for TAF during pregnancy.
- First-trimester exposure to TAF is not associated with increased risk of congenital anomalies.

Human Studies in Pregnancy

Pharmacokinetics

TAF pharmacokinetics (PK) can differ during pregnancy, depending on the concomitant antiretrovirals administered. However, TAF exposures appear to be adequate in the second and third trimesters based on comparisons with historical data in nonpregnant adults.

TAF PKs were evaluated as part of International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Network P1026s in 31 women taking TAF 10 mg with cobicistat, 27 women taking TAF 25 mg without a pharmacoenhancer,[1] and 29 women taking TAF 25 mg with a pharmacoenhancer (cobicistat or ritonavir).[2] TAF area under the curve (AUC) did not differ between pregnancy and postpartum for women taking TAF 10 mg with cobicistat[1] or those taking TAF 25 mg with a pharmacoenhancer.[2] TAF AUC at a 25 mg dose without a pharmacoenhancer was 33% to 43% lower during pregnancy compared to postpartum but comparable to exposures in nonpregnant adults.[1] The Pharmacokinetics of Newly Developed Antiretroviral Agents in HIV-infected pregnant women (PANNA) Network also evaluated TAF and TFV PK in 20 pregnant and postpartum European women receiving TAF 10 mg with cobicistat or TAF 25 mg without a pharmacoenhancer.[3] PK results from both dosing combinations were pooled and showed that TAF and TFV AUCs were 46% and 33% lower during pregnancy, respectively, than postpartum. Despite these decreases, 94% of pregnant women remained above the predefined TAF AUC efficacy target of 53.1 ng•h/mL.

Placental and Breast Milk Passage

Limited data exist on TAF and TFV concentrations in placental blood and breast milk. TAF was below the assay limit of quantification (<3.9 ng/mL) in 43 of 44 cord blood samples tested and all infant washout samples in women receiving TAF 25 mg without a pharmacoenhancer[1] and in all cord blood and infant washout samples in women receiving TAF 25 mg with ritonavir or cobicistat. Maternal plasma TAF concentrations at delivery were measurable in only 4 of 45 paired samples in women receiving TAF 25 mg without a pharmacoenhancer[1] and in 2 of 25 paired samples in women receiving TAF 25 mg with ritonavir or cobicistat.[2] A separate study also did not detect TAF in any paired cord blood or maternal delivery samples, but it was able to quantify TFV and estimated a median placental transfer ratio of 0.81 from 13 paired samples.[3]

TAF breast milk transfer has been examined in smaller PK studies. One study examined TAF breast milk transfer in five breastfeeding women with HIV and identified a breast milk–to-plasma ratio of

4.09 for TAF[4] and a median estimated infant daily dose of 0.007 mg/kg. A separate PK study in eight breastfeeding women with hepatitis B virus (HBV) infection receiving TAF for at least 4 weeks estimated breast milk–to-plasma ratios for TAF and TFV to be 0.029 and 2.809, respectively.[5] The relative TAF dose was estimated at 0.005% of the maternal dose. TFV was detectable in the urine of three of seven infants at a median steady-state concentration of 5 ng/mL, which was 300 times less than urine concentrations measured in adults on TAF. TFV breast milk transfer was examined in 12 women receiving TAF 25 mg and 4 women receiving TDF 300 mg for HBV treatment.[6] TFV exposures in breast milk through 8 hours postdose were approximately fivefold higher at Day 3 postdelivery in women taking TAF than in women taking TDF. TFV concentrations with TAF decreased by 43% and 47% at 15 and 30 days postpartum, respectively, compared to Day 3. TFV has poor oral bioavailability, and TAF and infant plasma concentrations were not quantified, so the clinical relevance of higher TFV in breast milk with TAF is unclear.

Teratogenicity

The Antiretroviral Pregnancy Registry has monitored sufficient numbers of first-trimester TAF exposures 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 3.9% (36 of 915 live births; 95% confidence interval [CI], 2.8% to 5.4%), not statistically significantly higher than the total prevalence in the U.S. population, according to the Centers for Disease Control and Prevention birth defects surveillance system Metropolitan Atlanta Congenital Defects Program (2.7%; 95% CI, 2.7–2.8) or the Texas Birth Defects Registry (4.2%; 95% CI, 4.15–4.19).[7]

Adverse Pregnancy Outcomes

Overall Adverse Pregnancy Outcomes

IMPAACT 2010/Virologic Efficacy and Safety of ART Combinations with TAF/TDF, EFV, and DTG (VESTED) was a randomized trial of dolutegravir (DTG)- and efavirenz (EFV)- containing ART regimens in pregnancy, which found lower composite adverse outcomes in the group receiving DTG and emtricitabine (FTC) with TAF (DTG+FTC/TAF) than in the group receiving DTG and FTC with TDF (DTG+FTC/TDF) or EFV and FTC with TDF (EFV+FTC/TDF) and a lower neonatal mortality than the arm receiving EFV+FTC/TDF (3.7% vs. 1.9%).[8] A post-hoc risk–benefit analysis of weighted infant outcomes showed a more favorable overall tradeoff for infants born to mothers in the DTG+TAF/FTC arm than in the DTG+TDF/FTC and EFV+TDF/FTC arms.[9,10]

Fetal Growth Effects

Length-for-age z-scores and weight-for-age z-scores among infants exposed to DTG+TAF/FTC *in utero* did not significantly differ from those exposed to DTG+TDF/FTC at 26 or 50 weeks of age but were higher than those measured in infants exposed to EFV+TDF/FTC.[11] There were no differences in weight-for-length z-scores between treatment regimens. All infants showed severely stunted growth through the first year of age.

Other Safety Data

Maternal Safety Outcomes

The DTG+FTC/TAF arm of IMPAACT 2010/VESTED had higher maternal weight gain than the other two arms.[8] Although greater weight gain was seen in mothers receiving DTG+FTC/TAF, the extent of average weekly weight gain that occurred was still below the recommended amount by the Institute of Medicine. Follow-up analyses did not identify significant differences in metabolic issues between study arms as measured by hemoglobin A1C or random glucose levels among pregnant women or infants,[12] and they also showed that lower antepartum weight gain was associated with a higher risk of adverse pregnancy outcomes.[13] However, a separate analysis of weight gain patterns within the United States did show a 1.7-fold higher relative risk of excessive gestational weight gain among pregnant women on TAF with an integrase strand transfer inhibitor (INSTI) than among those not exposed to these drugs.[14] Although INSTI use alone was not associated with excessive weight gain, all women on TAF were also on an INSTI, so the effect of TAF alone could not be examined. No differences in pregnancy outcomes or gestational diabetes were identified, but there was a higher risk of hypertensive disorders in the INSTI group than in those not on INSTIs or on TDF.

Renal safety also has been examined in a separate retrospective cohort of 100 pregnant women with HIV receiving TAF- or TDF-containing ART, and no significant differences in renal function, toxicity, or treatment discontinuations due to renal toxicity among regimens were identified.[15]

Animal Studies

Carcinogenicity

Carcinogenicity studies for TFV have only been performed with TDF, but given the lower TFV exposure with TAF, the associated carcinogenicity is assumed to be commensurate or lower. Refer to the TDF section for more information.

Reproduction/Fertility

There is no evidence of impaired fertility or mating performance with TAF administration in rats or rabbits at exposures up to 53 times those seen in humans.[16]

Teratogenicity/Adverse Pregnancy Outcomes

No effects on early embryonic development were seen in rats at TAF doses that produced exposures that were 62 times those seen in humans who received the therapeutic dose.[16]

Placental and Breast Milk Passage

Rat studies demonstrated secretion of TFV in breast milk after administration of TDF, but secretion of TAF or TFV in animal milk after administration of TAF has not been evaluated.[16]

Excerpt from Table 14

Note: When using fixed-dose combination (FDC) tablets, refer to other sections in Appendix B and Table 14 in the Perinatal Guidelines 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) • 25-mg tablet 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	Pregnancy *PKs in Pregnancy* • AUC is lower in pregnancy, depending on the dose and concomitant ARV, but overall exposures 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., BIC, COBI, DRV, EVG, FTC, RPV). 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	TAF: low placental transfer to fetus[b] TFV: high placental transfer to fetus; plasma and cord blood concentrations lower than TDF[b] No evidence of human teratogenicity (can rule out twofold increase in overall birth defects) Renal function should be monitored because of the potential for renal toxicity.

Excerpt from Table 14

[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 12).

[b] Placental transfer categories are determined by mean or median cord blood–to–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)

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Tenofovir disoproxil fumarate (TDF) is an orally bioavailable prodrug form of tenofovir (TFV). For information about tenofovir alafenamide (TAF), see the TAF section.

Summary

- No dose adjustments are required for TDF during pregnancy.
- First-trimester exposure to TDF is not associated with increased risk of congenital anomalies.
- *In utero* exposure to TDF has been associated with an increased risk of preterm birth and fetal growth restriction in some but not all studies.

Human Studies in Pregnancy

Pharmacokinetics

Plasma TFV exposures with TDF are lower during pregnancy without evidence of adverse impact on virologic efficacy; thus, standard dosing of TDF during pregnancy continues to be recommended.

HIV Treatment

In a prospective pharmacokinetic (PK) study of 37 women who received TDF-based combination therapy during pregnancy and postpartum, TFV trough levels and area under the curve (AUC) were 17% lower during the third trimester than postpartum.[1] 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 approximately 25% lower in pregnancy than postpartum but were not associated with virologic failure.[2] Population PK studies revealed that pregnant women receiving TDF had a 39% higher apparent oral clearance of TFV than nonpregnant women, and apparent clearance decreased slightly but significantly with increasing age.[3] In a separate population PK study, apparent oral clearance was 28% higher in pregnancy than postpartum, and weight and lower serum creatinine were independently associated with higher apparent oral clearance.[4]

The presence of a pharmacoenhancer also can affect TDF PK during pregnancy. TFV exposures in pregnant women receiving TDF with a ritonavir-boosted protease inhibitor (PI/r) are approximately 30% higher than in women receiving TDF without PI/r.[5] A separate analysis did not identify a difference in TFV exposures between pregnancy and postpartum among women receiving concomitant lopinavir/ritonavir (LPV/r), whereas TFV exposures were 27% lower in pregnant women who did not receive LPV/r.[6] TFV exposures were also higher in women receiving LPV/r than in those receiving atazanavir/ritonavir or other antiretroviral regimens during the third trimester, but no differences were identified among these groups in the postpartum period.

HIV Pre-Exposure Prophylaxis (PrEP)

In a study of women who did not have HIV and were using TDF as part of PrEP, intracellular concentrations of TFV diphosphate (TFV-DP) in dried blood spots (DBS) in pregnant women were

approximately 70% of those in nonpregnant women, even after adjusting for adherence.[7] A separate study in pregnant and postpartum adolescent and young women receiving TDF/FTC under directly observed therapy identified a similar magnitude of difference between pregnancy and postpartum in DBS concentrations.[8] Baseline creatinine clearance was associated with TFV-DP in DBS, with every 1 mL/min increase associated with a decrease in TFV-DP by 0.96%.

Placental and Breast Milk Passage

HIV Treatment

In studies of pregnant women receiving chronic TDF, the cord blood–to–maternal plasma ratio of TFV ranged from 0.60 to 1.03, indicating high placental transfer.[1,2,9] Intracellular TFV concentrations were detected in 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%) at birth.[10]

In a study of 59 breastfeeding women with HIV in Uganda and Nigeria who received TDF/lamivudine (3TC)/efavirenz (EFV), no infant had detectable TFV in plasma after observed dosing.[11] A separate study in Ugandan women showed that breast milk composition among women with HIV who received TDF had higher calcium levels at 14 weeks postpartum, but then demonstrated greater declines through the first year of breastfeeding than in those without HIV.[12]

HIV PrEP

In a study of 50 breastfeeding women without HIV who received TDF/FTC for PrEP under directly observed therapy for 10 days, 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 below the limit of quantitation (<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.[13]

Reproduction/Fertility

HIV Treatment

In a retrospective analysis of 7,275 women with HIV 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.[14]

HIV PrEP

By contrast, in a trial involving Kenyan and Ugandan women without HIV but whose sexual partners had HIV (serodiscordant heterosexual couples), women randomized to receive daily TDF, TDF/FTC, or placebo for PrEP did not show a significant difference in pregnancy incidence among arms.[15]

Teratogenicity

HIV Treatment

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: the Pediatric AIDS Clinical Trials Group (PACTG) 219/219C (n = 2,202, with 214 first-trimester TDF exposures); P1025 protocol (n = 1,112, with 138 first-trimester TDF exposures)[16,17]; and Pediatric HIV/AIDS Cohort Study (PHACS) (n = 2,580, with 431 first-trimester TDF exposures).[18] 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 (OR) of 1.5 (n = 13,124, with 823 first-trimester TDF exposures).[19]

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 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 2.6% (125 of 4,840 live births; 95% confidence interval [CI], 2.2% to 3.1%), compared with a total prevalence of 2.7% in the U.S. population, based on Centers for Disease Control and Prevention surveillance.[20]

HIV PrEP

No difference was observed in the risk of congenital anomalies 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/FTC.[15]

Adverse Pregnancy Outcomes

Available evidence is mixed regarding the relationship between TDF and adverse pregnancy outcomes, such as fetal growth effects and preterm birth. While the role of concomitant medications and other confounders requires further investigation, the data are reassuring overall.

HIV Treatment

An observational study in Botswana of >11,000 births among women with HIV who received ART during pregnancy found that 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 SGA) 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 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 a lower risk for adverse birth outcomes than other antiretroviral regimens.[21]

See the TAF section for a discussion of the findings of the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT 2010)/Virologic Efficacy and Safety of ART Combinations with TAF/TDF, EFV, and DTG (VESTED) trial, which suggests that TDF, compared with TAF, may be associated with a higher rate of adverse pregnancy outcomes when dolutegravir (DTG) regimens are started in pregnancy.[22,23]

HIV PrEP

A randomized, open-label, non-inferiority study of TDF/FTC for PrEP initiated either during or after pregnancy showed that for the composite adverse pregnancy outcome of preterm and very preterm birth, low birth weight (LBW) and very LBW, SGA, and stillbirth, immediate PrEP was non-inferior to deferred PrEP.[24] Individual outcomes of preterm birth and SGA were non-inferior for those with TDF/FTC exposure in comparison to those without TDF/FTC exposure during pregnancy, but non-inferiority of very preterm birth, LBW, very LBW, and stillbirth was inconclusive.

Fetal Growth Effects

Maternal TDF use was linked to an increased risk of LBW (<2,500 g) in a Dutch study of 74 HIV-exposed infants (including 9 with *in utero* TDF exposure).[25] SGA at birth was more frequent in the DTG plus TDF/FTC arm (45 of 200 infants [23%]) than in the DTG plus TAF/FTC arm (33 of 202 infants [16%]) in the VESTED trial, but this difference was not statistically significant.[22] A separate large observational study in Botswana showed that TDF/FTC/EFV was associated with a lower risk of SGA infants than all other regimens.[21] Several other large cohort and randomized studies have not identified significant differences in infants exposed to HIV and TDF *in utero* when examining risk of LBW[26-28] or very LBW, SGA,[26,27,29] and newborn length-for-age and head circumference–for-age z-scores (LAZ and HCAZ, respectively),[26] or body size parameters at birth.[30] Duration of maternal TDF use also has not been associated with long-bone (femur and humerus) growth in the infant[31] or infant length at birth.[32]

In PrEP studies, maternal TDF/FTC use during pregnancy has also shown no difference in SGA rates, LBW, or very LBW than in those with no TDF/FTC exposure.[24,33]

Preterm Delivery

In the Promoting Maternal–Infant Survival Everywhere (PROMISE) trial, no significant differences were observed between the TDF-containing ART arm and the ZDV-containing ART arms in the incidence of preterm delivery (delivery at <37 weeks; 18.5% vs. 19.7%, respectively, $P = 0.77$). However, TDF-containing 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-containing ART.[28] Subsequent analyses demonstrated persistence of this association even after adjustment for multiple well-established clinical, demographic, and obstetrical risk factors.[34] Potential explanations include a lower than expected very preterm delivery rate in the ZDV-containing 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 concentrations in DBS and very preterm delivery/early neonatal death.[35] A separate observational, multicenter Canadian study also showed a significantly higher rate of preterm delivery in mothers who received TDF-containing ART compared to regimens without TDF (19.4% vs. 15.2%, $P = 0.024$), and no associations with the concomitant anchor drug class were identified.[36]

Other studies have shown either no difference[22,27] or a lower risk[37] of these outcomes with TDF-containing therapy. However, in the Botswana study that showed a lower overall risk, there was a higher risk of preterm delivery among women who started treatment with TDF/FTC/EFV in the year prior to conception than those who started the same regimen late in the second trimester (adjusted risk ratio 1.33; 95% CI, 1.04–1.7).[21]

In PrEP studies, maternal TDF/FTC use during pregnancy was not associated with preterm or very preterm birth or stillbirth in comparison to no TDF/FTC use.[24,33]

Other Safety Data

Maternal Safety Outcomes

TDF has not been associated with an increased risk of renal side effects in pregnancy but has shown variable effects on maternal bone mineral density (BMD), with more notable declines in women with HIV.

Retrospective analyses in pregnant women with HIV receiving TDF have not identified significant differences between pregnancy and postpartum for changes in serum creatinine and estimated glomerular filtration rate,[38] nor when comparing TDF- to TAF-containing ART regarding renal function changes, toxicity, or treatment discontinuations due to renal toxicity.[39] A separate retrospective analysis did identify lower creatinine clearance and maternal phosphate levels, in addition to higher rates of hypophosphatemia, in women randomized to TDF-containing ART than to ZDV alone or ZDV in combination with other antiretrovirals. However, these differences were not deemed to be clinically relevant, and no significant differences were seen in these measures among infants.[40]

Significant decreases in lumbar spine and total hip BMD were identified in pregnant women receiving TDF-containing regimens compared with pregnant women receiving non-TDF-containing regimens,[41] and in total hip BMD compared with pregnant women without HIV.[42] Areal BMD did not return to baseline values in women with HIV but did in the reference group for total hip (-3.1% vs. +0.1%, $P = 0.0008$) and for whole body less head (-2.4% vs. -0.1%, $P = 0.002$).[42] However, a separate study among pregnant women with HIV/hepatitis B virus (HBV) coinfection did not identify significant differences in BMD at the lumbar spine or femoral neck at delivery and 26 weeks postpartum among women exposed to TDF in comparison to those unexposed to TDF.[43]

Infant Safety Outcomes

Maternal TDF has not been associated with an increase in the likelihood of adverse infant metabolic, growth and developmental, cardiac, neurological, or neurodevelopmental outcomes after adjusting for birth cohort and other factors[44] or in infant mortality.[45]

Infant Growth Effects

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.[46] Available evidence is further detailed throughout the rest of this section.

