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)

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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/).

Table of Contents

What's New in the Guidelines v

Guidelines Panel Members xi

Financial Disclosure xiv

Introduction A-1

- Table 1. Outline of the Guidelines Development Process A-5
- Table 2. Rating Scheme for Recommendations A-7

Pregnancy and Postpartum HIV Testing and Identification of Perinatal and Postnatal HIV Exposure A-12

Pre-Exposure Prophylaxis (PrEP) to Prevent HIV During Periconception, Antepartum, and Postpartum Periods A-25

Prepregnancy Counseling and Care B-1

- Overview B-1
  - Table 3. Drug Interactions Between Antiretroviral Agents and Hormonal Contraceptives B-6
- Reproductive Options When One or Both Partners Have HIV B-25

Antepartum Care C-1

- Antepartum HIV Care C-1
  - Table 4. HIV-Related Antepartum Screenings and Assessments During Pregnancy C-6
- Initial Evaluation and Continued Monitoring of HIV During Pregnancy C-11
  - Table 5. HIV-Related Laboratory Monitoring Schedule During Pregnancy C-15
- Antiretroviral Drug Resistance and Resistance Testing in Pregnancy C-23

Recommendations for the Use of Antiretroviral Drugs During Pregnancy C-30

- Recommendations for the Use of Antiretroviral Drugs During Pregnancy: Overview C-30
- Use of Antiretroviral Drugs to Prevent Perinatal HIV Transmission and Improve Health During Pregnancy C-41
- Antiretroviral Therapy When Trying to Conceive C-46
- Lack of Experience With Antiretroviral Drugs During Pregnancy and Prior to Pregnancy (Antiretroviral-Naive) C-49
- Antiretroviral Therapy Use During Prepregnancy and Early Pregnancy C-56
- Previous Experience With Antiretroviral Medications but Not Currently on Antiretroviral Therapy During Current Pregnancy C-63
- Lack of Viral Suppression While on Antiretroviral Therapy in Pregnancy C-68
- Table 6. What to Start: Initial Antiretroviral Regimens During Pregnancy When Antiretroviral Therapy Has Never Been Received C-76
- Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs During Pregnancy and When Trying to Conceive C-87

Teratogenicity C-95
Table 8. Drug-Specific Risk Assessment by the Antiretroviral Pregnancy Registry C-97
Antiretroviral Drug Regimens and Pregnancy Outcomes C-101
Special Populations C-113
Hepatitis B Virus/HIV Coinfection C-113
Hepatitis C Virus/HIV Coinfection C-122
HIV-2 Infection and Pregnancy C-135
Prenatal Care, Antiretroviral Therapy, and HIV Management When HIV Was Perinatally Acquired C-144
Early (Acute and Recent) HIV Infection C-150
Intrapartum HIV Care D-1
Table 9. Intrapartum Care and Recommended Interventions to Prevent Perinatal HIV Transmission Based on HIV RNA Levels at the Time of Delivery D-12
Postpartum HIV Management and Follow-Up E-1
Preventing HIV Transmission During Infant Feeding E-11
Care of Infants With Perinatal Exposure to HIV E-31
Antiretroviral Management of Infants With *In Utero*, Intrapartum, or Breastfeeding Exposure to HIV E-31
Table 10. Neonatal Antiretroviral Management According to Risk of HIV Infection in the Newborn E-34
Table 11. Antiretroviral Management for Infants With In Utero or Intrapartum Exposure to HIV E-37
Table 11.1. Drug Dosing Recommendations for Antiretroviral Prophylaxis and Presumptive HIV Therapy in Infants With *In Utero* or Intrapartum Exposure to HIV E-40
Table 12. Antiretroviral Management of Infants With Exposure to HIV During Breastfeeding E-48
Table 12.1. Antiretroviral Prophylaxis Dosing for Infants Who Are Breastfed E-50
Diagnosis of HIV Infection in Infants and Children E-70
Table 13. Recommended Virologic Testing Schedules for Infants With Perinatal and Breastfeeding Exposure to HIV E-75
Initial Postnatal Management of the Neonate Exposed to HIV E-91
Long-Term Follow-Up of Infants Exposed to Antiretroviral Drugs E-97
Appendix A: Key to Acronyms F-1
Appendix B: Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy G-1
Table 14. Antiretroviral Drug Use in Pregnancy: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy G-4
Nucleoside and Nucleotide Reverse Transcriptase Inhibitors G-34
Abacavir G-34
Emtricitabine G-40
Lamivudine G-47