HIV Treatment

Multiple studies have shown varying effects of TDF exposure on infant growth measures despite no differences being identified at birth. In the U.S. PHACS study, infants exposed to combination regimens with TDF had a slightly but significantly lower adjusted mean LAZ and HCAZ than those without TDF exposure at 1 year of age (LAZ: -0.17 vs. -0.03, $P = 0.04$; HCAZ: 0.17 vs. 0.42, $P = 0.02$). No difference was observed in weight-for-age z-score (WAZ) or when defining low LAZ or HCAZ as ≤1.5 z-score. Thus, these slightly lower mean LAZ and HCAZ scores are of uncertain

significance.[26] In the U.S. P1025 study, TDF exposure after the first trimester was associated with being underweight (WAZ <5%) at age 6 months (OR 2.06; 95% CI, 1.01–3.95; $P = 0.04$) when compared to no exposure.[30] A Kenyan cohort study also found an association between maternal TDF use (compared to ART without TDF) and lower infant 6-week WAZ; however, TDF exposure was not associated with infant WAZ differences at age 9 months or any other infant anthropometric measures at the 6-week or 9-month time points.[47] Maternal TDF use was also linked to lower 6-month WAZ and height-for-age z-scores after adjusting for differences in birth weight and prematurity in the Dutch study of 74 HIV-exposed infants.[25]

Conversely, other studies have not identified an effect of TDF on infant growth rates.[32,45] In IMPAACT 2010/VESTED, growth as measured by LAZ and WAZ among infants exposed to DTG+TDF/FTC *in utero* did not significantly differ from those exposed to DTG+TAF/FTC at 26 and 50 weeks of age. LAZ and WAZ in the DTG+TDF/FTC arm were higher than those measured in infants exposed to EFV+TDF/FTC at both these time points.[48] There were no differences in weight-for-length z-scores between treatment regimens, but all infants showed severely stunted growth through the first year of age.

Infant Bone Effects

The impact of maternal TDF use on infant bone mineral status remains uncertain and requires further longitudinal evaluation. Available evidence is further summarized throughout this section.

HIV Treatment

A study examining whole-body, dual-energy X-ray absorptiometry scans performed within 4 weeks of birth among infants exposed to >8 weeks of TDF *in utero* (n = 74) versus those with no TDF exposure (n = 69) identified a significantly lower adjusted mean whole-body bone mineral content (BMC) in the TDF group (-6.5 g; $P = 0.004$) in addition to whole body less head BMC (-2.6 g; $P = 0.056$).[49] A separate analysis in breastfed infants exposed to maternal TDF-based ART also showed lower lumbar spine BMC than infants receiving NVP prophylaxis at week 26 (mean difference -0.13 g, $P = 0.007$), although the clinical relevance of this finding is unclear.[50] There were also no significant differences in creatinine clearance between treatment groups. A separate 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.[51]

Other studies have not identified any effects of TDF exposure on infant bone development. In a cross-sectional study of 68 children aged 1 to 6 years who were exposed to HIV (but not infected) and had *in utero* exposure to combination regimens that contained TDF (n = 33) or did not contain TDF (n = 35), quantitative bone ultrasound measures and bone metabolism marker levels were similar for both groups.[52] A separate small, randomized trial among pregnant women in China with HBV/HIV coinfection showed that BMD and BMC at age 6 months were not significantly lower in TDF-exposed infants (n = 14) than those not exposed to TDF (n = 13).[53] In the randomized PROMISE trial, no difference was observed in BMC between infants whose mothers received LPV/r-based ART with TDF and those whose mothers received LPV/r-based ART with ZDV.[54]

Animal Studies

Carcinogenicity

TDF was mutagenic in one of two *in vitro* assays and has shown no evidence of clastogenic activity. Long-term oral carcinogenicity studies of oral TDF were carried out at 16 times the exposure in humans and showed increased incidence of liver adenomas in mice, but no effects were seen in rats at 5 times the exposure.[55]

Reproduction/Fertility

TDF was not associated with impaired fertility or harm to the fetus in reproductive toxicity studies at exposures up to 14 times (in rats) and 19 times (in rabbits) the human dose. No effects were observed on fertility, mating performance, or early embryonic development when TDF was administered producing TFV exposures equivalent to 10 times the human dose based on body surface area in male or female rats, but an alteration of the estrous cycle in female rats was observed.[55]

Teratogenicity/Adverse Pregnancy Outcomes

Fetal monkeys with chronic, high-level TFV exposure equivalent to 25 times the AUC achieved with therapeutic dosing in humans had lower fetal circulating insulin-like growth factor (IGF)-1, higher IGF binding protein-3 levels, lower body weights, and slightly reduced fetal bone porosity compared with TFV-unexposed fetal monkeys.[55]

Placental and Breast Milk Passage

Intravenous administration of TFV to pregnant cynomolgus monkeys resulted in a cord blood–to–maternal plasma ratio of 0.17, demonstrating that TFV crosses the placenta.[56]

Excerpt from Table 14

Note: When using fixed-dose combination (FDC) tablets, refer to other sections in Appendix B and Table 14 in the Perinatal Guidelines 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 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) *Symfi* (TDF/EFV/3TC) *Symfi Lo* (TDF/3TC) *Temixys* (TDF/FTC) *Truvada* Note: Generic products are available for some formulations.	TDF (Viread) *Tablet*[c] • 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 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	Pregnancy *PK in Pregnancy* • AUC is lower in third trimester than postpartum, but trough levels are adequate. *Dosing in Pregnancy* • No change in dose is indicated. For guidance about the use of combination products in pregnancy, please see the specific sections on other components (i.e., 3TC, COBI, DOR, EFV, EVG, FTC, RPV). Standard Adult Doses *TDF (Viread)* • Tablet o TDF 300 mg once daily without regard to food • Powder o 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	High placental transfer to fetus[b] No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects) Human studies demonstrate no consistent link to LBW, but data are conflicting about potential effects on growth outcomes later in infancy. If patient has HBV/HIV coinfection, 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.

Excerpt from Table 14

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations[a]	Use in Pregnancy
	TDF/FTC (Truvada) • TDF 300-mg/FTC 200-mg tablet	*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 *TDF/EFV/3TC (Symfi or Symfi Lo)* • One tablet once daily on an empty stomach and preferably at bedtime *TDF/3TC (Temixys)* • One tablet once daily without regard to food *TDF/FTC (Truvada)* • One tablet once daily without regard to food	

[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 12).

[b] Placental transfer categories are determined by mean or median cord blood–to–maternal delivery plasma drug ratio:

High: >0.6
Moderate: 0.3–0.6
Low: <0.3

[c] Generic product is available.

Key: 3TC = lamivudine; ARV = antiretroviral; AUC = area under the curve; COBI = cobicistat; DOR = doravirine; EFV = efavirenz; EVG/c = elvitegravir/cobicistat; FTC = emtricitabine; HBV = hepatitis B virus; LBW = low birth weight; PK = pharmacokinetic; RPV = rilpivirine; TDF = tenofovir disoproxil fumarate

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Zidovudine (Retrovir, ZDV)

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Summary

- No dose adjustments are required for zidovudine (ZDV) during pregnancy.
- First-trimester exposure to ZDV is not associated with increased risk of congenital anomalies.

Human Studies in Pregnancy

Pharmacokinetics

ZDV pharmacokinetics (PKs) are not significantly altered by pregnancy, and standard adult doses are recommended during pregnancy.[1,2] 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.[3] However, standard dosing of IV ZDV during labor continues to be recommended for people 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.[4]

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[5] is 1.5. 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 exposed to ZDV only via breast milk.[6-8]

Teratogenicity/Adverse Pregnancy Outcomes

In Pediatric AIDS Clinical Trials Group 076 (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.[1,9] Similarly, no increase in the incidence of birth defects was detected among infants enrolled in the large observational cohorts PACTG 219/219C and P1025.[10,11] 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.[12,13] In the Pediatric HIV/AIDS Cohort Study/Surveillance Monitoring for Antiretroviral Therapy Toxicities (PHACS/SMARTT) study cohort, no association was identified between first-trimester exposure to ZDV and congenital anomalies.[14]

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 twofold 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% (136 of 4,252 births; 95% confidence interval [CI], 2.7% to 3.8%), compared with a total prevalence in the U.S. population of 2.7%, based on Centers for Disease Control and Prevention surveillance.[15] 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).[16] 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.[17]

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 non-exposures; 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 (9 of 4,000 infants exposed during the first trimester, rate 0.23; 22 of 9,047 infants with later exposure, rate 0.24, $P = 1.00$) and regimens that did not contain ZDV (2 of 1,839 infants exposed during the first trimester, rate 0.11; 3 of 538 infants with later exposure, rate 0.56, $P = 0.08$).[18]

In the ANRS 135 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 with infants whose mothers received LPV/r alone.[19] In a study that performed fetal echocardiography on 42 fetuses who had been exposed to HIV but 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.[20] 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.[21] A small follow-up study by the same authors identified hypertension among infants with *in utero* exposure to ZDV.[22]

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,[23] in prospective cohort studies,[24] and in matches between HIV surveillance and cancer registries.[25,26]

Other Safety Information

Mitochondrial dysfunction in mothers and infants exposed to nucleoside reverse transcriptase inhibitors during pregnancy has been described by some, but not all, case reports, case series, prospective cohorts, and surveillance systems. As part of its surveillance for such dysfunction, 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 whether 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).[27,28]

Animal Studies

Carcinogenicity

Late-appearing, non-metastasizing vaginal squamous cell carcinomas were seen in mice and in rats, predominantly among those given the highest dose (approximately 3–24 times the estimated human exposure with a dose of 100 mg every 4 hours).[29]

With transplacental exposure followed by postnatal exposure in mice (approximately three times the exposure of humans receiving the recommended dose), vaginal tumors were noted.[29]

One group of authors attributed the vaginal tumors in ZDV-treated mice to vaginal exposure from high urine ZDV concentrations.[30]

Reproduction/Fertility

ZDV has been shown to have no effect on reproduction or fertility in rodents.[29]

Teratogenicity/Adverse Pregnancy Outcomes

Embryotoxicity was seen in rats exposed preconceptionally and during gestation (exposure was approximately 33 times higher than that seen in humans receiving the recommended clinical dose), and rabbits exposed gestationally (approximately 108 times the estimated exposure of humans receiving the recommended dose).[29]

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 (the estimated area under the curve [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.[29]

Excerpt from Table 14

Note: When using fixed-dose combination (FDC) tablets, refer to other sections in Appendix B and Table 14 in the Perinatal Guidelines 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	Pregnancy *PKs in Pregnancy* • PKs not significantly altered in pregnancy *Dosing in Pregnancy* • No change in dose indicated • 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. For guidance about the use of combination products in pregnancy, please see the specific sections on other components (i.e., ABC, 3TC). Standard Adult Doses *ZDV (Retrovir)* • ZDV 300 mg twice daily or ZDV 200 mg three times a day without regard to food *ZDV/3TC (Combivir)* • One tablet twice daily without regard to food *ZDV/ABC/3TC (Trizivir)* • One tablet twice 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)

[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 12).

[b] Placental transfer categories are determined by mean or median cord blood–to–maternal delivery plasma drug ratio:

High: >0.6
Moderate: 0.3–0.6
Low: <0.3

Key: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; IV = intravenous; PK = pharmacokinetic; ZDV = zidovudine

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Doravirine (Pifeltro, DOR)

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Reviewed: January 31, 2024

Summary

- Pharmacokinetic data are insufficient to make dosing recommendations for doravirine (DOR) during pregnancy.
- Clinical data are insufficient to characterize the risk for congenital anomalies associated with *in utero* exposure to DOR. No reproductive toxicity or teratogenicity concerns were identified in animal studies.

Human Studies in Pregnancy

Pharmacokinetics

No clinical pharmacokinetic studies of DOR in pregnant women have been reported. Bukkems et al. used full-body, physiologically based pharmacokinetic (PBPK) modeling to predict maternal DOR exposures during pregnancy. Their model predicted lower maternal serum exposures (compared to nonpregnant adults) as pregnancy progresses, with decreases of trough plasma concentration of 65%, 75%, and 84% at 26, 32, and 40 weeks of gestation, respectively. [1]

Placental and Breast Milk Passage

Placental transfer of DOR was noted in two *ex vivo* dually perfused human cotyledon models.[1,2] The study by Le et al. integrated human placenta perfusion experiments with PBPK modeling, which predicted substantial fetal exposure to DOR. No data are available on breast milk passage of DOR in humans.

Teratogenicity/Adverse Pregnancy Outcomes

The Antiretroviral Pregnancy Registry[3] has prospectively monitored 10 patients who were first exposed to DOR during the first trimester and 2 patients who were first exposed to DOR during the second or third trimesters; one infant with first trimester exposure was noted to have a birth defect. These[3] data are insufficient to make conclusions regarding the safety of DOR during pregnancy.

Animal Studies

Carcinogenicity

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 exposures 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* and *in vivo* mutagenicity assays.[4]

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.[4]

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.[4]

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 postdose on lactation Day 14.[4]

Excerpt from Table 14

Note: When using fixed-dose combination (FDC) tablets, refer to other sections in Appendix B and Table 14 in the Perinatal Guidelines 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
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	Pregnancy *PKs in Pregnancy* • No PK studies in human pregnancy *Dosing in Pregnancy* • Insufficient data to make dosing recommendations For guidance about the use of combination ARV drug products in pregnancy, please see the specific sections on other drug components (i.e., 3TC, TDF). 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	No human *in vivo* data are available on the placental transfer of DOR, but passage is noted in *ex vivo* models. Insufficient data are available to assess for teratogenicity in humans. No evidence exists 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 12).

Key: 3TC = lamivudine; ARV = antiretroviral; DOR = doravirine; PK = pharmacokinetic; TDF = tenofovir disoproxil fumarate

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Efavirenz (Sustiva, EFV)

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Summary

- Standard adult dosing (600 mg daily) is recommended for efavirenz (EFV) in pregnancy. Reduced EFV doses (i.e., 400 mg daily) may not provide therapeutic drug levels due to the induction of cytochrome P450 2B6 (CYP2B6) during pregnancy.
- First-trimester exposure to EFV is not associated with increased risk of neural tube defects or other congenital anomalies. The Perinatal Guidelines support the use of EFV in the preconception period and during pregnancy (see Table 7).
- Newer data are concerning for increased incidence of microcephaly and neurodevelopmental delay in infants exposed to EFV *in utero*.

Human Studies in Pregnancy

Pharmacokinetics/Pharmacogenomics

A 2014 review of five pharmacokinetic (PK) studies of EFV during pregnancy found that EFV concentrations were not affected significantly by pregnancy and that high rates of HIV RNA suppression at delivery were achieved with EFV-based regimens.[1] Two more recent studies demonstrated commensurate pregnancy and postpartum EFV exposure. In an analysis of International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) 1026s and Pharmacokinetics of Newly Developed Antiretroviral Agents in HIV-infected Pregnant Women (PANNA) PK data from 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 area under the curve (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.[2] A study in 19 pregnant women in Ghana similarly found that PK parameters—specifically, maximum (peak) plasma drug concentration (C_{max}), minimum plasma drug concentration (C_{min}), area under the plasma concentration-time curve from 0 to 24 hours ($AUC_{0–24h}$), and apparent clearance (CL/F)—were similar in pregnancy and postpartum. Pregnancy and postpartum geometric mean ratios for EFV C_{max}, C_{min}, $AUC_{0–24h}$, and CL/F were 1.10 (95% confidence interval [CI], 0.93–1.31), 0.88 (95% CI, 0.67–1.17), 0.84 (95% CI, 0.71–0.98), and 1.20 (95% CI, 1.02–1.40), respectively.[3]

In an open-label, two-center study in the United Kingdom and Uganda, 25 pregnant women with virally suppressed HIV (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, $AUC_{0–24h}$, 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.[4]

Although the prospective data with reduced EFV are reassuring, a PK modeling study using pooled data from seven studies of women who were taking regimens that included EFV raises significant concerns regarding the adequacy of exposure due to a variation in CYP2B6 metabolism. 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 12-hour concentrations during the third trimester that were 91% and 87% of the values observed among nonpregnant women, respectively.[5] A more recent physiologically based pharmacokinetic (PBPK) modeling study evaluated EFV exposure in the third trimester in women with extensive, intermediate, and poor 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.[6] 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 American people.[7] Additional modeling data suggest increased EFV clearance with cigarette smoking.[8]

Placental and Breast Milk Passage

EFV crosses the placenta and also is excreted into breast milk. Low levels of EFV are found in the serum of some breastfed infants but do not appear to affect the growth and development of breastfed infants without HIV.[9] 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 with available washout data, median elimination half-life was 65.6 hours (interquartile range, 40.6–129 hours).[2] An older study of 25 mother–infant pairs similarly found that the median EFV cord blood–to–maternal blood concentration ratio was 0.49 (range 0.37–0.74).[7]

In a study of 13 women in Rwanda, EFV was given during the third trimester and for 6 months after delivery.[10] 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 less than the minimum therapeutic concentration of 1,000 ng/mL that is recommended for treatment of adults with HIV.

In a study of 134 women in Nigeria who received EFV 600 mg once daily, the median milk–to–maternal plasma concentration ratio was 1.10 (range 0.57–1.71), and the median infant EFV concentration was 157 ng/mL (range 28.6–1360 ng/mL).[11] 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).[12] 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.

Teratogenicity/Adverse Pregnancy Outcomes

In pregnancies with prospectively reported exposure to EFV-based regimens in the Antiretroviral Pregnancy Registry through January 2022, birth defects were observed in 28 of 1,193 live births with first-trimester exposure (2.4%; 95% CI, 1.6% to 3.4%) compared with a 2.7% total prevalence in the U.S. population, based on Centers for Disease Control and Prevention surveillance.[13] 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 is 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.[13]

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, 44 infants with birth defects among 2,026 live births to women who received EFV during the first trimester were observed. The pooled proportion of overall birth defects was 1.63% (95% CI, 0.78% to 2.48%).[14] 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, <0.01–0.28), 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%.)[15]

A contemporary French study of 13,124 live births between 1994 and 2010 included an analysis of 372 infants born after first-trimester exposure to EFV.[16] 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). Similarly, 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.[17]

More 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, three NTDs were observed (0.04%; 95% CI, 0.01% to 0.11%), which is similar to the rate of NTDs observed among infants born to 89,372 women without HIV (0.08%; 95% CI, 0.06% to 0.10%).[18] 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.[19]

The U.S. 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 people 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.[20-22] EFV should be continued in pregnant people 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.[23]

A 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.[24] 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 worse 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; $P = 0.05$); Developmental Milestones Checklist (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 better 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.[25] 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).[26]

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 the upper limit of normal 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.[27]

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.[28-32] (see Prepregnancy Counseling and Care for Persons of Childbearing Age with HIV and Table 3).

Animal Studies

Carcinogenicity

EFV was neither mutagenic nor clastogenic in the majority 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.[33] Long-term animal carcinogenicity studies with EFV have been completed in mice and rats. In female mice, an increase in tumor incidence was seen for hepatocellular adenomas and carcinomas and pulmonary alveolar/bronchiolar adenomas.[34]

Reproduction/Fertility

EFV has had no observable effects on reproduction or fertility in rodents.[34]

Teratogenicity/Adverse Pregnancy Outcomes

Animal data, specifically NTD in cynomolgus monkeys, set off concern for potential risk of human teratogenicity; however, the same malformations have not been observed in human fetuses. 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.[35] The malformations included anencephaly and unilateral anophthalmia in one fetus, microphthalmia in another fetus, and cleft palate in a third fetus.[34]

Additionally, an increase in fetal resorption was observed in female rats at EFV doses that produced peak plasma concentrations and AUC values less than or equal to those in humans who received the recommended dose of EFV 600 mg once daily.[34] An additional 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.[36]

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.[34]

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.[34]

Excerpt from Table 14

Note: When using fixed-dose combination (FDC) tablets, refer to other sections in Appendix B and Table 14 in the Perinatal Guidelines 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) *Symfi* (EFV/3TC/TDF) *Symfi Lo* Note: Generic products are available for some formulations.	EFV (Sustiva)[c] *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	Pregnancy *PK in Pregnancy* • AUC is decreased during the third trimester compared with postpartum, but nearly all third-trimester participants exceeded target exposure. *Dosing in Pregnancy* • No change in dose is indicated. For guidance about the use of combination products in pregnancy, please see the specific sections on other components (i.e., 3TC, FTC, TDF). 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. *EFV/3TC/TDF (Symfi or Symfi Lo)* • One tablet once daily on an empty stomach and preferably at bedtime	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 because 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 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 People with HIV Who are Taking Antiretroviral Therapy When They Become Pregnant).

[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 12).

Excerpt from Table 14

[b] Placental transfer categories are determined by mean or median cord blood–to–maternal plasma drug ratio:

High: >0.6
Moderate: 0.3–0.6
Low: <0.3

[c] Generic product is available.

Key: 3TC = lamivudine; ARV = antiretroviral; AUC = area under the curve; EFV = efavirenz; FDA = U.S. Food and Drug Administration; FTC = emtricitabine; NTD = neural tube defect; PK = pharmacokinetics; TDF = tenofovir disoproxil fumarate; WHO = World Health Organization

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Etravirine (Intelence, ETR)

Updated: January 31, 2024
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Summary

- No dose adjustments are required for etravirine (ETR) during pregnancy.
- Clinical data are insufficient to characterize the risk for congenital anomalies associated with *in utero* exposure to ETR. No reproductive toxicity or teratogenicity concerns were identified in animal studies.

Human Studies in Pregnancy

Pharmacokinetics

ETR pharmacokinetics (PKs) 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 area under the curve (AUC), minimum plasma concentration (C_{min}), and maximum plasma concentration (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[1] with least-squares mean ratios of approximately 0.9 to 1.2. 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).[2] 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.[3]

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).[2] 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).[1] 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).[4]

Plasma and breast milk concentrations were measured on postpartum Days 5 and 14 in eight women who began taking ETR on postpartum Day 1.[5] Plasma PK parameters were similar between Days 5 and 14 and were similar to the published PK parameters of ETR in nonpregnant adults. ETR AUC from 0 to 12 hours postdose 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–to–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–to–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.[4,6] One infant was born with a small accessory auricle on the right ear but no other malformations, and no birth defects were noted in the other children.[4] Seventy-three 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.[7]

Animal Studies

Carcinogenicity

ETR was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests.[8] ETR was evaluated for carcinogenic potential in mice and rats for up to approximately 104 weeks. Because of intolerance of the formulation, the AUCs 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 of hepatocellular adenomas or carcinomas combined were observed. Whether these liver tumor findings in mice are relevant to humans is unclear.[8]

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.[8]

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.[8]

Excerpt from Table 14

Note: When using fixed-dose combination (FDC) tablets, refer to other sections in Appendix B and Table 14 in the Perinatal Guidelines 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
Etravirine (ETR) *Intelence*	Tablet • 25 mg • 100 mg • 200 mg For patients who are unable to swallow tablets whole, the tablets may be dissolved in a glass of water.	Pregnancy *PKs 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 is indicated. Standard Adult Doses • 200 mg twice daily with food	Placental transfer varies; it is usually in the moderate-to-high category, ranging from 0.19 to 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 12).

[b] Placental transfer categories are determined by mean or median cord blood–to–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)

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Summary

- No dose adjustments are required for nevirapine (NVP) during pregnancy.
- First-trimester exposure to NVP is not associated with increased risk of congenital anomalies.
- Data are conflicting regarding the risk of hepatotoxicity in pregnancy. Skin reactions appear to be increased with NVP use during pregnancy.

Human Studies in Pregnancy

Pharmacokinetics

The pharmacokinetic (PK) studies 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[1]; however, two other studies found up to 30% lower exposure in pregnancy.[2,3] No dose adjustment is recommended currently 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).[4,5]

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.[6-8]

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 3.1% (36 of 1,178 live births; 95% confidence interval [CI], 2.1% to 4.2%) compared with a total prevalence of 2.7% in the U.S. population, based on Centers for Disease Control and Prevention surveillance.[9] 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.[10] During 2013 and 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 9.28, 2.27–37.94); 2 of 52 infants with NVP exposure versus 29 of 7,592 without NVP exposure.[11]

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%.[12,13] 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 monitored regularly 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/mm^3 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/mm^3. Some researchers have suggested that genetic variation in drug metabolism polymorphisms (e.g., cytochrome P450 Family 2 Subfamily B Member 6 [CYP2B6] variants), tumor necrosis factor receptor–associated factor 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.[12]

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 syndrome. 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/mm^3 (OR 1.4; 95% CI, 0.8–2.4).[20] Another systematic review[24] reported a significant association between increased toxicity risk and the initiation of NVP-based ART therapy in pregnant women with CD4 counts ≥250 cells/mm^3. 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 people with CD4 counts ≥250 cells/mm^3 only if the benefit clearly outweighs the risk. Pregnant patients with CD4 counts <250 cells/mm^3 can receive NVP-based regimens, and

patients 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 patients 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 and aspartate aminotransferase) 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 patients who develop a rash while receiving NVP. Patients who develop suggestive clinical symptoms accompanied by elevation in serum transaminase levels 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 that contained NVP were more likely to experience certain adverse events than women on ART that did not contain NVP. Such events include hypertension (30% vs. 16%), severe hypertension (3.3% vs. 1.2%), gestational hypertension (18% vs. 10%), and early gestational hypertension (12% vs. 7%).[27]

Animal Studies

Carcinogenicity

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.[12]

Reproduction/Fertility

Female rats showed impaired fertility at systemic NVP exposures comparable to human therapeutic exposures.[12]

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.[12]

Excerpt from Table 14

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[c] *Oral Suspension* • 50 mg/5 mL[c] Viramune XR *Tablets* • 100 mg • 400 mg[c]	Pregnancy *PK in Pregnancy* • PK 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 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 the 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.	High placental transfer to fetus[b] No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects and 2-fold increase in cardiovascular and genitourinary defects) An increased risk of symptomatic liver toxicity exists 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 people with CD4 counts ≥250 cells/mm^3 only if benefit clearly outweighs risk. A potential increased risk of life-threatening hepatotoxicity exists in pregnant people with high CD4 counts. Elevated transaminase levels at baseline may increase the risk of NVP toxicity. Patients 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 12).

[b] Placental transfer categories are determined by mean or median cord blood–to–maternal delivery plasma drug ratio:

High: >0.6
Moderate: 0.3–0.6
Low: <0.3

[c] Generic formulation available.

Key: ARV = antiretroviral; CD4 = CD4 T lymphocyte; NVP = nevirapine; PK = pharmacokinetic; XR = extended release

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Rilpivirine (Edurant, RPV)

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Summary

- Rilpivirine (RPV) plasma concentrations after oral dosing are decreased by approximately 20% to 50% during pregnancy.
- Higher-than-standard oral doses have not been studied, and not enough data are available to recommend a dosing change during pregnancy. Pregnant individuals receiving standard oral dosing should have their viral loads monitored more frequently than individuals who are not receiving RPV.
- Pharmacokinetic data are insufficient to make dosing recommendations for long-acting injectable RPV during pregnancy or breastfeeding.
- First-trimester exposure to RPV is not associated with increased risk of congenital anomalies.

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 concentration (AUC) and trough concentration (C_{trough}) after oral dosing were about 20% to 30% lower in the second and third trimesters than in the postpartum period. Median RPV C_{trough} 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 C_{trough} above the protein-adjusted 90% maximal effective concentration (EC_{90}) for RPV. PK parameters between participants were highly variable in this study.[1]

Another study in 16 pregnant women with HIV similarly found that exposure after oral dosing was approximately 50% lower in the third trimester than in the postpartum period, with 4 of the 16 women having C_{trough} below the target levels during pregnancy.[2] Schalkwijk et al. recommended the use of therapeutic drug monitoring during the third trimester.[2] Furthermore, they recommended that providers remind patients to take RPV doses with meals. A third study reported that total RPV exposure after oral dosing 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.[3]

Cervicovaginal fluid RPV concentrations were described in a study of 24 women who took RPV orally 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.[4] 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 these groups.[5] For considerations regarding switching antiretroviral drugs during pregnancy, see People With HIV Who Are Taking Antiretroviral Therapy When They Become Pregnant. Pregnant people who receive the standard oral dose of RPV should have their viral loads monitored more frequently than people who are not receiving RPV (see Initial Evaluation and Continued Monitoring of HIV-Related Assessments During Pregnancy).

No studies have been conducted on the PKs of ongoing intramuscular injections of long-acting cabotegravir (CAB) and RPV during pregnancy. Clinical trial data reported to date are limited to pregnant women who stopped receiving the long-acting injectable formulations for the treatment or prevention of HIV once pregnancies were recognized and began alternative oral antiretroviral regimens throughout the remainder of their pregnancies. From the Phase 2b/3/3b clinical trials of long-acting injectable CAB and RPV for the treatment of HIV, PK data are available for seven of the nine participants with live birth outcomes. Plasma concentrations were within the range of observed concentrations of nonpregnant women who discontinued long-acting injectable CAB and RPV.[6] A physiologically-based PK model of pregnant individuals initiating long-acting injectable CAB and RPV early in the second trimester predicted a reduction in plasma concentrations of 29.5% and 23.0%, respectively, at the first trough after the first injection. After the sixth injection in the second and third trimesters, plasma concentrations were 31.1% and 29.2% lower for CAB and RPV, respectively. These reductions are attributable to the predicted induction of uridine diphosphate glucuronosyltransferase 1A1 and cytochrome P450 3A4 during the second and third trimesters.[7]

See Cabotegravir for data about CAB.

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 RPV plasma 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).[1] 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).[3] Similarly, Schalkwijk et al. found a median cord blood–to–maternal plasma ratio of 0.5 (range: 0.35–0.81) in five women.[2] An *ex vivo* human cotyledon perfusion model also showed that RPV crosses the placenta,[8,9] with fetal transfer rates ranging from 17% to 37%. No data exist on whether RPV is excreted in breast milk in humans.

Teratogenicity/Adverse Pregnancy Outcomes

The Antiretroviral Pregnancy Registry monitored sufficient numbers of first-trimester exposures to oral 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 2.1% (14 infants out of 668 live births; 95% confidence interval, 1.2% to 3.5%) compared with a 2.7% total prevalence in the U.S. population, according to Centers for Disease Control and Prevention surveillance.[10]

In the Phase 2b/3/3b trials of long-acting injectable CAB and RPV, 25 of 325 women of reproductive potential became pregnant while exposed to CAB and RPV (5 oral, 20 long-acting injectable),

resulting in 8 elective abortions, 6 spontaneous abortions (5 in the first trimester), 1 ectopic pregnancy, and 10 live births (1 oral, 9 long-acting injectable). Of the 10, there was 1 congenital ptosis in a term infant with intrauterine growth restriction and 1 late preterm delivery due to induction of labor.[6]

Animal Studies

Carcinogenicity

RPV was neither mutagenic nor clastogenic in a series of *in vitro* and *in vivo* screening tests. RPV was neither carcinogenic nor genotoxic in animal studies.[11]

Reproduction/Fertility

RPV had no effect on fertility in animal studies.[11]

Teratogenicity/Adverse Pregnancy Outcomes

No significant toxicological effects were seen in RPV animal studies.[11]

Placental and Breast Milk Passage

Studies in lactating rats and their offspring indicate that RPV is present in rat milk.[11]

Excerpt from Table 14

Note: When using fixed-dose combination (FDC) tablets, refer to other sections in Appendix B and Table 14 in the Perinatal Guidelines 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
Rilpivirine (RPV) *Edurant* (RPV/FTC/TDF) *Complera* (RPV/DTG) *Juluca* (RPV/FTC/TAF) *Odefsey* (CAB and RPV) *Cabenuva* CAB and RPV is a two-drug co-packaged product for IM injection.	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 CAB and RPV (Cabenuva) • CAB 200-mg/mL suspension for IM injection • RPV 300-mg/mL suspension for IM injection	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 people receiving standard dosing should have their viral loads monitored more frequently than people who are not receiving RPV. For guidance about the use of combination products in pregnancy, please see the specific sections on other components (CAB, DTG, FTC, TAF, TDF). Standard Adult Doses *RPV (Edurant)* • RPV 25 mg 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.

Excerpt from Table 14

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations[a]	Use in Pregnancy
		RPV/FTC/TDF (Complera) • One tablet once daily with food *RPV/DTG (Juluca)* • One tablet once daily with food *RPV/FTC/TAF (Odefsey)* • One tablet once daily with food *CAB and RPV (Cabenuva)* • Refer to Cabotegravir for dosing and instructions.	

[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 12).

[b] Placental transfer categories are determined by mean or median cord blood–to–maternal delivery plasma drug ratio:

High: >0.6
Moderate: 0.3–0.6
Low: <0.3

Key: ARV = antiretroviral; AUC = area under the curve; CAB = cabotegravir; DTG = dolutegravir; FDC = fixed-dose combination; FTC = emtricitabine; IM = intramuscular; PK = pharmacokinetic; RPV = rilpivirine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

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Atazanavir (Reyataz, ATV)

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Reviewed: January 31, 2024

Summary

- Atazanavir (ATV) concentrations are reduced during pregnancy.
  - Only ritonavir-boosted ATV (ATV/r) should be used in pregnancy, as drug levels are too low if unboosted ATV or cobicistat (COBI)-boosted ATV (ATV/c) is used in pregnancy.
  - ATV levels are further reduced when given concomitantly with tenofovir disoproxil fumarate (TDF) or an H2-receptor antagonist.
  - Intracellular ATV levels in women taking the standard dose (ATV/r 300 mg/100 mg) without concomitant TDF appear reassuringly stable throughout pregnancy.
  - An increased dose (ATV/r 400 mg/100 mg once daily with food) during the second and third trimesters should be used if ATV is given concomitantly with TDF or an H2-receptor antagonist.
- First-trimester exposure to ATV is not associated with increased risk of congenital anomalies.
- Regimens with protease inhibitors (PIs), including ATV/r, may be associated with increased rates of preterm delivery.

Human Studies in Pregnancy

Pharmacokinetics

ATV/r without Concomitant TDF

In studies that evaluated full pharmacokinetic (PK) profiles of daily ATV/r 300 mg/100 mg without concomitant TDF during pregnancy, the ATV area under the curve (AUC) was lower during pregnancy than the ATV AUC reported in other studies of nonpregnant adults with HIV.[1-4] In one of the studies, no difference was observed in the ATV AUC during pregnancy and postpartum, but the AUC at both times was lower than the AUC observed in historic nonpregnant controls with HIV.[4] In the other studies, the ATV AUC was lower during pregnancy than it was in the same patients postpartum and in nonpregnant control populations.[1-3,5] Intracellular ATV levels in women taking ATV/r 300 mg/100 mg appear stable throughout pregnancy.[6] Genetic variants appear to partially explain the interpatient variability in third-trimester ATV exposure seen in pregnant women who receive ATV/r.[7]

In studies that evaluated the use of a once-daily increased dose (ATV/r 400 mg/100 mg) during pregnancy,[3,5] pregnant women who received this 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. Viral suppression (<50 copies/mL) before delivery was observed in 90% to 100% of women receiving standard or increased-dose regimens; none of the infants had evidence of HIV infection.[3,5]

ATV/r with Concomitant TDF

ATV/r combined with TDF and emtricitabine (FTC) provides a complete, once-daily antiretroviral therapy regimen for use during pregnancy. 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.[1,2] 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.[1] 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 (C_{trough}) <0.15 mg/L (the target C_{trough} for antiretroviral-naive patients) in pregnant women during their third trimester.[8] In a therapeutic drug monitoring study of 103 women (most of whom were African) in Paris, the proportions of women with an ATV C_{trough} of <0.15 mg/L were similar for women who did and women who did not take concomitant TDF.[9]

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.[3,5] An increased dose of ATV during the second and third trimesters is recommended for antiretroviral-experienced pregnant women who also are receiving either TDF or an H2-receptor antagonist.[10] For additional details about interactions between concomitant medications, see Drug–Drug Interactions in the Adult and Adolescent Antiretroviral Guidelines.

ATV Boosted with Cobicistat

The pharmaco-enhancing effect of COBI on ATV is impacted during pregnancy. Pregnant women who received ATV boosted with COBI had ATV C_{trough} that were 66% and 72% lower during the second and third trimesters, respectively, compared with paired postpartum data ($P = 0.0625$ and $P = 0.0313$, respectively).[11] Concomitant use of ATV and COBI **is not recommended** during pregnancy because of these substantial reductions in drug exposures (see Cobicistat).[12]

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.[1,4,13]

In a study of three women, the median ratio of breast milk ATV concentration to plasma ATV concentration[14] was 0.13.