Tenofovir Alafenamide G-53
Tenofovir Disoproxil Fumarate G-61
Zidovudine G-75
Non-nucleoside Reverse Transcriptase Inhibitors G-82
Doravirine G-82
Efavirenz G-86
Etravirine G-98
Nevirapine G-102
Rilpivirine G-109
Protease Inhibitors G-115
Atazanavir G-115
Darunavir G-125
Lopinavir G-132
Entry Inhibitors G-141
Fostemsavir G-141
Ibalizumab G-145
Maraviroc G-149
Capsid Inhibitor G-153
Lenacapavir G-153
Integrase Inhibitors G-157
Bictegravir G-157
Cabotegravir G-163
Dolutegravir G-170
Elvitegravir G-178
Raltegravir G-183
Pharmacoenhancers G-191
Cobicistat G-191
Ritonavir G-197
Archived Drugs G-202
Amprenavir G-203
Delavirdine G-204
Didanosine G-205
Enfuviritide G-208
Fosamprenavir G-211
Indinavir G-214

Nelfinavir G-217
Saquinavir G-220
Stavudine G-223
Tipranavir G-226
Zalcitabine G-228
Antiretroviral Pregnancy Registry G-229
Appendix C: Antiretroviral Counseling Guide for Health Care Providers H-1
Appendix D: Review of Clinical Trials of Antiretroviral Interventions to Prevent Perinatal HIV Transmission (Archived) I-1
Supplemental Table 1. Results of Major Studies on Antiretroviral Prophylaxis to Prevent Perinatal HIV Transmission I-5

What's New in the Guidelines

JUNE 12, 2025

The U.S. Department of Health and Human Services Panel on Treatment of HIV During Pregnancy and Prevention of Perinatal Transmission (the Panel) has reviewed and updated guidelines sections to address new data and publications where relevant. Key updates are summarized below. Three sections developed in collaboration with the Panel on Antiretroviral Therapy and Medical Management of Children Living With HIV were published on December 19, 2024. All revisions are highlighted in yellow in the PDF version of the guidelines.

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

- When determining the timing of repeat HIV testing in the third trimester of pregnancy, some clinicians conduct testing at or around 28 weeks of gestation in conjunction with the recommended timing of syphilis testing. This approach limits the number of blood draws and allows adequate time for syphilis treatment and congenital syphilis prophylaxis. Some clinicians also conduct a third test for HIV at the time of delivery hospitalization admission.

Prepregnancy Counseling and Care

- The Panel has added a bulleted recommendation about the care for partners in the setting of childbearing potential with HIV. Assess knowledge about partner HIV status and the need to screen partner(s) for HIV and sexually transmitted infections; provide testing or refer for services as needed. Discuss whether HIV status has been disclosed to sexual partner(s); discuss options for pre-exposure prophylaxis (PrEP) when indicated.

Lack of Experience With Antiretroviral Drugs During Pregnancy and Prior to Pregnancy (Antiretroviral-Naive)

- Bictegravir (BIC) plus tenofovir alafenamide (TAF) plus emtricitabine (FTC) (available as the fixed-dose combination [FDC] BIC/TAF/FTC) is now recommended as a *Preferred* antiretroviral therapy (ART) regimen for HIV during pregnancy. BIC/TAF/FTC is also now recommended as a *Preferred* regimen when trying to conceive if ART and long-acting cabotegravir (CAB-LA) as PrEP have never been previously used. BIC/TAF/FTC was previously recommended as an *Alternative* ART regimen.
- Table 6. What to Start: Initial Antiretroviral Regimens During Pregnancy When Antiretroviral Therapy Has Never Been Received has been revised to reflect updated Panel recommendations for people who are antiretroviral (ARV) naive and list the advantages and disadvantages of ARV combinations and regimens.

Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs During Pregnancy and When Trying to Conceive

- BIC, which is available in the FDC BIC/TAF/FTC, is now recommended as a *Preferred* ARV for use in pregnancy and when trying to conceive based on available data that suggest sufficient pharmacokinetics, efficacy, and safety in pregnancy.
- Abacavir (ABC) is now recommended as an *Alternative* rather than a *Preferred* ARV for use in pregnancy and when trying to conceive due to the need for HLA-B*5701 testing prior to initiating therapy and concerns over cardiac safety with ABC.
- 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.

Antiretroviral Drug Regimens and Pregnancy Outcomes

- The Panel has updated bulleted recommendations and revised the section text to streamline content and focus on recent, relevant data.
- The Panel recommends that ART should not be avoided or withheld before conception or in early pregnancy for the purpose of preventing preterm birth.
- ART should not be avoided or withheld to prevent hypertensive disorders of pregnancy (HDP) or stopped if HDP develops.
- Enhanced antenatal surveillance of fetal growth in the third trimester may be considered, especially if ART with boosted protease inhibitors is prescribed during pregnancy, due to the increased risk for low birth weight or small-for-gestational-age infants.

HIV-2 Infection and Pregnancy

- The Panel has added new bulleted recommendations about HIV-2- during pregnancy that align with the Adult and Adolescent Antiretroviral Guidelines to address monitoring response to treatment, lack of validated HIV-2 genotypic or phenotypic resistance assays for clinical use, and ART regimens for use with virologic and immunologic failure. Monitoring HIV-2 plasma viral loads 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.
- The Panel now recommends that ARV management of infants with potential *in utero* or intrapartum exposure to HIV-2 mono-infection or HIV-1/HIV-2 coinfection should follow recommendations for infants perinatally exposed to HIV-1 infection using drugs that are active against HIV-2, see Care of Infants With *In Utero*, Intrapartum, and Breastfeeding Exposure to HIV-2 in the section text. Nevirapine should not be used because it lacks activity against HIV-2. Additional information is available in Antiretroviral Management of Infants With *In Utero*, Intrapartum, or Breastfeeding Exposure to HIV, Table 11, Table 12, and Table 12.1.
- If HIV-2 infection is suspected or confirmed during pregnancy or at delivery, infant diagnostic testing for HIV-2 can follow the same schedule as for infants with potential *in utero* or intrapartum exposure to HIV-1 using virologic assays to diagnose HIV-2 infection. See Diagnosis of HIV Infection in Infants and Children and Table 13. Recommended Virologic

Testing Schedules for Infants With Perinatal and Breastfeeding Exposure to HIV for guidance about infant testing.

Early (Acute and Recent) HIV Infection

- The Panel has revised bulleted recommendations about ARV resistance testing and ART for early (acute or recent) HIV to reflect updated Panel recommendations about *Preferred* ART in pregnancy and to align with the Early (Acute and Recent) HIV Infection section of the Adult and Adolescent Antiretroviral Guidelines.
- *Preferred* ART regimens recommended for treating early (acute or recent) HIV infection when ART and CAB-LA as PrEP have not previously been used now include BIC plus TAF plus FTC *or* dolutegravir (DTG) plus (TAF or tenofovir disoproxil fumarate [TDF]) plus (FTC or 3TC).
- For instances of early (acute and recent) HIV infection and a history of CAB-LA use as PrEP, a regimen of ritonavir-boosted darunavir with (TAF or TDF) plus (FTC or 3TC) is recommended for initial ART.
    - Use of an empiric integrase strand transfer inhibitor (INSTI)–containing regimen is not recommended unless genotype testing shows no evidence of INSTI resistance. This is because INSTI resistance may be present in those who acquire HIV during and possibly after the use of CAB-LA as PrEP.
    - If baseline drug-resistance tests show no evidence of INSTI resistance, a switch to one of the *Preferred* INSTI-based regimens with DTG or BIC (listed above) should be considered.
- When early HIV infection is diagnosed during the postpartum period, decisions on HIV drug-resistance testing and ARV regimens should be guided by recommendations outlined in the Early (Acute and Recent) HIV Infection section of the Adult and Adolescent Antiretroviral Guidelines.

Intrapartum HIV Care

- When HIV RNA is >1,000 copies/mL or is unknown near the time of birth, scheduled cesarean birth at 38 weeks of gestation is recommended to minimize perinatal HIV transmission. However, given the potential for rapid decreases in viral load with current ART options, individualized birth plans to extend these pregnancies beyond 38 weeks to avoid the need for a cesarean birth can be considered with expert consultation and shared decision-making. Expert guidance from the National Perinatal HIV/AIDS Clinical Consultation Center (1-888-448-8765) may be helpful when choosing to develop an individualized birth plan.
- Fetal scalp electrodes should be avoided when virologic suppression is achieved during pregnancy and should not be used when virologic suppression (≥50 copies/mL) is not achieved during pregnancy.