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 musculoskeletal system (aOR 2.55; $P = 0.007$).[15] On the other hand, there was no association between first-trimester ATV exposure and birth defects in a French cohort, although this study[16] had <50% power to detect an aOR of 1.5. 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

2.5% (37 of 1,478 live births; 95% confidence interval [CI], 1.8% to 3.4%) compared with a 2.7% total prevalence in the U.S. population, based on Centers for Disease Control and Prevention surveillance.[17]

See 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.[18] In late pregnancy, an increased dose (ATV/r 400 mg/100 mg) without concomitant TDF, compared with the standard dose of ATV/r without concomitant TDF, is associated with twice the risk of elevated maternal bilirubin levels.[3] It is unknown whether elevated maternal indirect bilirubin throughout pregnancy has any effect on the fetus. Dangerous or pathologic postnatal elevations in bilirubin have not been reported in infants born to mothers who received ATV during pregnancy.[1,3,4,13,19-21] Maternal bilirubin levels do not correlate well with neonatal bilirubin levels.[22] 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.[19,20] Elevated neonatal bilirubin in neonates exposed to ATV is not associated with UGT-1 genotypes that have been linked to decreased UGT function.[21]

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.[23,24] 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 with children without ATV exposure, but this association was not significant at 24 months.[25]

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.[13] This report of infant hypoglycemia is similar to a prior report in which two 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.[26]

Animal Studies

Carcinogenicity

In *in vitro* and *in vivo* assays, 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/r 300 mg/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.[13]

Reproduction/Fertility

No effect of ATV on reproduction or fertility in male and female rodents was observed at drug exposure levels (as measured by 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.[13]

Teratogenicity/Adverse Pregnancy Outcomes

In animal reproduction studies, no evidence of teratogenicity was observed 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.[13] A separate study demonstrated an association between maternal PI use (including the use of ATV) and lower progesterone levels, which correlated with lower birthweight in mice.[27,28] Maternal administration of ATV (with TDF/FTC or abacavir/lamivudine) was associated with delayed postnatal (infant) growth and neurodevelopment in mice.[29]

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 adenosine triphosphate–binding cassette transporter responsible for drug efflux across the placenta.[30]

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.[13]

Excerpt from Table 14

Note: When using fixed-dose combination (FDC) tablets, refer to other sections in Appendix B and Table 14 in the Perinatal Guidelines 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[c] (generic product only) • 200 mg[c] • 300 mg[c] *Oral Powder* • 50-mg packet ATV/c (Evotaz) • ATV 300-mg/COBI 150-mg tablet	Pregnancy *PK in Pregnancy* • ATV (Reyataz) o ATV concentrations are reduced during pregnancy, and they are further reduced when ATV is given concomitantly with TDF or an H2-receptor antagonist. o Intracellular ATV levels in women taking the standard dose (ATV/r 300 mg/100 mg) without concomitant TDF appear reassuringly stable throughout pregnancy. • ATV/c (Evotaz) o 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) o Use of unboosted ATV **is not recommended** during pregnancy. o Use of unboosted ATV **is not recommended** during pregnancy for ARV-experienced patients who are taking TDF and an H2-receptor antagonist.	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 6 and Table 7 for discussions about avoiding the use of ATV/c during pregnancy.

Excerpt from Table 14

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations[a]	Use in Pregnancy
		○ 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. Increased ATV dosing is recommended for pregnant people in the second and third trimesters who are also receiving either TDF or an H2-receptor antagonist. • ATV/c (Evotaz) ○ ATV/c should not be used in pregnancy because atazanavir C_{min} is substantially reduced (see COBI). For guidance about the use of combination products in pregnancy, see the specific sections on other components (i.e., COBI). 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.	

Excerpt from Table 14

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations[a]	Use in Pregnancy
		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. *ATV/c (Evotaz)* • One tablet once daily with food	

[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 12).

[b] Placental transfer categories are determined by mean or median cord blood–to–maternal delivery plasma drug ratio:

High: >0.6
Moderate: 0.3–0.6
Low: <0.3

[c] Generic product is available.

Key: ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; C_{min} = minimum plasma concentration; COBI = cobicistat; EFV = efavirenz; PK = pharmacokinetic; PPI = proton pump inhibitor; RTV = ritonavir; TDF = tenofovir disoproxil fumarate

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Darunavir (Prezista, DRV)

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Summary

- Darunavir (DRV) trough concentrations (C_{trough}) are reduced during pregnancy by approximately 10% with use of DRV boosted with ritonavir (DRV/r) 600 mg/100 mg twice daily and by approximately 50% with use of DRV/r 800 mg/100 mg once daily.
- DRV C_{trough} are reduced during pregnancy by approximately 90% with use of DRV boosted with cobicistat (DRV/c) 800 mg/150 mg once daily.
- The Panel on Treatment of HIV During Pregnancy and Interventions to Reduce Perinatal HIV Transmission (the Panel) recommends the use of twice-daily dosing with DRV/r 600mg/100 mg during pregnancy and does not recommend use during pregnancy of once-daily dosing with DRV/r 800 mg/100 mg or the use of DRV/c 800 mg/150 mg.
- First-trimester exposures to DRV have not been associated with increased risk of congenital anomalies.

Human Studies in Pregnancy

Pharmacokinetics

Several studies of the pharmacokinetics (PK) of DRV/r during pregnancy have been completed.[1-4] During the third trimester, DRV plasma area under the curve (AUC) 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, compared with postpartum.[1-5] During the third trimester, DRV C_{trough} 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, compared with postpartum.[2-4]

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.[1,3,4] 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.[2,6] The U.S. Food and Drug Administration recommends the use of once-daily DRV/r 800-mg/100-mg dosing only for pregnant people who were virally suppressed on a stable, once-daily DRV/r regimen before pregnancy and whose adherence or ability to tolerate a regimen may be compromised by a switch to twice-daily DRV/r.[7] After reviewing the available evidence, the Panel does not recommend once-daily dosing of DRV/r in pregnancy. Because use of 800-mg DRV doses administered twice daily did not increase DRV exposure in pregnant women, the Panel recommends the use of twice-daily 600-mg DRV dosing during pregnancy.[5]

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 with postpartum PK parameters, total DRV AUC was reduced by 56% and 50%, and C_{trough} 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 C_{trough} 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 with postpartum. Six of seven participants remained virally suppressed during pregnancy. One woman who was not virally 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 the larger PK study, which included data from 29 pregnant women who received DRV/c as part of clinical care and showed that 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 C_{trough} 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 five 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%.[1-3,9,12]

Breast milk transfer of DRV was low in two mother–infant pairs where the mother was receiving DRV/r while breastfeeding, with a median DRV breast milk–to–maternal plasma concentration ratio of 0.12, median estimated infant DRV dose of 0.05 mg/kg, and no detectable DRV in infant plasma.[13]

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 3.7% (27 of 737 live births; 95% confidence interval, 2.4% to 5.3%) compared with a 2.7% total prevalence in the U.S. population, based on Centers for Disease Control and Prevention surveillance.[14]

Animal Studies

Carcinogenicity

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 predisposed rats, but not humans, to thyroid neoplasms.

At the highest tested doses, the systemic exposures to DRV (based on 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 DRV/r 600 mg/100 mg twice daily or DRV/r 800 mg/100 mg once daily.[7]

Reproduction/Fertility

No effects on fertility or early embryonic development were seen in rats that received DRV.[7]

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 because of the toxicity and mortality observed in juvenile rats dosed with DRV up to 23 to 26 days of life.[7]

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.[7]

Excerpt from Table 14

Note: When using fixed-dose combination (FDC) tablets, refer to other sections in Appendix B and Table 14 in the Perinatal Guidelines 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	Pregnancy *PK in Pregnancy* • Decreased exposure in pregnancy with use of DRV/r *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 people. • 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 use of combination products in pregnancy, please see the specific sections on other components (i.e., COBI, FTC, TAF). 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	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.

Excerpt from Table 14

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations[a]	Use in Pregnancy
		• DRV/c 800 mg/150 mg once daily with food *ARV-Experienced Patients 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	

[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 12).

[b] Placental transfer categories are determined by mean or median cord blood–to–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; FTC = emtricitabine; the Panel = Panel on Treatment of HIV During Pregnancy and Interventions to Reduce Perinatal HIV Transmission; PK = pharmacokinetics; RTV = ritonavir; TAF = tenofovir alafenamide

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Lopinavir/Ritonavir (Kaletra, LPV/r)

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Summary

- Lopinavir/ritonavir (LPV/r) concentrations are decreased by approximately 30% during pregnancy.
- Some experts recommend increased doses of LPV/r during the second and third trimesters of pregnancy (LPV/r 600/150 mg twice daily or LPV/r 500/125 mg twice daily), especially in protease inhibitor (PI)–experienced patients and patients who start treatment during pregnancy with a baseline viral load >50 copies/mL. Once-daily dosing of LPV/r during pregnancy **is not recommended.**
- First trimester exposure to LPV/r is not associated with increased risk of congenital abnormalities.
- PI-based regimens, including LPV/r, may be associated with increased rates of preterm delivery.
- LPV/r oral solution should not be used during pregnancy because it contains 42.4% alcohol and 15.3% propylene glycol.

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.[1,2] Pharmacokinetic (PK) studies of standard adult LPV/r doses (400 mg/100 mg twice daily) that used either the capsule or tablet formulations in pregnant women have demonstrated a reduction in lopinavir (LPV) plasma concentrations during pregnancy of around 30% compared with those seen in nonpregnant adults.[3-5] A further 33% reduction in LPV exposure was demonstrated in food-insecure, malnourished pregnant women in Uganda compared with historical well-nourished pregnant controls. The authors attributed this reduction to decreased bioavailability of LPV.[6] 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.[7,8]

Clinical experience suggests that most, but not all, pregnant women who receive standard LPV/r tablet dosing during pregnancy will have LPV trough concentrations (C_{trough}) that exceed 1.0 mcg/mL, the usual target for C_{trough} in therapeutic drug monitoring programs for antiretroviral (ARV)-naive subjects. However, higher C_{trough} are recommended for PI-experienced subjects, and some PI-experienced women who take the standard LPV/r dose during pregnancy will not achieve these concentrations.[1,4] 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 C_{trough} when taking the standard dose during pregnancy.[9] 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.[10] 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.[11] In a study of 12 women, total LPV exposure was decreased significantly throughout pregnancy, but the area under the curve and concentration at 12 hours postdose 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.[12,13] 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.[14] 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 with 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.[15]

These studies have led some experts to support the use of an increased dose of LPV/r during the second and third trimesters of pregnancy, especially in patients 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.[12] 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 4 PK study of selected ARV drugs 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.[16] 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.[16-21]

Teratogenicity/Adverse Pregnancy Outcomes

The French Perinatal Cohort found no association between birth defects and LPV or ritonavir (RTV) use with 85% power to detect a 1.5-fold increase.[22] The Pediatric HIV/AIDS Cohort Study (PHACS) found no association between LPV and congenital anomalies.[23] 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.[24] 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 1,451 live births; 95% confidence interval, 1.4% to 2.9%) compared with a 2.7% total prevalence in the U.S. population based on Centers for Disease Control and Prevention surveillance.[25]

In the Promoting Maternal and Infant Survival Everywhere (PROMISE) study, administering LPV/r with zidovudine (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).[26] Compared with 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 PHACS also found an increased rate of preterm birth among women who received PI-based ARV therapy, although not with specific individual drugs.[27] 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.[28] 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.[29] For a more detailed discussion of ARV drug regimens and adverse pregnancy outcomes, please refer to 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 the Lopinavir/Ritonavir section in the Pediatric Antiretroviral Guidelines.[30,31]

Animal Studies

Carcinogenicity

Neither LPV nor RTV was found to be mutagenic or clastogenic in a battery of *in vitro* and *in vivo* assays. Mice and rats showed an increased incidence of benign hepatocellular adenomas and an increased combined incidence of hepatocellular adenomas plus carcinoma at doses of approximately 1.6 times to 2.2 times (in mice) and 0.5 times (in rats) those seen in humans.[32]

Reproduction/Fertility

No effects on fertility were observed in male and female rats.[32]

Teratogenicity/Adverse Pregnancy Outcomes

In rats treated with a maternally toxic dose, 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. In a perinatal and postnatal study in rats, a decrease in survival of pups between birth and postnatal Day 21 occurred. In rabbits, no embryonic or fetal developmental toxicities were observed with a maternally toxic dose. 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 correlated directly with lower fetal weight.[33]

Placental and Breast Milk Passage

No information is available on placental transfer of LPV in animals.[32]

Excerpt from Table 14

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations[a]	Use in Pregnancy
Lopinavir/Ritonavir (LPV/r) *Kaletra* Note: Generic products are available for all formulations.	LPV/r (Kaletra)[c] *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.	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. Standard Adult Doses • LPV/r 400 mg/100 mg twice daily, *or* • LPV/r 800 mg/20 mg once daily	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.

Excerpt from Table 14

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations[a]	Use in Pregnancy
		Tablets • Take without regard to food. *Oral Solution* • Take with a 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	

[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 12).

[b] Placental transfer categories are determined by mean or median cord blood–to–maternal delivery plasma drug ratio:

High: >0.6
Moderate: 0.3–0.6
Low: <0.3

[c] Generic formulation available

Key: EFV = efavirenz; LPV = lopinavir; LPV/r = lopinavir/ritonavir; NVP = nevirapine; PI = protease inhibitor; PK = pharmacokinetic; RTV = ritonavir

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Fostemsavir (Rukobia, FTR)

Updated: January 31, 2024
Reviewed: January 31, 2024

Fostemsavir (FTR) is a prodrug of the active drug temsavir, a gp120-directed attachment inhibitor.

Summary

- Pharmacokinetic data are insufficient to make dosing recommendations for fostemsavir (FTR) during pregnancy.
- Clinical data are insufficient to characterize the risk for congenital anomalies associated with *in utero* exposure to FTR. No reproductive toxicity or teratogenicity concerns were identified in animal studies.

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

Two live births of infants who were exposed to FTR during the first trimester have been reported to the Antiretroviral Pregnancy Registry; no birth defects were reported. These data are insufficient for drawing conclusions about the risk of birth defects among infants who were exposed to FTR.[1]

Animal Studies

Carcinogenicity

Temsavir was not genotoxic or mutagenic *in vitro*.[2]

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.[2]

Teratogenicity/Adverse Pregnancy Outcomes

No adverse embryo-fetal effects were observed in rats and rabbits at temsavir exposures of approximately 180 times (rats) and 30 times (rabbits) 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.[2]

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.[2]

Excerpt from Table 14

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations[a]	Use in Pregnancy
Fostemsavir (FTR) *Rukobia*	Extended-release tablet: 600 mg	Pregnancy *PK in Pregnancy* • No PK studies in human pregnancy *Dosing in Pregnancy* • Insufficient data to make dosing recommendation Standard Adult Doses *(FTR) Rukobia* • FTR 600 mg twice daily with or without food	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 12).

Key: ARV = antiretroviral; FTR = fostemsavir; PK = pharmacokinetic

References

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Ibalizumab-uiyk (Trogarzo, IBA)

Updated: January 31, 2024
Reviewed: January 31, 2024

Summary

- Pharmacokinetic (PK) data are insufficient to make dosing recommendations for ibalizumab (IBA) during pregnancy.
- Clinical data are insufficient to characterize the risk for congenital anomalies associated with *in utero* exposure to IBA. No reproductive toxicity or teratogenicity concerns were identified in animal studies.
- Results from an enhanced pre- and postnatal development (ePPND) study conducted in cynomolgus monkeys suggest IBA may cause reversible immunosuppression in infants born to mothers exposed to this drug during pregnancy.

Human Studies in Pregnancy

Pharmacokinetics

No PK 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 birthing parent 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 available on the risk of birth defects in infants born to women who received IBA during pregnancy.

The U.S. Food and Drug Administration requires collection of prospective data in individuals exposed to IBA during pregnancy to monitor maternal and pregnancy outcomes, including adverse effects on the developing fetus, neonate, and infant.

Animal Studies

Carcinogenicity

Carcinogenicity and mutagenicity studies of IBA have not been conducted.[1]

Reproduction/Fertility

Reproductive toxicology studies of IBA have not been conducted.[1]

Teratogenicity/Adverse Pregnancy Outcomes

Results from an ePPND study conducted in cynomolgus monkeys suggest IBA may cause reversible immunosuppression in infants born to mothers exposed to this drug during pregnancy. Decreases in CD4 T lymphocyte (CD4) T cells and B cells and increases in CD8 T cells were observed within the first 4 weeks after birth in cynomolgus monkeys with *in utero* exposure; lymphocyte counts returned to near-normal levels by 3 months of age in these infant monkeys. No data are available for human infants with *in utero* exposure. However, based on these animal data, immune phenotyping of the peripheral blood, including CD4 lymphocyte T cell and B cell counts, is recommended for infants with *in utero* exposure to IBA. If immune suppression is observed, expert consultation also is recommended to provide guidance on monitoring and management (e.g., need for antibiotics or immunoprophylaxis) of exposed infants based on the degree of immunosuppression observed. The safety of administering live or live-attenuated vaccines in exposed infants who have significant immune suppression is unknown. Of note, no malformations or premature births were observed in the ePPND study.[1]

Placental and Breast Milk Passage

No data are available on placental or breast milk passage of IBA in animals.

Excerpt from Table 14

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations[a]	Use in Pregnancy
Ibalizumab-uiyk (IBA) *Trogarzo*	IV Solution • 150 mg/mL	Pregnancy *PK in Pregnancy* • No PK studies in human pregnancy *Dosing in Pregnancy* • Insufficient data to make dosing recommendations Standard Adult Doses • IBA 2,000-mg loading dose, followed by IBA 800-mg maintenance doses administered every 2 weeks	No human data are available, but placental transfer of IBA, a monoclonal antibody, is possible and documented in monkeys. Based on data in cynomolgus monkeys with *in utero* exposure, the potential exists for reversible immunosuppression (CD4 T cell and B cell lymphocytopenia) in infants born to mothers exposed to IBA during pregnancy. The FDA requires collection of prospective data in individuals exposed to IBA during pregnancy to monitor maternal and pregnancy outcomes, including adverse effects on the developing fetus, neonate, and infant. 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 12).

Key: ARV = antiretroviral; CD4 = CD4 T lymphocyte; FDA = U.S. Food and Drug Administration; IBA = ibalizumab-uiyk; IV = intravenous; PK = pharmacokinetic

References

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Maraviroc (Selzentry, MVC)

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Reviewed: January 31, 2024

Summary

- No dose adjustments are required for maraviroc (MVC) during pregnancy. The dose of MVC should be determined after accounting for potential drug interactions with concomitantly administered medications, including antiretroviral (ARV) drugs.
- Clinical data are insufficient to characterize the risk for congenital anomalies associated with *in utero* exposure to MVC.
- No reproductive toxicity or teratogenicity concerns were identified in animal studies.

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 of 18 women who were taking MVC as part of clinical care.[1] 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 area under the curve (AUC) versus postpartum AUC was 0.72 (90% confidence interval [CI], 0.60–0.88); the geometric mean ratio for maximum MVC concentration in the third trimester versus maximum MVC concentration postpartum was 0.70 (90% CI, 0.58–0.85). 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 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.[2]

Placental and Breast Milk Passage

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), indicating moderate placental transfer.[1] An *ex vivo* human placental cotyledon perfusion model demonstrated minimal placental passage of MVC.[3] This may be due to the activity of multiple transporters (e.g., multidrug resistance–associated protein 1, organic anion transporting polypeptide 1A2, organic anion transporting polypeptide 1B3) that drive MVC away from fetal circulation into placental tissue, as demonstrated in a closed-circuit perfusion study of MVC across human placental cotyledon.[4] Whether MVC is secreted into human milk is unknown.

Teratogenicity/Adverse Pregnancy Outcomes

Thirty-one cases of first-trimester exposure to MVC have been reported to the Antiretroviral Pregnancy Registry to date,[5] and other first-trimester exposure data are available.[6] 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.[7] 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 MVC might influence placental drug transfer and cause drug–drug interactions.[8]

Animal Studies

Carcinogenicity

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 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 5 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.[9]

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.[10] Studies in lactating rats indicate that MVC is secreted extensively into rat milk.[9]

Excerpt from Table 14

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations[a]	Use in Pregnancy
Maraviroc (MVC) *Selzentry*	Tablets • 150 mg • 300 mg	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. 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 include all PIs except TPV/r and itraconazole	Moderate placental transfer to fetus[b] No evidence of teratogenicity in rats or rabbits; insufficient data to assess 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 12).

[b] Placental transfer categories are determined by mean or median cord blood–to–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 = pharmacokinetic; TPV/r = tipranavir/ritonavir

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Lenacapavir (LEN)

Updated: January 31, 2024
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Summary

- Pharmacokinetic data are insufficient to make dosing recommendations for oral or long-acting injectable lenacapavir (LEN) during pregnancy or breastfeeding.
- Clinical data are insufficient to characterize the risk for congenital anomalies associated with *in utero* exposure to LEN. No reproductive toxicity or teratogenicity concerns were identified in animal studies.

Human Studies in Pregnancy

Pharmacokinetics

No data are available on the pharmacokinetics (PK) of LEN with continuing subcutaneous injections during pregnancy.

Placental and Breast Milk Passage

No data are available regarding placental transfer of LEN. Additionally, no data are available describing breast milk passage of LEN in humans; because LEN is more than 98.5% protein bound, amounts found in breast milk are likely low.[1]

Teratogenicity/Adverse Pregnancy Outcomes

The Antiretroviral Pregnancy Registry has not monitored sufficient numbers of first-trimester exposures to LEN to report on the risk of overall birth defects.

Animal Studies

Carcinogenicity

LEN was not mutagenic in a series of *in vitro* and animal *in vivo* genotoxic assays; LEN was not carcinogenic in a mouse model.[2]

Reproduction/Fertility

In rats, no effects on fertility, mating performance, or early embryonic development were observed at LEN exposures 5 times greater than the exposure in humans at recommended doses.[2]

Teratogenicity/Adverse Pregnancy Outcomes

No significant toxicological effects on embryo-fetal development in rats and rabbits or pre- and postnatal development in rats were observed at area under the curve drug exposures approximately 16 times (rats) and 39 times (rabbits) the exposure in humans at recommended doses.[2]

Placental and Breast Milk Passage

LEN was detected at low levels in the plasma of nursing rat pups.[2]

Excerpt from Table 14

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations[a]	Use in Pregnancy
Lenacapavir (LEN) *Sunlenca*	LEN (Sunlenca) • LEN 300-mg tablets for oral administration • LEN 463.5 mg/1.5 ml for SQ injection	Pregnancy *PK in Pregnancy* • No PK studies in human pregnancy *Dosing in Pregnancy* • Insufficient data to make dosing recommendations Standard Adult Doses *Initiation Option 1* • Day 1: 927 mg by SQ injection (2 x 1.5 mL injections) and 600 mg orally (2 x 300-mg tablets) • Day 2: 600 mg orally (2 x 300-mg tablets). *Initiation Option 2* • Day 1: 600 mg orally (2 x 300-mg tablets) • Day 2: 600 mg orally (2 x 300-mg tablets) • Day 8: 300 mg orally (1 x 300-mg tablet) • Day 15: 927 mg by SQ injection (2 x 1.5 mL injections) *Maintenance Dosing* • 927 mg by SQ injection (2 x 1.5 mL injections) every 26 weeks +/- 2 weeks from date of last injection	No human data are available regarding placental passage or through breast milk. Data are insufficient 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 12).

Key: ARV = antiretroviral; LEN = lenacapavir; PK = pharmacokinetic; SQ = subcutaneous

References

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Bictegravir (BIC)

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Reviewed: January 31, 2024

Summary

- No dose adjustment for bictegravir (BIC) is recommended in pregnancy.
- First-trimester exposure to BIC has not been associated with an increased risk of congenital anomalies.

Human Studies in Pregnancy

Pharmacokinetics

BIC pharmacokinetics (PK) during pregnancy have been reported in two clinical studies and a case series. Preliminary PK results among 27 pregnant women showed that BIC area under the curve (AUC) and concentrations at 24 hours postdose (C_{24h}) were decreased by 56% and 71%, respectively, at the third trimester compared to postpartum (n = 11 with paired data).[1] Thirteen of 21 (62%) women with PK results also fell below the 10th percentile AUC for nonpregnant adults during the third trimester, but none of these women had a detectable viral load. Additionally, all C_{24h} values across the second and third trimesters were above the BIC protein-adjusted 95% maximal effective concentration (EC_{95}) of 0.162 ug/mL, with median values 4.4- and 5.9-fold above the EC_{95}.[1] Virologic suppression (<20 copies/mL) was maintained in 76% to 88% of participants across pregnancy and postpartum, and only one participant had a viral load above 200 copies/mL. Additionally, 90% of participants were suppressed at delivery and no infant HIV infections occurred.

A separate study[2] in 33 pregnant women showed that total BIC AUC was approximately 56% to 59% lower, and BIC trough concentrations (C_{trough}) were approximately 71% lower during the second or third trimester compared to 6 or 12 weeks postpartum. Total BIC AUC in the pregnant women was 41% lower during the third trimester compared with historical data in nonpregnant adults with HIV. Because BIC is highly protein bound and pregnancy can be associated with decreased plasma protein binding, unbound drug concentrations were also assessed. The AUC for unbound BIC was approximately 38% to 41% lower during pregnancy than postpartum. The mean unbound fractions were higher during pregnancy than postpartum (0.351% and 0.365% during the second and third trimester, respectively, compared with 0.261% and 0.252% at 6 and 12 weeks postpartum, respectively). Mean C_{trough} values during the second and third trimesters were about 6.5-fold above the BIC protein-adjusted EC_{95}, and all but one individual C_{trough} value was above this threshold. All women maintained virologic suppression (<50 copies/mL) through week 18 postpartum, including at delivery, and no infant HIV infections occurred.

A case series describing two pregnant women, one of whom had paired PK data during pregnancy and postpartum, has also been detailed.[3,4] This patient's AUC, trough concentration, and maximum plasma concentration were 35%, 49%, and 19% lower, respectively, at 33 weeks gestation than at 6 weeks postpartum. The patient remained virologically suppressed through delivery.

Collectively, these findings demonstrate that despite lower AUC and C_{24h} or C_{trough} values during pregnancy, drug exposures were still above those needed to maintain virologic suppression when using standard BIC doses.

Placental and Breast Milk Passage

Placental transfer of BIC is high, with a mean umbilical cord blood–to–maternal plasma ratio of 1.4 (coefficient of variance percentage 35%) at delivery.[2] The estimated median half-life in neonates was 43 hours (interquartile range 38 – 58). These umbilical cord blood–to–maternal plasma ratios are comparable to a previous case series where ratios of 1.49 were measured in one patient 20 hours after BIC dosing and 1.42 in another patient 7 hours after BIC dosing.[3] A separate case report conveyed an umbilical cord blood–to–maternal plasma ratio of 0.68 approximately 16 hours after BIC dosing.[4] The concentration of BIC was 2,826 ng/mL in cord blood at delivery, 2,097 ng/mL in the infant on Day 3 after birth, and undetectable (<5 ng/mL) in the infant by Day 22.

Data on the passage of BIC in human breast milk are very limited. BIC milk–to–plasma ratios have only been reported in one individual, which revealed a ratio of 0.01 and subsequent estimated infant daily dose of 0.01 mg/kg.[5] Additional data are needed to refine our understanding of the breast milk passage of BIC.

Teratogenicity/Adverse Pregnancy Outcomes

The Antiretroviral Pregnancy Registry has monitored sufficient numbers of first-trimester exposures to BIC 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 BIC. Among the cases of first-trimester BIC exposure that had been reported to the Antiretroviral Pregnancy Registry as of January 31, 2023, the prevalence of birth defects was 4.32% (14 of 324 live births; 95% confidence interval, 2.38–7.14).[6]

Animal Studies

Carcinogenicity

BIC has not been shown to be genotoxic or mutagenic *in vitro*.[7]

Reproduction/Fertility

BIC did not affect fertility, reproductive performance, or embryonic viability in male or female rats at exposures (based on AUC) that were 29 times higher than those observed in humans who received the recommended dose.[7]

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).[7]

Placental and Breast Milk Passage

No data are available on placental passage of BIC in animals. In a prenatal 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.[7]

Excerpt from Table 14

Note: When using fixed-dose combination (FDC) tablets, refer to other sections in Appendix B and Table 14 in the Perinatal Guidelines 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 available only as part of an FDC tablet.	BIC/FTC/TAF (Biktarvy) • BIC 50-mg/FTC 200 mg/TAF 25-mg tablet • BIC 30-mg/FTC 120-mg/TAF 15-mg tablet	Pregnancy *PK in Pregnancy* • AUC and C_{24h}/C_{trough} are 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 use of combination products in pregnancy, please see the specific sections on other components (i.e., FTC, TAF). Standard Adult Doses • One tablet of BIC 50 mg/FTC 200 mg/TAF 25 mg once daily with or without food	High placental transfer to fetus[b] No evidence of human teratogenicity (can rule out twofold increase in overall birth defects) 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 12).

[b] Placental transfer categories are determined by mean or median cord blood–to–maternal delivery plasma drug ratio:

High: >0.6
Moderate: 0.3–0.6
Low: <0.3

Key: ARV = antiretroviral; AUC = area under the curve; BIC = bictegravir; C_{24h} = concentrations at 24 hours postdose; FDC = fixed-dose combination; FTC = emtricitabine; PK = pharmacokinetics; TAF = tenofovir alafenamide

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Cabotegravir (CAB)

Updated: January 31, 2024
Reviewed: January 31, 2024

Summary

- Pharmacokinetic (PK) data are insufficient to make dosing recommendations for oral cabotegravir (CAB) or long-acting (LA) injectable cabotegravir (CAB-LA) during pregnancy or breastfeeding.
- Clinical data are insufficient to characterize the risk for congenital anomalies associated with *in utero* exposure to CAB. No reproductive toxicity or teratogenicity concerns were identified in animal studies.

Human Studies in Pregnancy

Pharmacokinetics

No studies have been conducted on the PK of CAB and rilpivirine (RPV) with ongoing intramuscular (IM) injections during pregnancy. Clinical trial data reported to date are limited to pregnant women who stopped receiving CAB injections for the treatment or prevention of HIV once pregnancy was recognized and began an alternative oral antiretroviral regimen throughout the remainder of their pregnancies. From the Phase 2b/3/3b clinical trials of long-acting injectable CAB and RPV for the treatment of HIV, PK data are available for seven of the nine participants exposed to long-acting injectable CAB and RPV therapy with live birth outcomes. Plasma concentrations were within the range of observed concentrations of nonpregnant women who discontinued long-acting injectable CAB and RPV.[1] In HPTN 084, which assessed the efficacy and safety of CAB-LA for HIV prevention, PK data are available in 26 participants who received at least one dose of CAB prior to the confirmation of pregnancy and discontinuation of CAB. The apparent terminal-phase half-life ($t_{1/2app}$) in pregnant participants was comparable to nonpregnant individuals, although body mass index greater than 27.2 was associated with longer CAB $t_{1/2app}$.[2] One physiologically based (PB) PK model predicted that pregnancy will have minimal influence on the PK of CAB-LA and that dose adjustments will not be indicated; the model did not specify whether CAB was initiated in pregnancy or continued from prior to pregnancy.[3] A newer PBPK model of pregnant individuals initiating long-acting injectable CAB and RPV in the early second trimester predicted a reduction in plasma concentrations of 29.5% and 23.0%, respectively, at the first trough after the first injection. After the sixth injection in the second and third trimesters, plasma concentrations were 31.1% and 29.2% lower for CAB and RPV, respectively. These reductions are attributed to the predicted induction of uridine diphosphate glucuronyl transferase 1A1 and cytochrome P450 3A4 during the second and third trimesters.[4]

Placental and Breast Milk Passage

Median (interquartile range 25–75) CAB maternal-to-fetal concentration ratio assessed using an *ex vivo*, dually perfused human cotyledon model was 10% (5–16), suggesting low placental transfer.[5] No data are available describing breast milk passage of CAB in humans.[6] See Rilpivirine for data about RPV.

Teratogenicity/Adverse Pregnancy Outcomes

The Antiretroviral Pregnancy Registry has not monitored sufficient numbers of first-trimester exposures to CAB to report on the risk of overall birth defects.[7]

In the Phase 2b/3/3b trials of CAB and RPV, 25 of 325 women of reproductive potential became pregnant while exposed to CAB and RPV (5 oral, 20 long-acting injectable), resulting in 8 elective abortions, 6 spontaneous abortions (5 in the first trimester), 1 ectopic pregnancy, and 10 live births (1 oral, 9 long-acting injectable). Of the 10 live births, 1 case of congenital ptosis was reported in a preterm infant with intrauterine growth restriction, and 1 late preterm delivery occurred due to induction of labor.[1] In HPTN 084, among 29 confirmed pregnancies (of whom 26 received at least one injection), 4 pregnancy losses occurred prior to 20 weeks, 1 occurred between 20 to 36 weeks, and 22 live births occurred. No congenital anomalies, preterm births, or drug-related maternal or neonatal adverse events have been reported to date in the live births of infants from mothers who conceived while receiving IM injections of CAB alone.[8] Increased adverse events (grade 1–3) during pregnancy were noted in the CAB arm of HPTN 084 (compared to the tenofovir disoproxil fumarate/emtricitabine arm) but were deemed unrelated to the study drug. See Rilpivirine for additional information about oral RPV.

Animal Studies

Carcinogenicity

CAB was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests. Long-term carcinogenicity studies of CAB in mice did not show any carcinogenic potential at systemic exposures that were sevenfold (in females) or eightfold (in males) greater than human exposure at the recommended dose. In rats, no drug-related increases in tumor incidence were observed at CAB exposures up to approximately 26 times higher than those in humans at the recommended dose.[9]

CAB was not genotoxic in the bacterial reverse mutation assay, mouse lymphoma assay, or *in vivo* rodent micronucleus assay.[10] See Rilpivirine for data about RPV.

Reproduction/Fertility

In rats, no effects on fertility were observed at CAB exposures at least 20 times greater than the exposure in humans at recommended doses. See Rilpivirine for data about RPV.

Teratogenicity/Adverse Pregnancy Outcomes

Studies in pregnant rats showed that CAB crosses the placenta and can be detected in fetal tissue. Treatment of rat dams with CAB during pregnancy and postpartum had no effects on fetal viability, although a minor decrease was observed in fetal body weight with exposures 28 times those seen in humans at the recommended dose. No drug-related fetal toxicities were observed with rat dam exposures approximately 13 times those seen in humans at the recommended dose, and no fetal malformations were observed at any rat dam dose. A delay in the onset of parturition and increases in the number of stillbirths and neonatal deaths were seen with exposure of rat dams to CAB at 28 times the human exposure with recommended doses, but not with exposure at 13 times the human exposure with recommended doses.

No drug-related fetal toxicities were observed after CAB exposures of rabbit dams of up to approximately 0.7 times those seen in humans at the recommended dose.[9]

A recent study in mouse models demonstrated decreased human embryonic stem cell counts and pluripotency and induced dysregulation of genes involved in early differentiation at subtherapeutic levels of CAB.[11] Additionally, a study of zebrafish found that although CAB did not cause gross morphological defects at low doses, pericardial edema, uninflated swim bladder, decreased heartbeats, growth delay, and decreased hatching rate were observed at the highest concentrations. At subtherapeutic doses, decreased locomotion was observed, suggesting alterations of nervous system integrity.[12] Clinical data and clinical trials data in humans are insufficient to refute or corroborate these findings.

See Rilpivirine for data about RPV.

Placental and Breast Milk Passage

Studies in lactating rats and their offspring indicate that CAB is present in rat milk. See Rilpivirine for data about RPV.

Excerpt from Table 14

Note: When using fixed-dose combination (FDC) tablets, refer to other sections in Appendix B and Table 14 in the Perinatal Guidelines 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
Cabotegravir (CAB) *Vocabria (oral)* *Apretude (injection for HIV pre-exposure prophylaxis)* (CAB) *Cabenuva* Note: CAB and RPV is a two-drug co-packaged product for IM injection.	CAB • CAB 30-mg tablets for oral administration • CAB 200-mg/mL suspension for IM injection CAB and RPV • CAB 200-mg/mL suspension for IM injection • RPV 300-mg/mL suspension for IM injection	Pregnancy *PK in Pregnancy* • No PK studies in human pregnancy *Dosing in Pregnancy* • Insufficient data to make dosing recommendations For guidance about the use of combination products in pregnancy, please see the specific sections on other components (i.e., RPV). Standard Adult Doses *Oral Lead-in Therapy (Optional)* • CAB (Vocabria) o One 30-mg tablet once daily in combination with RPV (Edurant) 25-mg once daily taken with a meal for 4 weeks • CAB (Apretude) o Initiation ▪ CAB 600-mg (3 mL) injections given 1 month apart for 2 consecutive months (on the last day of an oral lead-in, if used, or within 3 days) o Continuation Therapy ▪ CAB 600-mg (3 mL) injections every 2 months thereafter	No human data are available regarding placental passage. Insufficient data to assess for teratogenicity in humans. No evidence of teratogenicity in rats or rabbits.