Initial Postnatal Management of the Neonate Exposed to HIV

- The Panel has updated recommendations and content about infant safety monitoring. Longitudinal laboratory monitoring for adverse events is not needed in otherwise healthy infants receiving currently recommended ARV drugs for prophylaxis in the first 6 weeks of life (see Safety of Antiretroviral Drugs Used for Infant Prophylaxis in Antiretroviral Management of Infants With *In Utero*, Intrapartum, or Breastfeeding Exposure to HIV).

- New bulleted Panel recommendations have been added to include information about infant testing for viral coinfections: screening for congenital cytomegalovirus (cCMV), testing for infants perinatally exposed to hepatitis B surface antigen (HBsAg) positive, and testing for infants with perinatal exposure to hepatitis C virus. Additional information is available in the Pediatric Opportunistic Infection Guidelines (see Cytomegalovirus, Hepatitis B Virus/HIV Coinfection, Hepatitis C Virus/HIV Coinfection).

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

- Table 14. Antiretroviral Drug Use in Pregnancy: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy and the individual drug sections have been reviewed and updated where indicated. The drug sections have been revised to include standardized language about the Antiretroviral Pregnancy Registry with a link to updated data provided through an interim report released twice a year.

December 19, 2024

Preventing HIV Transmission During Infant Feeding

- Bulleted recommendations now include information from the text on counseling about the infant feeding options of formula feeding, use of banked donor milk, or breastfeeding. Recommendations also address clinical management if viremia is identified.
    - In the case of a detectable viral load during breastfeeding, the Panels recommend breastfeeding be stopped temporarily or discontinued and replacement feeding initiated while the viral load is rechecked; causes for the viremia are assessed, and, when applicable, adherence counseling is reinforced **(AII).** Most experts recommend permanent discontinuation of breastfeeding when HIV RNA is ≥200 copies/mL **(CIII).**
    - Depending on the level and persistence of viremia during breastfeeding, next steps may include initiating or modifying infant antiretroviral (ARV) prophylaxis, permanently stopping breastfeeding, and considering the need for additional infant HIV testing.
    - If the repeat viral load is undetectable, a joint decision should be made by the parent and providers about whether breastfeeding may resume **(AIII).**

Diagnosis of HIV Infection in Infants and Children

- Section text and Table 3. Recommended Virologic Testing Schedules for Infants With Perinatal and Breastfeeding Exposure to HIV have been revised to align with changes in Antiretroviral Management of Infants With *In Utero*, Intrapartum, or Breastfeeding Exposure to HIV.
- The Panels recommend virologic diagnostic testing at birth using an HIV nucleic acid test, which should generally be performed for all infants with perinatal HIV exposure but is not necessary for infants at low risk of HIV acquisition (defined as being perinatally exposed to HIV RNA levels <50 copies/mL from 20 weeks of gestation through delivery). Birth testing should be performed in infants at low risk of HIV acquisition if there is a plan to breastfeed or there are concerns about loss to follow-up **(BIII).**

Antiretroviral Management of Infants With In Utero, *Intrapartum or Breastfeeding Exposure or HIV Infection*

- This section has been extensively revised and the title has been updated to reflect changes in recommendations, associated content about infant ARV management according to risk from *in utero* and intrapartum HIV exposure, and guidance for infant ARV prophylaxis during breastfeeding.
- The Panels have added Table 12. Transmission Risk Assessment by HIV RNA Levels and Antenatal Time Period, which summarizes risk of transmission from exposure during three antenatal time periods. Because robust data are not available to define thresholds of risk across pregnancy, the Panels have selected time points balancing available data with implications for clinical management. Transmission risk categories inform ARV choice and management of prophylaxis and presumptive HIV therapy for infants with HIV exposure.
- Revised criteria for infant risk of HIV infection from *in utero* or intrapartum exposure and recommended ARV management are summarized in Figure 1. Antiretroviral Management Algorithm for Infants With *In Utero* or Intrapartum HIV Exposure by Risk of Transmission and Table 13. Antiretroviral Management for Infants With *In Utero* or Intrapartum Exposure to HIV. The Panels recommend the following:
  - Infants at high risk of HIV infection from *in utero* or intrapartum exposure, defined as being perinatally exposed to viremia (HIV RNA ≥50 copies/mL) in the 4 weeks prior to delivery, should be provided a three-drug ARV regimen, administered from birth for 2 to 6 weeks, that serves as presumptive HIV therapy or enhanced prophylaxis. If the duration of the three-drug regimen is shorter than 6 weeks, zidovudine (ZDV) should be continued alone to complete a total of 6 weeks of prophylaxis **(AII).**
  - Infants at low risk of *in utero* and intrapartum HIV acquisition, defined as being perinatally exposed to HIV RNA levels <50 copies/mL from 20 weeks of gestation through delivery, should receive ZDV alone for a duration of 2 weeks **(AII).**
  - Infants not meeting the criteria for high or low risk should have ARV regimens and durations based on case-specific factors related to the level and timing of viremia during the pregnancy **(AII).**
- The section now includes updated recommendations and expanded content about ARV prophylaxis for infants who are being breastfed. Recommendations of the Panels are summarized in a new table, Table 14. Antiretroviral Management of Infants With Exposure to HIV During Breastfeeding.
  - For infants with low risk of HIV acquisition during breastfeeding, some Panel members do not recommend extended ARV prophylaxis; however, other Panel members do recommend extended ARV prophylaxis with either nevirapine or lamivudine **(CIII).** The Panels did not reach consensus.
  - Infants are considered at low risk of transmission during breastfeeding when (1) maternal antiretroviral therapy is being used while breastfeeding and sustained maternal virologic suppression (HIV RNA <50 copies/mL) was achieved for at least 3 months prior to delivery and (2) the provider and patient are confident that maternal ART adherence will be maintained during breastfeeding **(AII).**