Excerpt from Table 14

		• CAB and RPV (Cabenuva) o Initiation ▪ CAB 600-mg (3 mL) and RPV 900-mg (3 mL), given as two separate injections in separate ventrogluteal sites for 2 consecutive months (on the last day of an oral lead-in if used) o Continuation Therapy ▪ *Monthly:* CAB 400-mg (2 mL) and RPV 600-mg (2 mL), given as two separate injections in separate ventrogluteal sites once a month with allowance for a +/- 7-day administration window ▪ *Every 2 months:* Starting in month 4, CAB 600-mg (2 mL) and RPV 900-mg (2 mL), given as two separate injections in separate ventrogluteal sites once a month with allowance for a +/- 7-day administration window ▪ Patients should be monitored for approximately 10 minutes for post-injection reactions. A 23-gauge, 1.5-inch IM needle is recommended for the injection and is provided in the packaging. Longer, 2-inch needles should be used in patients with BMIs >30 kg/m^2. *Changing Dosing Frequency and Managing Missed Doses* • Refer to the package insert for instructions about changing the frequency of continuation doses and managing missed doses (see Apretude and Cabenuva)	

Excerpt from Table 14

[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 12).

[b] Placental transfer categories are determined by mean or median cord blood–to–maternal delivery plasma drug ratio:

High: >0.6
Moderate: 0.3–0.6
Low: <0.3

Key: ARV = antiretroviral; BMI = body mass index; CAB = cabotegravir; IM = intramuscular; PK = pharmacokinetic; RPV = rilpivirine

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Dolutegravir (Tivicay, Tivicay PD, DTG)

Updated: January 31, 2024
Reviewed: January 31, 2024

Summary

- No dose adjustment for dolutegravir (DTG) is recommended in pregnancy.
- First-trimester exposure to DTG has not been associated with increased risk of congenital anomalies, including neural tube defects (NTDs).

Human Studies in Pregnancy

Pharmacokinetics

DTG pharmacokinetics (PK) in human pregnancy have been reported in three studies and a series of case reports.[1-7] 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 area under the curve (AUC) reduced by 21% during pregnancy. Although trough concentrations (C_{trough}) were reduced by 34% during the third trimester compared to postpartum, C_{trough} 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.[5] 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.[7]

In contrast, PK sampling during pregnancy and the early postpartum period of 17 African women who were receiving DTG showed a small reduction in DTG maximum concentration (C_{max}) and no differences in the 24-hour concentration and AUC from 0 to 24 hours 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 not yet fully returned to the nonpregnant state.[6] In the case reports, DTG was used safely and effectively in individual pregnant women and plasma exposures were adequate.[1-4]

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.[8] In two *in vivo* PK studies,[5,6] the median DTG cord blood–to–maternal plasma concentration ratios were 1.21 and 1.25. High placental transfer of DTG has also been reported in several of the case reports.[1,3,4] In 17 breastfeeding mothers, the median ratio of DTG in breast milk to maternal plasma was 0.03. Their infants had a median DTG C_{max} of 66.7 ng/mL (range 21–654 ng/mL) and a median C_{min} 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.[6]

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 had been reported to the Antiretroviral Pregnancy Registry as of January 31, 2021, the prevalence of birth defects was 3.3% (29 of 874 live births; 95% confidence interval, 2.2–4.7).[9]

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).[5] 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.[6] In 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.[10-12] No increased incidence of birth defects or adverse perinatal outcomes was observed in 57 French women receiving DTG during pregnancy compared to matched controls who did not receive integrase strand transfer inhibitors (INSTIs) during pregnancy.[13] In contrast, in 257 pregnancies in women with HIV in Denver, Colorado, diverse congenital anomalies (with no NTDs) were detected in 7 of 24 infants (29.2%) exposed to DTG in the first trimester compared to 13 of 109 infants (11.9%) with first-trimester exposure to non-INSTI antiretrovirals (ARVs).[14]

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 ARV drug exposure (0.30% vs. 0.10%).[15] Expanded and ongoing surveillance of birth outcomes in Botswana among pregnant women receiving ARVs between August 2014 and March 2022 revealed a prevalence of NTDs with DTG use at conception of 0.11%, which was identical to the NTD prevalence in women with HIV receiving other ARVs at conception.[16] In a report from an ongoing birth outcome surveillance program in Eswatini, NTD prevalence was 0.08% in 4,832 pregnancies with DTG use at conception compared to 0.16% in 1,248 pregnancies with use of non-DTG regimens at conception and 0.08% in 17,270 pregnancies without HIV infection.[17] When the data from the Botswana and Eswatini programs are combined, the NTD prevalence is 0.098% in more than 14,000 women receiving DTG at conception, which is not significantly different from the NTD rates in women receiving other ARV regimens at conception or women without HIV in these countries.[9]

INSTI regimens, including those with DTG, are associated with weight gain and other metabolic effects, such as hyperglycemia and changes in folate metabolism, in both nonpregnant and pregnant adults with HIV.[18,19] The impact of these metabolic effects on pregnancy outcomes is unknown.[19] In high-resource countries where undernutrition is less common, the increase in gestational weight gain associated with use of DTG has the potential to lead to more adverse pregnancy outcomes, such as gestational hypertension, gestational diabetes mellitus, and macrosomia.[20] In low-resource countries where undernutrition is common, the increase in gestational weight gain associated with DTG use may reduce the number of women at risk for certain severe adverse pregnancy outcomes associated with low maternal weight, as well as increase the number at risk of adverse pregnancy outcomes

associated with high maternal weight.[21] Additional research is critically needed to describe the impact of the metabolic effects of DTG on pregnancy outcomes.

Animal Studies

Carcinogenicity

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.[22]

Reproduction/Fertility

DTG did not affect fertility in male and female rats and rabbits at doses that produced exposures (based on AUC) that were approximately 27-fold higher than that achieved in humans who received the recommended dose.[22]

Teratogenicity/Adverse Pregnancy Outcomes

Studies of DTG in rats and rabbits have shown no evidence of developmental toxicity, teratogenicity, or effects on reproductive function.[22]

Placental and Breast Milk Passage

Studies in rats have demonstrated that DTG crosses the placenta and is excreted into breast milk.[22]

Excerpt from Table 14

Note: When using fixed-dose combination (FDC) tablets, refer to other sections in Appendix B and Table 14 in the Perinatal Guidelines 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	Pregnancy *PK 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). Standard Adult Doses *In ARV-Naive or ARV-Experienced (but INSTI-Naive) Patients* • DTG (Tivicay) o One 50-mg tablet once daily, without regard to food • DTG (Tivicay PD) o Six 5-mg tablets (30 mg) dissolved in water once daily, without regard to food • DTG/3TC (Dovato) o One tablet once daily, without regard to food • DTG/RPV (Juluca) o One tablet once daily, with food	High placental transfer to fetus[b] No evidence of teratogenicity in rats or rabbits. The most recent data from Botswana indicate the prevalence of NTDs in infants born to pregnant women with HIV receiving DTG at conception is no longer statistically different than in those receiving other antiretrovirals. DTG is a *Preferred* antiretroviral drug for use during pregnancy, irrespective of trimester, and for people who are trying to conceive (see Recommendations for Use of Antiretroviral Drugs During Pregnancy and Table 7). 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.

Excerpt from Table 14

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations[a]	Use in Pregnancy
		• DTG/ABC/3TC (Triumeq) o 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) o One 50-mg tablet twice daily, without regard to food • DTG (Tivicay PD) o Six 5-mg tablets (30 mg) dissolved in water twice daily, without regard to food *In INSTI-Experienced Patients* • DTG (Tivicay) o One tablet twice daily, without regard to food	

[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 12.

[b] Placental transfer categories are determined by mean or median cord blood–to–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; 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)

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Summary

- Elvitegravir (EVG) trough concentrations are reduced during pregnancy by approximately 85% with use of EVG boosted with cobicistat (EVG/c).
- EVG/c **is not recommended** for use in pregnancy; see Table 7.
- First-trimester exposure to EVG is not associated with increased risk of congenital anomalies.

Human Studies in Pregnancy

Pharmacokinetics

Pharmacokinetics (PK) and safety data from 30 pregnant U.S. women with HIV who received a fixed-dose combination of EVG, cobicistat (COBI), emtricitabine, and tenofovir disoproxil fumarate demonstrate that 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.[1] 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 90% effective concentration (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.[2]

Two case reports of EVG and COBI PK, 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.[3,4] 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.[4]

Because studies have reported reduced EVG exposure when pregnant women receive fixed-dose combination 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.[5] 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 minerals, such as iron or calcium, including prenatal vitamins.[5]

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 blood–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.[1] A European study reported similar results, with a median cord blood–to–maternal delivery plasma ratio of 0.75 in seven women.[2] 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.[6] Among the cases of first-trimester EVG exposure, the prevalence of birth defects was 3.0% (13 of 432 live births; 95% confidence interval, 1.6% to 5.1%) compared with a 2.7% total prevalence in the U.S. population, according to Centers for Disease Control and Prevention surveillance.[6]

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).[1] 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.[7]

Animal Studies

Carcinogenicity

In long-term studies of 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.[5]

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.[5]

Teratogenicity/Adverse Pregnancy Outcomes

Studies have shown no evidence of teratogenicity and no effect on reproductive function in rats and rabbits receiving EVG.[5]

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.[5]

Excerpt from Table 14

Note: When using fixed-dose combination (FDC) tablets, refer to other sections in Appendix B and Table 14 in the Perinatal Guidelines 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	Pregnancy *PK 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). Standard Adult Doses *Genvoya and Stribild* • One tablet once daily with food	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 persons who become pregnant while taking EVG/c, consider frequent viral load monitoring or switching to a more effective, recommended regimen. If a pregnant person 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 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 12).

[b] Placental transfer categories are determined by mean or median cord blood–to–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; FTC = emtricitabine; PK = pharmacokinetics; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

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Raltegravir (Isentress, Isentress HD, RAL)

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Summary

- No dose adjustments are required for raltegravir (RAL) during pregnancy. There are no pharmacokinetic data to support use of daily RAL high dose (HD) during pregnancy at this time.
- First-trimester exposure to RAL is not associated with increased risk of congenital anomalies.

Human Studies in Pregnancy

Pharmacokinetics

RAL pharmacokinetics (PK) 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 during pregnancy showed extensive variability that was similar to the variability seen in nonpregnant individuals. Median RAL area under the curve (AUC) was reduced by approximately 50% during pregnancy. No significant difference was seen in trough concentrations between the third trimester and postpartum. 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.[1] 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 on the use of newly developed ARV agents in pregnant individuals with HIV, the geometric mean ratios (GMRs) of third-trimester and postpartum values were 0.71 for AUC from 0 to 12 hours postdose (90% confidence interval [CI], 0.53–0.96), 0.82 for maximum concentration (C_{max}) (range 0.55–1.253), and 0.64 for concentration 12 hours postdose (C_{12h}) (range 0.34–1.22). One individual was below the target C_{12h} in the third trimester, and none were below the threshold postpartum. No change in dosing during pregnancy was recommended based on these data.[2] 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.[3]

A population PK model of once-daily 1,200-mg RAL pooled 11 PK studies (n = 221) with the primary target for efficacy set as the lower bound of the 90% CI of the trough concentration >0.75. The simulated trough GMR for once-daily 1,200-mg RAL was 0.51 (90% CI, 0.41–0.63), falling below the primary target for efficacy and supporting the current recommendation against daily RAL dosing in pregnancy.[4]

Caution is advised when RAL is coadministered with atazanavir, a uridine diphosphate glucuronosyltransferase A1 inhibitor, because this combination can result in elevated levels of RAL in nonpregnant adults with no medical conditions.[5]

Placental and Breast Milk Passage

An *ex vivo* study of term placentas from normal pregnancies reported high bidirectional transfer of RAL across the placenta.[6]

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.[1] In the P1097 study, the median ratio of cord blood–to–maternal delivery plasma RAL concentrations was 1.48 (range 0.32–4.33), and in the PANNA study, it was 1.21.[2,7] In the above-mentioned 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 cord blood–to–maternal plasma RAL concentration ratio was 1.03.[3] Other case reports have shown cord blood–to–maternal blood drug level ratios of 1.00 to 1.06.[8-10] 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.[11]

Limited data indicate that maternal doses of up to 1,200 mg daily of RAL are transferred in low levels in breast milk and are not expected to cause any adverse effects in breastfed infants.[12] A small Swiss cohort found the median milk-to-plasma ratio was 0.96 for once-daily RAL and 0.39 for twice-daily RAL.[13] A single case study demonstrated low RAL transfer into breast milk and little accumulation.[14]

Teratogenicity/Adverse Pregnancy Outcomes

In a retrospective study of 703 women in the French Perinatal Cohort who received RAL during pregnancy, rates of birth defects among infants born to women who were on RAL at conception were slightly higher than those born to women who initiated RAL later in pregnancy (6.4% vs. 2.3%, $P = 0.04$). When compared with matched controls, RAL exposure at conception was not associated significantly with birth defects, and no specific pattern of birth defects emerged during the study. No differences in other perinatal outcomes between groups were observed.[15] Merck reviewed data on 456 periconception exposures to RAL and found no instances of neural tube defects; this review included data from the Merck database, the Antiretroviral Pregnancy Registry, and the U.K./Ireland and French pregnancy cohorts.[16]

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, but no such increase has been observed. Among the cases of first-trimester RAL exposure that have been reported to the Antiretroviral Pregnancy Registry, the prevalence of birth defects was 3.9% (22 of 570 live births; 95% CI, 2.4% to 5.8%), compared with a 2.7% total prevalence in the U.S. population, based on Centers for Disease Control and Prevention surveillance.[17,18]

The IMPAACT P1081 study randomized 408 ARV 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/mL at or near delivery.[19] 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.[20-26]

Safety

In the P1026s study, P1081 study, and PANNA study, RAL was well tolerated, with no treatment-related serious adverse events observed in pregnant women.[1,2,19] 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.[27] 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 patients on RAL during pregnancy or the postpartum period.[28] 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 associated significantly with prior use of zidovudine, higher baseline CK levels, and a higher body mass index.[29]

Because RAL is highly protein bound to albumin, concern exists about displacement of bilirubin from albumin in the neonate, which potentially could 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.[30] 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).[30] 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.[7] 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.[31]

Animal Studies

Carcinogenicity

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.[32]

Reproduction/Fertility

RAL had no adverse effects on the fertility of male or female rats at exposures 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 in which 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 with RAL exposures that were threefold higher than the exposure seen in humans who received the recommended daily dose.[32]

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 postdose, 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.[32]

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.[32]

Excerpt from Table 14

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	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 individuals until more information is available. 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	High placental transfer to fetus[b] No evidence of human teratogenicity (can rule out a 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 reactions 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 12).

[b] Placental transfer categories are determined by mean or median cord blood–to–maternal delivery plasma drug ratio:

High: >0.6
Moderate: 0.3–0.6
Low: <0.3

Key: ARV = antiretroviral; HD = high dose; HSR = hypersensitivity reaction; PK = pharmacokinetics; RAL = raltegravir

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Cobicistat (Tybost, COBI)

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Reviewed: January 31, 2024

Summary

- Cobicistat (COBI) concentrations are decreased substantially—by approximately 45% to 85%—during pregnancy. The pharmaco-enhancing effects of COBI for atazanavir (ATV), darunavir (DRV), and elvitegravir (EVG) concentrations are similarly decreased.
- Although COBI exposure is reduced markedly during pregnancy, higher-than-standard doses have not been studied. The Panel on Treatment of HIV During Pregnancy and Interventions to Reduce Perinatal HIV Transmission does not recommend COBI for use with protease inhibitors and integrase strand transfer inhibitors during pregnancy; see Table 7.
- First-trimester exposure to COBI is not associated with increased risk of congenital anomalies.

Human Studies in Pregnancy

Pharmacokinetics

COBI pharmacokinetics (PK) have been described in pregnant and postpartum women who were taking concomitant EVG, ATV, and 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. COBI trough concentrations (C_{trough}) (24 hours postdose) were 60% lower in the second trimester and 76% lower in the third trimester than during the postpartum period. COBI C_{trough} 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.[1] Another study of 14 women taking EVG/c reported COBI AUC reduced by 49% during pregnancy.[2] Studies have also described decreases of similar magnitudes in COBI exposures when COBI is coadministered with DRV[3,4] or ATV[1] in pregnant women. In one of these studies, COBI AUC was decreased by 63% in the second trimester and 49% in the third trimester compared to the AUC postpartum. COBI C_{trough} decreased by 83% in both the second and third trimesters.

The pharmaco-enhancing effect of COBI on EVG was impacted during pregnancy; EVG AUC was reduced by 44% and C_{trough} were reduced by 89% in the third trimester when compared to postpartum AUC and C_{trough}. EVG apparent oral clearance during pregnancy and postpartum was associated negatively with COBI AUC.[5] Similarly, another study reported that EVG C_{trough} were reduced by 77% in the third trimester, with 85% of women having EVG C_{trough} below the 90% maximal effective concentration.[2]

The pharmaco-enhancing effect of COBI on DRV and ATV also was reduced during pregnancy. Two studies have described DRV exposures with COBI boosting in pregnancy. In a study of 29 pregnant women, the AUC of DRV was reduced by 53% in the second trimester and 56% in the third trimester compared to postpartum.[4] In a smaller study of seven pregnant women, DRV AUC was reduced by 56% in the second trimester and 50% in the third trimester compared to postpartum. This study also reported unbound DRV concentrations, and unbound DRV AUC was 45% and 40% lower during the second and third trimesters, respectively. The effect on DRV C_{trough} 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 C_{trough}. One of six women in this study experienced virologic failure during the third trimester, and virologic failure continued through the postpartum period.[3] ATV C_{trough} were 80% and 85% lower in the second and third trimesters, respectively, compared to historical ATV C_{trough} in nonpregnant adults with HIV.[1] Because of these substantial reductions in drug exposures during pregnancy, use of COBI-boosted EVG, DRV, or ATV **is not recommended** for patients starting or changing regimens during pregnancy.[6-8]

One study evaluated tenofovir alafenamide (TAF) exposure in pregnant women when TAF was administered as a daily 10-mg dose with COBI 150 mg. No differences were seen 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.[9] However, TAF 10 mg with COBI is available only 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 pharmaco-enhancer (either RTV 100 mg or COBI 150 mg). TAF exposures during pregnancy and postpartum did not differ.[10]

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.[11] In another study, median maternal plasma COBI concentration at delivery in 15 pregnant women was 172 ng/mL, and COBI was quantifiable in cord blood from 7 of their deliveries with a median cord blood–to–maternal plasma ratio of 0.09.[5] 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.[5] 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 3.6% (20 of 560 live births; 95% confidence interval, 2.2% to 5.5%) compared with a 2.7% total prevalence in the U.S. population, based on Centers for Disease Control and Prevention surveillance.[12]

Animal Studies

Carcinogenicity

No increases in tumor incidence relevant to humans were seen in rodent studies.[13]

Reproduction/Fertility

COBI did not affect fertility in male or female rats.[6]

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.[13]

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.[13]

Excerpt from Table 14

Note: When using fixed-dose combination (FDC) tablets, refer to other sections in Appendix B and Table 14 in the Perinatal Guidelines 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	Pregnancy *PK in Pregnancy* • Based on limited data, COBI exposure and its pharmaco-enhancing effect on ATV, DRV, and EVG are reduced markedly in pregnancy. • When coadministered with COBI, TAF exposure is not significantly different between pregnancy and the postpartum period. *Dosing in Pregnancy* • Although COBI exposure is reduced markedly during pregnancy, higher-than-standard doses have not been studied. The Panel recommends RTV as the preferred pharmaco-enhancer for PIs and INSTIs during pregnancy until more data are available on COBI activity during pregnancy. For guidance about the use of combination products in pregnancy, please see the specific sections on other components (i.e., FTC, TAF, TDF, ATV, DRV, EVG). 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.	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.