- Bulleted recommendations and associated content have been added to provide guidance about infant ARV prophylaxis or use of presumptive HIV therapy when new maternal viremia occurs while breastfeeding or there are concerns about future risk of viremia.
- Table 14.1. Antiretroviral Prophylaxis Dosing for Infants Who Are Breastfed has been revised to provide updated dosing information and to address infant ARV management for scenarios when maternal viremia develops or maternal HIV is diagnosed during breastfeeding.

Panel Roster

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Reviewed: February 20, 2025

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

Revisions to the February 20, 2025, *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).

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Key: DSMB = Data and Safety Monitoring Board; C = Consultant; CC = Panel Co-chairs; ES = Executive Secretary; ExOM = *Ex Officio* Member; HHS = Member from U.S. Department of Health and Human Services; M = Member; N/A = not applicable

Introduction

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Recommendations regarding HIV screening in pregnancy, HIV treatment during pregnancy, 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 pregnancies with HIV, scheduled cesarean delivery when 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 with perinatal HIV exposure 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 for reducing HIV acquisition risk during conception, pregnancy, postpartum, and breastfeeding (see Pre-Exposure Prophylaxis (PrEP) to Prevent HIV During Periconception, Antepartum, and Postpartum Periods).

In addition to standard primary prevention for HIV infection, the best way to prevent perinatal HIV transmission is to emphasize overall medical care before, during, and after pregnancy; 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 ART is initiated as early as possible during pregnancy—or ideally before conception—to sustainably suppress viral replication below the level of viral load assay detection.

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—recommends that prenatal counseling include patient-centered, evidence-based information on infant feeding options, including breastfeeding[15,16] (see Preventing HIV Transmission During Infant Feeding).

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 before and during pregnancy. 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 during pregnancy (or before a planned pregnancy), 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 during pregnancy is required.[17]

In addition to considering direct evidence about short-term safety during pregnancy, 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 pregnancy 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 during pregnancy or while breastfeeding, or in those who are of reproductive potential.[19-23]

In the meantime, to ensure that the best available ART is not denied during pregnancy—while acknowledging that some drugs have not yet been evaluated sufficiently for evidence of fetal or maternal harm—the Panel uses a graded approach to make recommendations for regimens to use during pregnancy. Selection of ARV drugs should be individualized during pregnancy according to ARV history, results of drug-resistance testing, and presence of comorbidities. In general, any fully suppressive regimen already used when pregnancy occurs should be continued throughout pregnancy. The Panel classifies ARV drugs for use during pregnancy or before conception 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 When Antiretroviral Therapy Has Never Been Received and Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs During Pregnancy and When 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 pregnancy, fetal development, and newborn health. Some *Preferred* drugs may have minor toxicity or incompletely evaluated teratogenicity risks that are offset by other advantages during pregnancy or preconception.

- *Alternative:* Preferred ARV drugs for nonpregnant adults that do not meet the above criteria can be considered as options for *Alternative* drugs during pregnancy 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 during pregnancy or preconception.
- *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 during pregnancy. In some cases, it may be appropriate to continue using these drugs or drug combinations if pregnancy occurs while 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 because of specific safety concerns or very limited safety and efficacy data in pregnancy, prior ART use may prompt the 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 fetal or maternal safety concerns.