Excerpt from Table 14

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations[a]	Use in Pregnancy
		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	

[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 12).

[b] Placental transfer categories are determined by mean or median cord blood–to–maternal delivery plasma drug ratio:

High: >0.6
Moderate: 0.3–0.6
Low: <0.3

Key: ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; COBI = cobicistat; DRV = darunavir; DRV/c = darunavir/cobicistat; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FTC = emtricitabine; INSTI = integrase strand transfer inhibitor; the Panel = Panel on Treatment of HIV During Pregnancy and Interventions to Reduce Perinatal HIV Transmission; PI = protease inhibitor; PK = pharmacokinetics; RTV = ritonavir; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

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Ritonavir (Norvir, RTV)

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Summary

- No dose adjustments are required for ritonavir (RTV) used as a booster during pregnancy.
- First-trimester exposure to RTV is not associated with increased risk of congenital anomalies.

Human Studies in Pregnancy

Pharmacokinetics

RTV concentrations were lower during pregnancy than during the postpartum period when RTV was administered in combination with zidovudine and lamivudine to pregnant women with HIV at doses sufficient for HIV suppression in nonpregnant adults (500 mg or 600 mg twice daily).[1] 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 (PIs); however, RTV is an effective booster of the PIs lopinavir (LPV), atazanavir (ATV), and darunavir (DRV) in pregnant women.[2-4] By contrast, the newer booster, cobicistat, is not an effective booster of PIs in pregnant women, and its use is not recommended during pregnancy.[5]

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.[6] In a Pediatric AIDS Clinical Trials Group 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%.[1] 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 mcg/mL in the remaining woman.[7] By 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 LPV but negligible transfer via breastfeeding.[8]

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 2.5% (88 of 3,554 live births; 95% confidence interval, 2.0% to 3.0%), compared with a total prevalence of 2.7% in the U.S. population, according to Centers for Disease Control and Prevention surveillance.[9]

Animal Studies

Carcinogenicity

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.[10]

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.[10]

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, decreased fetal weight) also was observed only at maternally toxic doses (1.8 times human therapeutic exposure based on body surface area).[10]

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.

Excerpt from Table 14

Note: When using fixed-dose combination (FDC) tablets, refer to other sections in Appendix B and Table 14 in the Perinatal Guidelines 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) *Capsule* • RTV 100 mg *Tablet* • 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.	Pregnancy *PK 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 of pregnancy, especially in patients who are PI-experienced and in those 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). Standard Adult Dose of RTV (Norvir) When Used as a 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).	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 a 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.

Excerpt from Table 14

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations[a]	Use in Pregnancy
		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 *Tablet* • 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	

[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 12).

[b] Placental transfer categories are determined by mean or median cord blood–to–maternal delivery plasma drug ratio:

High: >0.6
Moderate: 0.3–0.6
Low: <0.3

Key: ARV = antiretroviral; EFV = efavirenz; LPV = lopinavir; LPV/r = lopinavir/ritonavir; NVP = nevirapine; PI = protease inhibitor; PK = pharmacokinetics; 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 (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)

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

Enfuvirtide is classified as Food and Drug Administration Pregnancy Category B.

Animal Studies

Carcinogenicity

Enfuvirtide was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests. Long-term animal carcinogenicity studies of enfuvirtide have not been conducted.

Reproduction/Fertility

Reproductive toxicity has been evaluated in rats and rabbits. Enfuvirtide produced no adverse effects on the fertility of male or female rats at doses up to 30 mg/kg/day administered SQ (a dose that is 1.6 times the maximum recommended adult human daily dose on a body surface area basis).

Teratogenicity/Adverse Pregnancy Outcomes

Studies in rats and rabbits have shown no evidence of teratogenicity and no effect on reproductive function with enfuvirtide.[1]

Placental and Breast Milk Passage

A study in rats revealed no evidence of harm to the fetus when enfuvirtide was administered in doses up to 27 times the adult human daily dose on a body surface area basis. A separate study in rabbits likewise revealed no harm to the fetus from enfuvirtide doses that were up to 3.2 times the adult human daily dose. Studies of radiolabeled enfuvirtide administered to lactating rats indicated radioactivity in the milk; however, it is not known if this reflected radiolabeled enfuvirtide or metabolites (amino acid and peptide fragments) of enfuvirtide.[1]

Human Studies in Pregnancy

Pharmacokinetics

Data on the use of enfuvirtide during human pregnancy are limited to case reports of a small number of women treated with the drug.[2-9]

Placental and Breast Milk Passage

In vitro and *in vivo* studies suggest that enfuvirtide does not readily cross the human placenta. Minimal placental passage of enfuvirtide was reported in published studies that included a total of eight peripartum patients and their neonates. These findings were supported by data from an *ex vivo* human placental cotyledon perfusion model.[2,5,10-12]

Teratogenicity/Adverse Pregnancy Outcomes

In the Antiretroviral Pregnancy Registry and in a national cohort of pregnant women with HIV infection in Italy, insufficient numbers of first-trimester exposures to enfuvirtide in humans have been monitored to be able to make a risk determination.[13,14]

Excerpt from Table 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]

In a PK study of combination therapy evaluated 25 women at 30 to 36 weeks' gestation and 12 women at 6 to 12 weeks postpartum who received the nelfinavir 625-mg tablet formulation, given as 1250 mg twice daily. Peak nelfinavir levels and area under the curve were lower during the third trimester than postpartum.[5] Only 16% of women (4 of 25) during the third trimester and 8% of women (1 of 12) postpartum had trough values greater than the suggested minimum trough of 800 ng/mL; however, viral load was <400 copies/mL in 96% of women in the third trimester and 86% postpartum.

Placental and Breast Milk Passage

In PACTG 353, transplacental passage of nelfinavir was minimal.[2] In addition, in a study of cord blood samples from 38 women who were treated with nelfinavir during pregnancy, the cord blood nelfinavir concentration was less than the assay limit of detection in 24 women (63%), and the cord blood concentration was low (with a median of 0.35 µg/mL) in the remaining 14 women.[6] Among 20 mother-infant pairs in the Netherlands, the cord blood-to-maternal-plasma ratio for nelfinavir was 0.14 compared to 0.67 for nevirapine and 0.24 for lopinavir.[7]

Nelfinavir also has low breast milk passage. In a PK study conducted in Kisumu, Kenya, concentrations of nelfinavir and its active metabolite, M8, were measured in maternal plasma and breast milk from 26 mothers who received nelfinavir as part of antiretroviral therapy and from plasma samples collected from their 27 infants at birth, 2, 6, 14, and 24 weeks.[8] Peak nelfinavir concentrations were recorded in maternal plasma and breast milk at 2 weeks. Median breast milk-to-plasma ratio was 0.12 for nelfinavir and 0.03 for its active metabolite (i.e., M8). Nelfinavir and M8 concentrations were below the limit of detection in 20 of 28 (71%) infant plasma dried blood spots tested from nine infants over time points from delivery though 24 weeks. Overall transfer to breast milk was low and resulted in nonsignificant exposure to nelfinavir among breastfed infants through age 24 weeks.

Teratogenicity/Adverse Pregnancy Outcomes

In the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposures to nelfinavir have been monitored to be able to detect at least a 1.5-fold increased risk of overall birth defects and a two-fold increased risk of birth defects in the cardiovascular and genitourinary systems. No such increase in birth defects has been observed with exposure to nelfinavir. Among cases of first-trimester nelfinavir exposure reported to the Antiretroviral Pregnancy Registry, prevalence of birth defects was 3.9% (47 of 1,212 births; 95% CI, 2.9% to 5.1%) compared with a 2.7% total prevalence in the U.S. population, based on Centers for Disease Control and Prevention surveillance.[9]

In the U.S. PHACS/SMARTT cohort study, after adjusting for birth cohort and other factors, maternal use of nelfinavir led to no increase in the likelihood of adverse metabolic, growth/development, cardiac, neurological, or neurodevelopmental outcomes.[10]

Excerpt from Table 10[a]

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations	Use in Pregnancy
Nelfinavir (NFV) *Viracept*	NFV (Viracept): *Tablets:* • 250 mg • 625 mg (tablets can be dissolved in a small amount of water) *Powder for Oral Suspension:* • 50 mg/g	Standard Adult Dose: • NFV 1250 mg twice daily, *or* • NFV 750 mg 3 times daily with food PK in Pregnancy: • Lower NFV exposure was observed during the third trimester than postpartum in women receiving NFV 1250 mg twice daily; however, adequate drug levels are generally achieved during pregnancy, although levels are variable in late pregnancy. Dosing in Pregnancy: • NFV 750 mg 3 times daily with food is not recommended during pregnancy. No change in standard dose (NFV 1250 mg twice daily with food) indicated.	NFV should not be used during pregnancy. Minimal to low placental transfer to fetus.[b] No evidence of human teratogenicity; can rule out 1.5-fold increase in overall birth defects and 2-fold increase in risk of cardiovascular and genitourinary birth defects. Contains aspartame; should not be used in individuals with phenylketonuria.

[a] Individual ARV drug dosages may need to be adjusted in patients with renal or hepatic insufficiency (for details, see the Adult and Adolescent Guidelines, Appendix B, Table 8).

[b] Placental transfer categories are determined by mean or median cord blood/maternal delivery plasma drug ratio:

High: >0.6 Moderate: 0.3–0.6 Low: <0.3

Key to Acronyms: NFV = nelfinavir; PK = pharmacokinetic

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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 10[a]

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations	Use in Pregnancy
Saquinavir (SQV) *Invirase* Note: Must be combined with low-dose RTV for PK boosting	SQV (Invirase) *Tablet:* • 500 mg *Capsule:* • 200 mg	Standard Adult Dose: • SQV 1000 mg plus RTV 100 mg twice a day with food or within 2 hours after a meal PK in Pregnancy: • Based on limited data, SQV exposure may be reduced in pregnancy, but this effect is not sufficient to warrant a dose change. Dosing in Pregnancy: • No change in dose indicated.	SQV should not be used during pregnancy. Contraindicated in patients with pre-existing cardiac conduction system disease. Baseline ECG recommended before starting, because PR and/or QT interval prolongations have been observed. Low placental transfer to fetus.[b] Insufficient data to assess for teratogenicity in humans. No evidence of teratogenicity in rats or rabbits. Must be boosted with low-dose RTV.

[a] Individual ARV drug dosages may need to be adjusted in patients with renal or hepatic insufficiency (for details, see the Adult and Adolescent Guidelines, Appendix B, Table 8).

[b] Placental transfer categories are determined by mean or median cord blood/maternal delivery plasma drug ratio:

High: >0.6 Moderate: 0.3–0.6 Low: <0.3

Key to Acronyms: ECG = electrocardiogram; PK = pharmacokinetic; RTV = ritonavir; SQV = saquinavir

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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 10[a]

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations	Use in Pregnancy
Stavudine (d4T) *Zerit* Note: Generic products are available for all formulations.	d4T (Zerit) *Capsules:* • 15 mg • 20 mg • 30 mg • 40 mg *Oral Solution:* • 1 mg/mL following reconstitution Note: Extended-release capsule formulation (Zerit XR) has been discontinued by the manufacturer.	Standard Adult Doses[e] *Body Weight ≥60 kg:* • 40 mg twice daily without regard to meals *Body Weight <60 kg:* • 30 mg twice daily without regard to meals Dosing in Pregnancy: • No change in dose indicated. PK in Pregnancy: • PK not significantly altered in pregnancy.	d4T is not recommended for pregnant women. High placental transfer.[b] No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects). Lactic acidosis, sometimes fatal, has been reported in pregn aant women receiving ddI and d4T together.

[a] Individual ARV drug dosages may need to be adjusted in patients with renal or hepatic insufficiency (for details, see Adult and Adolescent Guidelines, Appendix B, Table 8).

[b] Placental transfer categories—Mean or median cord blood/maternal delivery plasma drug ratio:
High: >0.6 Moderate: 0.3–0.6 Low: <0.3

[e] WHO recommends maximum dose of 30 mg twice daily regardless of weight.

Key to Acronyms: ARV = antiretroviral; d4T = stavudine; ddI = didanosine; PK = pharmacokinetic; WHO = World Health Organization

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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 10[a]

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations	Use in Pregnancy
Tipranavir (TPV) *Aptivus* Note: Must be combined with RTV for PK boosting	TPV (Aptivus) *Capsules:* • 250 mg *Oral Solution:* • 100 mg/mL	Standard Adult Dose: • TPV/r 500 mg/200 mg twice daily *With RTV Tablets:* • Take with food. *With RTV Capsules or Solution:* • Take without regard to food; however, administering with food may help make the dose more tolerable. Dosing in Pregnancy: • Insufficient data to make dosing recommendation PK in Pregnancy: • Limited PK data in human pregnancy	TPV should not be used during pregnancy. Moderate placental transfer to fetus reported in 1 patient.[b] Insufficient data to assess teratogenicity in humans. No evidence of teratogenicity in rats or rabbits. Must be given as low-dose, RTV-boosted regimen.

[a] Individual ARV drug dosages may need to be adjusted in patients with renal or hepatic insufficiency (for details, see the Adult and Adolescent Guidelines, Appendix B, Table 8).

[b] Placental transfer categories are determined by mean or median cord blood/maternal delivery plasma drug ratio:

High: >0.6 Moderate: 0.3–0.6 Low: <0.3

Key to Acronyms: PK = pharmacokinetic; RTV = ritonavir; TPV = tipranavir; TPV/r = tipranavir/ritonavir

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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.

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Antiretroviral Pregnancy Registry

Updated: March 28, 2014
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

Updated: January 31, 2024
Reviewed: January 31, 2024

Decision-Making About Antiretroviral Drugs for People Who Are Pregnant or Are Trying to Conceive

This guide summarizes current information about recommendations of the Panel on Treatment of HIV During Pregnancy and Prevention of Perinatal Transmission (the Panel) to support counseling about the use of antiretroviral (ARV) drugs and ARV therapy (ART) options during pregnancy for people who are pregnant or trying to conceive.

For people who are pregnant or trying to conceive, effective ART with sustained viral suppression maximizes their health and the prevention of perinatal HIV transmission. The risk of perinatal HIV transmission is reduced to the lowest levels (1% or less) in people with HIV who initiate ART prior to conception and have sustained viral suppression to undetectable levels throughout pregnancy. See Use of Antiretroviral Drugs to Prevent Perinatal HIV Transmission and Improve Health for Pregnant People.

Before, during, and after pregnancy, it is important to discuss future childbearing desires and plans, the potential benefits and risks of conceiving while taking specific ARV medications, and contraceptive options to prevent unintended pregnancy.

General Antiretroviral Counseling for People Who Are Pregnant or Are Trying to Conceive

- As part of shared decision-making, information should be provided to individuals who are pregnant or trying to conceive to help them understand and consider the benefits, advantages, disadvantages, and potential risks associated with the use of each individual ARV drug they are currently receiving or will be initiating. These factors include dosing frequency, side effects or tolerability issues, and adverse pregnancy outcomes (e.g., preterm delivery, birth defects). For additional information, refer to Table 6. What to Start: Initial Antiretroviral Regimens During Pregnancy for People Who Are Antiretroviral-Naive, Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs in Pregnant People and Nonpregnant People Who Are Trying to Conceive, Teratogenicity, and Antiretroviral Drug Regimens and Pregnancy Outcomes.
- People who are trying to conceive should receive information about the use of specific ARV regimens during pregnancy to enable them to make informed decisions before they become pregnant.
- It should be explained that not enough is known about the safety of using certain ARV drugs around the time of conception or during pregnancy or about the need for dosing changes during pregnancy, when relevant, because studies 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 the possible effects when using these drugs during pregnancy.

- The Antiretroviral Pregnancy Registry prospectively collects and reviews data about birth defects in order to detect any major teratogenic effect(s) involving the ARV drugs to which pregnant people are exposed. Clinicians are encouraged to report all cases of ARV drug exposure during pregnancy or in people who conceived while receiving ARV drugs to the Antiretroviral Pregnancy Registry.
    - When discussing the risks of birth defects with ARV medication exposure, it is important to point out the overall risk of defects in the general population and explain during which weeks of gestation the fetus is at risk for developing that defect. For example, a background risk of neural tube defects (NTDs) exists, regardless of the ARV regimen used or a person's HIV status during pregnancy. Most NTDs occur before the neural tube closes at 4 weeks postconception (approximately 6 weeks after the last menstrual period), often before a person is known to be pregnant. After 6 weeks' gestation, the additional risk of NTDs developing is thought to be much less likely. Folic acid supplementation should be encouraged for all people trying to conceive and in early pregnancy (see Prepregnancy Counseling and Care for Persons of Childbearing Age with HIV.
    - Early data from the Tsepamo study in Botswana raised concerns about a possible higher rate of NTDs among infants born to mothers who received dolutegravir (DTG) at the time of conception. Sufficient data now exist to indicate that DTG is not associated with an increased risk of NTDs. See Dolutegravir for additional information.
    - Based on the June 2023 Antiretroviral Pregnancy Registry report, sufficient numbers of first-trimester exposures to bictegravir (BIC) have been reported to detect at least a twofold increase in the risk of overall birth defects. No such increase in birth defects has been detected with BIC. Previously, not enough reported data had existed to assess the risk of birth defects with BIC.
    - Clinicians are encouraged to report all cases of ARV drug exposure during pregnancy or in people who conceived while receiving ARV drugs to the Antiretroviral Pregnancy Registry.
- The risk of other adverse pregnancy outcomes, many of which are more common than birth defects, also should be discussed. ARV regimens that contain ritonavir-boosted protease inhibitors may increase the risk of preterm delivery. See Antiretroviral Drug Regimens and Pregnancy Outcomes.
- In most cases, the Panel recommends that pregnant people with HIV continue their current regimen during pregnancy, provided that the regimen is tolerated and effective in suppressing viral replication (defined as a regimen that maintains an HIV viral load less than the lower limits of detection of the assay).
    - Explain that changes in ART during pregnancy can lead to an increase in viral load, which increases the risk of perinatal HIV transmission and may affect choices for future ARV regimens because of the possible development of drug resistance.
    - Counsel individuals who are receiving ARVs that are not *Preferred* or *Alternative* options for use during pregnancy about the benefits and risks of continuing their current ART or switching to another ARV regimen.
    - When individuals are receiving ARVs for which data about use in pregnancy are insufficient (e.g., long-acting cabotegravir, doravirine) or ARVs with pharmacokinetic (PK) changes that

could lead to lower drug levels and loss of viral suppression (e.g., cobicistat-boosted regimens), discuss whether to continue the current regimen with frequent viral load monitoring (i.e., every 1 to 2 months) or consider switching to another ARV drug or drug regimen. In making this decision, consider the tolerability of each drug, the ability to maintain viral suppression, the risk of perinatal HIV transmission, and the risk of potential adverse outcomes.