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

These guidelines update the 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 patients 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 HIV care for all pregnancies, including infant care and preconception guidance. The Panel recognizes the importance of the countless contributions to date

of the many 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.

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 pregnancy 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 support effective ART use in pregnancy, maximizing health benefits and reducing the risk of perinatal transmission. However, the Panel recognizes that women have the right to make informed choices about treatment during pregnancy, even when their choices differ from their health care providers' recommendations.

The current guidelines are designed to support pregnancy and infant care, beginning with prepregnancy considerations and continuing through antepartum, intrapartum, and postpartum management. 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 manage HIV treatment during pregnancy, 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 HIV care during pregnancy (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 pregnancy 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 for pregnancy 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 HIV care during pregnancy and postpartum, including guidance for infant care. 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 during pregnancy; 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: June 12, 2025
Reviewed: June 12, 2025

Panel's Recommendations

- HIV testing is recommended for all sexually active people and should be a routine component of pre-pregnancy care (AII).
- For all pregnancies, opt-out HIV testing should be done 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).
- For all pregnancies, partners should be referred for HIV testing when their status is unknown (AIII).
- Repeat HIV testing in the third trimester is recommended during pregnancies in which there are negative initial HIV tests and increased risk of acquiring HIV, including pregnancies in which the care is received in facilities that have an HIV incidence of ≥1 case per 1,000 patients experiencing pregnancy 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 when there is a sexually transmitted infection during pregnancy, when there are signs and symptoms of acute HIV infection, or when there is 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 when HIV status is undocumented as well as when HIV tests were negative early in pregnancy but there is increased risk of HIV infection and there was no retest 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 HIV Care.
- 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 there is a positive HIV test result during labor and delivery or postpartum, a maternal HIV-1/HIV-2 antibody differentiation assay and an HIV RNA assay should be performed (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 maternal HIV test results 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 standard maternal HIV diagnostic testing should be offered 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 Infants With *In Utero*, Intrapartum, or Breastfeeding Exposure to HIV for guidance.
    - When there is an initial positive HIV test during labor or delivery or immediately postpartum and there are plans to breastfeed, the Panel on Treatment of HIV During Pregnancy and Prevention of Perinatal Transmission recommends against breastfeeding. Breast milk should be expressed and stored appropriately until all supplemental HIV tests are reviewed and are negative (AI).

- When there is increased risk of HIV acquisition postpartum, HIV testing and PrEP should be offered. If breastfeeding is occurring, consult an HIV specialist regarding frequency of HIV testing for the breastfeeding dyad (AIII).
- Maternal HIV test results 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 maternal HIV status 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

Incident HIV infection during pregnancy, postpartum, or 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. 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 HIV status is undocumented during labor. 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 risk of acute HIV infection during pregnancy, particularly late in pregnancy, because there may be a negative result for HIV immunoassays during 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 Test Results

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 when there is 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) or as early as possible in pregnancy. In the United States, approximately 20% to 34% of infants with perinatal HIV exposure were born to mothers whose HIV diagnosis was not known before pregnancy.[6] Early diagnosis provides the best opportunity to improve maternal health and pregnancy outcomes and to prevent infant acquisition of HIV. Universal voluntary HIV testing is recommended as the standard of care during all pregnancies 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] HIV testing should be performed during pregnancy wherever care is provided (including emergency departments and prenatal clinics) to avoid missed opportunities to identify HIV infection. Repeat HIV testing should be performed in the third trimester when there is increased risk of acquiring HIV or when living in areas of high HIV incidence. Repeat testing is also recommended when a sexually transmitted infection (STI) is diagnosed during pregnancy, or when symptoms and signs of acute HIV infection are present. When HIV status is unknown or undocumented during labor, providers should test for HIV 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, OB HIV testing provides an opportunity for clinicians to initiate a discussion about preventive interventions, including educating and counseling about pre-exposure prophylaxis (PrEP) when there is risk for acquiring HIV during pregnancy. See Pre-exposure Prophylaxis (PrEP) to

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

Determining HIV status before pregnancy or during the antenatal period enables:

- Provision of 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 during pregnancy and HIV care 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 Infants With *In Utero*, Intrapartum, or Breastfeeding Exposure to HIV);
- Shared decision-making on infant feeding choice, specifically breastfeeding or use of replacement feeding (see Preventing HIV Transmission During Infant Feeding); *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 Infants With *In Utero*, Intrapartum, or Breastfeeding Exposure to HIV, and Table 6. What to Start: Initial Antiretroviral Regimens During Pregnancy When Antiretroviral Therapy Has Never Been Received).[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 notification that HIV testing will be performed as part of routine pregnancy care unless the choice is made 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 during pregnancy, 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 parental consent. In some areas, this applies to all newborns; in others, it applies only when prenatal or intrapartum maternal testing has been declined.

Repeat HIV Testing in the Third Trimester

Repeat HIV testing during the third trimester, before 36 weeks of gestation, is recommended when there were negative results on the initial HIV tests during pregnancy and:

- There is high risk of acquiring HIV (i.e., injection drug use or sex with people who inject drugs, exchange of sex for money or drugs, sex partner with HIV who has a detectable or unknown HIV viral load, new sex partner or more than one sex partner during the current pregnancy,[7] suspected or diagnosed STI during pregnancy,[10] recent immigration from a high-burden HIV setting, partner who either recently immigrated from a high-burden HIV setting or recently traveled to such a setting); *or*

- Health care is being provided by facilities where prenatal screening identifies one or more HIV cases per 1,000 patients experiencing pregnancy screened or the jurisdiction of residence (state or county) has an elevated incidence rate of HIV in females aged 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*
- The states or territories of residence have statutes or regulations that require third-trimester HIV 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] State-level clinical guidelines may also recommend third-trimester HIV testing (e.g., New York). Clinicians should check current requirements and recommendations in their jurisdictions; *or*
- There are 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]
- There is self-perception as being at increased risk for HIV infection (regardless of whether or not any of the above criteria apply). When testing is declined earlier in pregnancy, providers should offer 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 HIV acquisition risk during pregnancy 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]

When determining the timing of repeat HIV testing in the third trimester, some clinicians conduct testing at or around 28 weeks of gestation in conjunction with the recommended timing of syphilis testing. This approach limits the number of blood draws and allows adequate time for syphilis treatment and congenital syphilis prophylaxis. Some clinicians also conduct a third test for HIV at the time of delivery hospitalization admission.

HIV Testing During Labor When HIV Status is Unknown

When HIV status is undocumented during labor or HIV testing was negative early in pregnancy but there is an increased risk of HIV infection and there was no retesting in the third trimester, expedited HIV testing should be performed.[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 during labor. An HIV RNA assay should also be performed when there is 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 a maternal HIV RNA assay 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) 7 days a week. If possible, results of HIV RNA assays should be available in 24 hours or less.
- When there is a positive HIV test result or suspected acute HIV infection during labor, provide counseling about HIV test results and implications for care.
    - Initiate intravenous zidovudine during labor (see Intrapartum HIV Care).
    - Immediately initiate presumptive HIV therapy appropriate for infants who are at high risk of perinatal HIV transmission (see Antiretroviral Management of Infants With *In Utero*, Intrapartum, or Breastfeeding Exposure to HIV or contact the National Clinician Consultation Center Perinatal HIV/AIDS hotline).
    - When there are plans to breastfeed, the Panel on Treatment of HIV During Pregnancy and Prevention of Perinatal Transmission strongly advises against initiating breastfeeding given the high risk of perinatal transmission. Breast milk should be expressed and stored appropriately; it should not be used for infant feeding unless all supplemental HIV test results are reviewed and determined to be negative (see Preventing HIV Transmission During Infant Feeding).

HIV Testing During the Postpartum Period

When there has been no testing for HIV during pregnancy or labor, expedited testing during the immediate postpartum period should be offered. 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 HIV testing is requested postpartum or there is increased risk of HIV acquisition (e.g., injection drug use or sex with people who inject drugs, exchange of sex for money or drugs, sex partner with HIV who has a detectable or unknown HIV viral load, new sex partner or more than one sex partner during the current pregnancy,[7] suspected or diagnosed STI during pregnancy,[10] recent immigration from a high-burden HIV setting, partner that either recently immigrated from a high-burden HIV setting or recently traveled to such a setting) HIV testing and PrEP should be offered. See Pre-exposure Prophylaxis (PrEP) to Prevent HIV During Periconception, Antepartum, and Postpartum Periods for more information. If breastfeeding is occurring, consult an HIV specialist regarding frequency of HIV testing in the breastfeeding dyad.