- The Panel recognizes that to reach or maintain viral suppression, some people who are ART experienced may need to take ARV drugs that have insufficient data regarding use in pregnancy or are not recommended for use in pregnancy except in special circumstances.
- For additional information, see Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs in Pregnant People and Nonpregnant People Who Are Trying to Conceive and People with HIV Who Are Taking Antiretroviral Therapy When They Become Pregnant.

Antiretroviral Drugs That Are Recommended for Use in Pregnancy

- When making recommendations about the use of ARV drugs in pregnancy, the Panel considers available data from multiple sources about efficacy, PK, dosing, safety, and toxicity in pregnant and nonpregnant adults. The Panel requires adequate PK, dosing, and teratogenicity data from pregnant people to categorize a drug as *Preferred* or *Alternative* for use in people who are pregnant or trying to conceive. ARV drugs are assigned to one of the five categories (see Recommendations for Use of Antiretroviral Drugs During Pregnancy: Overview).
- Moderate amounts of data about pregnancy outcomes and birth defects exist for each of the drugs and drug combinations that are *Preferred*. Although these data are reassuring, it is important to note that among the *Preferred* drugs, a rigorous, systematic birth surveillance program that includes large numbers of women with periconception exposure is available only for DTG.
- *Preferred* ARV drug options include DTG used in combination with two nucleoside reverse transcriptase inhibitors (NRTIs): abacavir plus lamivudine (3TC) or emtricitabine (FTC), tenofovir disoproxil fumarate (TDF) plus 3TC or FTC, or tenofovir alafenamide (TAF) plus 3TC or FTC.
- DTG-based regimens are *Preferred* for people with early (acute or recent) HIV infection during pregnancy unless there is a history of prior exposure to long-acting cabotegravir for pre-exposure prophylaxis. After long-acting cabotegravir exposure, a regimen of darunavir/ritonavir (DRV/r) with TDF or TAF plus FTC or 3TC is the *Preferred* ART regimen pending results of genotype testing. For additional information, see Early (Acute and Recent) HIV Infection.
- BIC, raltegravir, atazanavir/ritonavir, DRV/r, EFV, and rilpivirine (RPV) are recommended as *Alternative* ARV drug options in pregnancy. *Alternative* drugs may have more limited data on use in pregnancy than *Preferred* drugs or may be associated with more concerns about PK, dosing, tolerability, drug interaction, efficacy, or resistance than those in the *Preferred* category, but they are acceptable for use in pregnancy.
- To maximize ARV absorption and effectiveness, it is important to reinforce the need to check and follow the instructions for taking the regimen (e.g., taking DRV and RPV with food, spacing administration of integrase strand transfer inhibitors with antacids or divalent cation–containing vitamins, avoiding proton pump inhibitors and spacing administration of H2 blockers with

atazanavir/cobicistat). See Appendix B: Supplement: Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy for instructions about dosing and administration.

- Cobicistat-boosted regimens (atazanavir/cobicistat, darunavir/cobicistat, or elvitegravir/cobicistat) are not recommended for use during pregnancy. PK studies suggest increased drug metabolism and lower therapeutic drug levels of cobicistat-boosted ARV drugs during pregnancy. Individuals who choose to continue one of these regimens should have more frequent viral load monitoring (i.e., every 1 to 2 months).
- If an ARV regimen is changed during pregnancy, drugs in the new regimen should include those that are recommended for use in pregnancy whenever possible (see Table 6. What to Start: Initial Antiretroviral Regimens During Pregnancy for People Who Are Antiretroviral-Naive and Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs in Pregnant People and Nonpregnant People Who Are Trying to Conceive), and viral load should be monitored more frequently (i.e., every 1 to 2 months).
- Recommendations regarding the use of specific ARV agents or ARV regimens change as more information on the safety, tolerability, and PK changes of these drugs in pregnancy becomes available. For additional information, see Recommendations for Use of Antiretroviral Drugs During Pregnancy: Overview, Table 6. What to Start: Initial Antiretroviral Regimens During Pregnancy for People Who Are Antiretroviral-Naive, Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs in Pregnant People and Nonpregnant People Who Are Trying to Conceive, and Appendix B: Supplement: Safety and Toxicity of Individual Antiretroviral Drugs in Pregnancy.

Appendix D: Review of Clinical Trials of Antiretroviral Interventions to Prevent Perinatal HIV Transmission

Updated: December 7, 2018
Reviewed: December 7, 2018

June 02, 2023: This Appendix was last reviewed in 2018 and no longer reflects the latest Panel recommendations. It has been maintained in the Guidelines to provide a resource for historical context of clinical trials to advance the prevention of perinatal HIV transmission.

One of the major achievements in HIV research was the demonstration by the PACTG 076 clinical trial that administering zidovudine to pregnant women and their infants could reduce the risk of perinatal transmission by nearly 70%.[1] Following the results of PACTG 076, researchers began to explore the development of shorter, less expensive prophylactic regimens that are more applicable in resource-constrained settings. In addition, multiple studies have tried to determine the optimal regimens for reducing the risk of postnatal transmission during breastfeeding. More recently, in the context of recommendations for universal antiretroviral therapy (ART), studies have also explored the efficacy of universal ART during pregnancy and breastfeeding. This Appendix provides a table summarizing the results of major studies of antiretroviral (ARV) interventions used to prevent perinatal transmission (see Supplemental Table 1) and a brief discussion of lessons learned. In many cases, a direct comparison of results from these trials is not possible because the studies involved diverse patient populations from different geographic locations, with differing viral subtypes and infant feeding practices. However, some generalizations are relevant to understanding the use of ARV drugs for prevention of perinatal transmission in both resource-limited and resource-rich countries. Furthermore, these studies have provided critical information elucidating the risks, timing, and mechanisms of perinatal transmission.

ART is more effective antenatally in reducing perinatal transmission than a single-drug prophylactic regimen.

ARV drugs are highly effective at preventing perinatal transmission, even in women living with advanced HIV.[2,3] Efficacy has been demonstrated for a number of short-course ARV regimens, including zidovudine alone, zidovudine plus lamivudine, single-dose nevirapine, and single-dose nevirapine combined with either short-course zidovudine or zidovudine/lamivudine.[4-13] In general, combination regimens are more effective than single-drug regimens in reducing the risk of perinatal transmission. In addition, administering ARV drugs during the antepartum, intrapartum, and postpartum periods is a more effective approach for preventing perinatal transmission than administering ARV drugs during only the antepartum and intrapartum periods or the intrapartum and postpartum periods.[5,14,15]

Almost all trials in resource-limited countries have included oral intrapartum prophylaxis, with varying durations of maternal antenatal and/or infant (and sometimes maternal) postpartum prophylaxis. Regimens with antenatal components, including those starting as late as 36 weeks' gestation, can reduce the risk of perinatal transmission, even when these regimens are lacking an infant prophylaxis component.[10-12] However, longer-duration antenatal zidovudine prophylaxis that begins at 28 weeks' gestation is more effective than shorter-duration zidovudine prophylaxis that begins at 35 weeks' gestation.[13] The Perinatal HIV Prevention Trial (PHPT)-5 trial demonstrated that women who received <8 weeks of prophylaxis during pregnancy had a significantly greater risk of

perinatal transmission than women who received longer durations of prophylaxis.[16] The European National Study of HIV in Pregnancy and Childhood demonstrated that each additional week of an antenatal, triple-drug regimen corresponded to a 10% reduction in risk of transmission.[17] More prolonged infant post-exposure prophylaxis does not appear to substitute for longer-duration maternal ARV prophylaxis.[13]

The Promoting Maternal and Infant Survival Everywhere (PROMISE) study was a large randomized clinical trial that demonstrated the superiority of ART over zidovudine-based prophylaxis for prevention of *in utero* transmission in women with CD4 T lymphocyte (CD4) cell counts >350 cells/mm^3.[18] Pregnant women were randomized to one of three study arms:

- Zidovudine plus single-dose nevirapine at delivery plus postpartum tenofovir disoproxil fumarate (TDF)/emtricitabine tail
- Zidovudine plus lamivudine plus lopinavir/ritonavir (LPV/r)
- TDF plus emtricitabine plus LPV/r

The rate of perinatal transmission through 1 week of life was significantly lower among women receiving ART (0.5%, 9 infections among 1,710 infants) than among those randomized to receive zidovudine plus single-dose nevirapine plus postpartum TDF/emtricitabine tail (1.8%, 25 infections among 1,386 infants).

Regimens that do not include maternal ARV therapy during pregnancy have been evaluated because some women may lack antenatal care and present for prenatal care for the first time when they go into labor. Regimens that include only intrapartum and postpartum drug administration also have been shown to be effective in reducing the risk of perinatal transmission.[4-6] However, without continued infant post-exposure prophylaxis, intrapartum pre-exposure prophylaxis alone with nucleoside reverse transcriptase inhibitor drugs (zidovudine/lamivudine) is not effective in reducing the risk of transmission.[5] The South African Intrapartum Nevirapine Trial (SAINT) trial demonstrated that intrapartum/postpartum zidovudine/lamivudine and single-dose intrapartum/newborn nevirapine are similar in efficacy and safety.[6]

Combination infant ARV prophylaxis is recommended in the United States for infants at high risk for HIV acquisition.

Delayed maternal HIV diagnosis or delayed presentation for pregnancy care may result in missing the opportunity to provide maternal ARV drugs during pregnancy or labor. In the absence of maternal therapy, the standard infant prophylaxis regimen of 6 weeks of zidovudine was effective in reducing the risk of HIV transmission compared with no prophylaxis, based on epidemiological data in resource-rich countries.[19] A trial in Malawi in breastfeeding infants demonstrated that adding 1 week of zidovudine therapy to infant single-dose nevirapine reduced risk of transmission by 36% compared with infant single-dose nevirapine alone.[7]

To define the optimal infant prophylaxis regimen in the absence of maternal antepartum ARV drug administration in a formula-fed population of infants such as in the United States, the NICHD-HPTN 040/P1043 (NCT00099359) clinical trial compared three infant ARV regimens in formula-fed infants born to mothers who did not receive ARV drugs during the current pregnancy:

- Standard 6 weeks of zidovudine alone

- 6 weeks of zidovudine plus three doses of nevirapine given in the first week of life (first dose given within 48 hours of birth, second dose given 48 hours after first dose, third dose given 96 hours after second dose)
- 6 weeks of zidovudine plus lamivudine and nelfinavir given from birth through age 2 weeks.[20]

The study demonstrated that both the dual- and triple-combination regimens reduced the risk of intrapartum transmission by approximately 50% compared with infant prophylaxis with zidovudine alone, although there was more hematologic toxicity with the triple regimen (see Supplemental **Table 1).** Based on these data, combination ARV prophylaxis is now recommended in the United States for infants born to women who are at increased risk for transmission (see Antiretroviral Management of Newborns With Perinatal HIV Exposure or Perinatal HIV).

Single-dose intrapartum nevirapine is not recommended for women in the United States who are receiving standard recommended antenatal ARV prophylaxis.

PACTG 316 (a clinical trial conducted in the United States, Europe, Brazil, and the Bahamas) demonstrated that adding single-dose nevirapine to combination antenatal ARV prophylaxis for non-breastfeeding women with very low viral loads at the time of delivery did not offer significant benefit.[21] Thus, adding single-dose intrapartum nevirapine is not recommended for women in the United States who are receiving standard recommended antenatal ARV prophylaxis (see Intrapartum Antiretroviral Therapy/Prophylaxis).

Breastfeeding by women with HIV infection is not recommended in the United States.

Breastfeeding by women living with HIV (including those receiving ARV drugs) **is not recommended** in the United States, where replacement feeding is affordable, feasible, acceptable, sustainable, and safe, and the risk of infant mortality due to diarrheal and respiratory infections is low.[22]

Clinical trials in resource-limited settings have demonstrated that both infant prophylaxis (daily infant nevirapine, lamivudine, and LPV/r) during breastfeeding and maternal triple-drug prophylaxis during breastfeeding decrease the risk of postnatal infection (see Supplemental Table 1).[2,23-31] The PROMISE trial was a large, randomized clinical trial that demonstrated that daily infant nevirapine and maternal ART have similar safety and efficacy for prevention of perinatal transmission during breastfeeding in women with CD4 cell counts ≥350 cells/mm^3.[18,32] At 6 to 14 days postpartum, the study randomized participants to receive either infant nevirapine or maternal ART until 18 months after delivery or breastfeeding cessation. The rates of perinatal transmission were similar (0.58%, 5 infections among 1,211 infants receiving nevirapine vs. 0.57%, 7 infections among 1,219 infants whose mothers received ART), both strategies were safe, and infant HIV-1–free survival was high across both arms (97.7% with infant nevirapine vs. 97.1% with maternal ART at 24 months).

Hypothetically, maternal triple-drug prophylaxis may be less effective than infant prophylaxis if the maternal regimen is first started postpartum or late in pregnancy, because it takes several weeks to months to achieve full viral suppression in breast milk.[27,33] Importantly, although prophylaxis significantly lowers the risk of postnatal infection, neither infant nor maternal postpartum ARV prophylaxis eliminates the risk of HIV transmission through breast milk. Therefore, breastfeeding is not recommended for women living in the United States (including those receiving combination ARV drug regimens).[22] Finally, both infant nevirapine prophylaxis and maternal ART during breastfeeding may be associated with the development of ARV drug resistance in infants who

acquire HIV despite prophylaxis; multiclass drug resistance has been described in breastfeeding infants with HIV despite maternal triple-drug prophylaxis.[34-38]

Supplemental Table 1. Results of Major Studies on Antiretroviral Interventions to Prevent Perinatal HIV Transmission

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

Supplemental Table 1. Results of Major Studies on Antiretroviral Interventions to Prevent Perinatal HIV Transmission

Study Name; Location(s); Mode of Infant Feeding	Antiretroviral Drugs	Antepartum and Intrapartum Interventions	Postpartum Interventions	Perinatal Transmission Rate and Efficacy
				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).
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, $P = 0.11$).

Supplemental Table 1. Results of Major Studies on Antiretroviral Interventions to Prevent Perinatal HIV Transmission

Study Name; Location(s); Mode of Infant Feeding	Antiretroviral Drugs	Antepartum and Intrapartum Interventions	Postpartum Interventions	Perinatal Transmission Rate and Efficacy
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

Supplemental Table 1. Results of Major Studies on Antiretroviral Interventions to Prevent Perinatal HIV Transmission

Study Name; Location(s); Mode of Infant Feeding	Antiretroviral Drugs	Antepartum and Intrapartum Interventions	Postpartum Interventions	Perinatal Transmission Rate and Efficacy
				(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%.
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

Supplemental Table 1. Results of Major Studies on Antiretroviral Interventions to Prevent Perinatal HIV Transmission

Study Name; Location(s); Mode of Infant Feeding	Antiretroviral Drugs	Antepartum and Intrapartum Interventions	Postpartum Interventions	Perinatal Transmission Rate and Efficacy
				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

Supplemental Table 1. Results of Major Studies on Antiretroviral Interventions to Prevent Perinatal HIV Transmission

Study Name; Location(s); Mode of Infant Feeding	Antiretroviral Drugs	Antepartum and Intrapartum Interventions	Postpartum Interventions	Perinatal Transmission Rate and Efficacy
				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.
PEPI-Malawi Trial; Malawi;[23] Breastfeeding	SD NVP plus ZDV for 1 week (control) vs.	No AP ARV drugs Oral IP	Infant SD NVP plus ZDV for 1 week (control) vs.	Postnatal Infection in Infants Without HIV at Birth • Perinatal transmission at 6 weeks was 5.1% in control arm vs.

Supplemental Table 1. Results of Major Studies on Antiretroviral Interventions to Prevent Perinatal HIV Transmission

Study Name; Location(s); Mode of Infant Feeding	Antiretroviral Drugs	Antepartum and Intrapartum Interventions	Postpartum Interventions	Perinatal Transmission Rate and Efficacy
	2 extended infant regimens (NVP or NVP/ZDV) for 14 weeks	• SD NVP (if mother presents in time)	Control plus NVP for 14 weeks vs. Control plus NVP/ZDV for 14 weeks	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.

Supplemental Table 1. Results of Major Studies on Antiretroviral Interventions to Prevent Perinatal HIV Transmission

Study Name; Location(s); Mode of Infant Feeding	Antiretroviral Drugs	Antepartum and Intrapartum Interventions	Postpartum Interventions	Perinatal Transmission Rate and Efficacy
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).
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 1 (Control) • Maternal ZDV/3TC for 1 week; infant SD NVP plus ZDV/3TC for 1 week	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

Supplemental Table 1. Results of Major Studies on Antiretroviral Interventions to Prevent Perinatal HIV Transmission

Study Name; Location(s); Mode of Infant Feeding	Antiretroviral Drugs	Antepartum and Intrapartum Interventions	Postpartum Interventions	Perinatal Transmission Rate and Efficacy
		Arm 2 • ZDV/3TC plus SD NVP *Arm 3* • ZDV/3TC plus SD NVP	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	(*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

Supplemental Table 1. Results of Major Studies on Antiretroviral Interventions to Prevent Perinatal HIV Transmission

Study Name; Location(s); Mode of Infant Feeding	Antiretroviral Drugs	Antepartum and Intrapartum Interventions	Postpartum Interventions	Perinatal Transmission Rate and Efficacy
				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 ($P = 0.014$).
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	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).

Supplemental Table 1. Results of Major Studies on Antiretroviral Interventions to Prevent Perinatal HIV Transmission

Study Name; Location(s); Mode of Infant Feeding	Antiretroviral Drugs	Antepartum and Intrapartum Interventions	Postpartum Interventions	Perinatal Transmission Rate and Efficacy
			after second dose Arm 3 • Control as above, plus 3TC and NFV from birth through age 2 weeks	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	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.

Supplemental Table 1. Results of Major Studies on Antiretroviral Interventions to Prevent Perinatal HIV Transmission

Study Name; Location(s); Mode of Infant Feeding	Antiretroviral Drugs	Antepartum and Intrapartum Interventions	Postpartum Interventions	Perinatal Transmission Rate and Efficacy
		continued through labor		
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%)
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: 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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