When an initial maternal or infant HIV test is positive or there is high suspicion of acute HIV infection, 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 Infants With *In Utero*, Intrapartum, or Breastfeeding Exposure to HIV). Providers should counsel 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 HIV negative maternal testing is confirmed. If supplemental test results are negative and acute HIV is excluded, infant ARV drugs can be discontinued. In the absence of ongoing HIV exposure, breastfeeding can be initiated.

Consultation with a pediatric HIV specialist is strongly recommended if questions remain about the potential for acute infection while lactating or ongoing infant risk of HIV exposure.

Infant HIV Testing When Maternal HIV Test Results Are Unavailable

When maternal HIV test results are unavailable (e.g., testing declined 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 maternal HIV test results are unavailable, the infant 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 Infants With *In Utero*, Intrapartum, or Breastfeeding Exposure to HIV for guidance), and standard maternal HIV diagnostic testing should be offered 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 when considering becoming pregnant, during all pregnancies and postpartum periods when there have been previous negative HIV tests, and when breastfeeding. When there are risk factors for HIV acquisition before, during, and after pregnancy, prevention counseling and appropriate interventions should be provided, including PrEP if indicated[36,37] (see Prepregnancy Counseling and Care and Pre-exposure Prophylaxis [PrEP] to Prevent HIV During Periconception, Antepartum, and Postpartum Periods for more information). When there is acute HIV during pregnancy or lactation, there is an increased risk of perinatal transmission; acute HIV also increase risk for sexual transmission of HIV (see Early [Acute and Recent] HIV Infection). 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. When acute HIV infection is possible and breastfeeding is ongoing, counsel about the Panel's recommendation to cease breastfeeding immediately until HIV infection is confirmed or excluded.[38] Breast milk can be expressed and stored appropriately while HIV diagnostic testing is completed. Expressed breast milk should not be used for infant feeding until all supplemental HIV test results are reviewed and determined to be negative. Breastfeeding can resume if HIV infection is excluded and there is no ongoing risk. Care during pregnancy or breastfeeding for the breastfeeding dyad when there is acute or early HIV should follow the recommendations in the Perinatal Guidelines (see Early [Acute and Recent] HIV Infection, Antiretroviral Management of Infants With *In Utero*, Intrapartum, or Breastfeeding Exposure to HIV, and Preventing HIV Transmission During Infant Feeding).

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 confirmed HIV, including infants with confirmed HIV. 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

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Reviewed: June 12, 2025

Panel's Recommendations
Health care professionals should discuss pre-exposure prophylaxis (PrEP) with all sexually active people without HIV, including those who are trying to conceive, pregnant, postpartum, or breastfeeding,[a] 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, and postpartum/breastfeeding periods (AII). Health care professionals should offer PrEP to those who desire PrEP or have specific indications for PrEP (AII). • The preferred PrEP option for preventing HIV transmission from **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 postpartum/breastfeeding. If pregnancy occurs while using TDF/FTC as PrEP, PrEP use can continue throughout pregnancy and breastfeeding. Risk for HIV acquisition should be reassessed, and counseling regarding the benefits and risks of PrEP use in pregnancy and during breastfeeding should be provided (AII). • Health care professionals 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). Patients with a planned PrEP discontinuation 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 (AII). • Health care professionals should offer routine PrEP follow-up, including HIV testing every 3 months and counseling on signs and symptoms of acute retroviral syndrome (AI) (see Pregnancy and Postpartum HIV Testing and Identification of Perinatal and Postnatal HIV Exposure and Centers for Disease Control and Prevention's PrEP for the Prevention of HIV in the United States—2021 Update). Consider more frequent testing when clinically indicated (e.g., adherence challenges, nonstandard visit schedule). Long-acting injectable cabotegravir (CAB-LA) is FDA-approved for vaginal exposure to HIV; however, only preliminary data have been presented for CAB-LA dosing, efficacy, and safety in pregnancy. If pregnancy occurs while receiving CAB-LA PrEP, 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 (CIII). Consider expert consultation. If pregnancy occurs while receiving PrEP, clinicians are strongly encouraged to register the pregnancy with the Antiretroviral Pregnancy Registry (AIII) (see Teratogenicity).
Rating of Recommendations: A = Strong; B = Moderate; C = Optional *Rating of Evidence: I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

HIV pre-exposure prophylaxis (PrEP) is the use of specific antiretroviral (ARV) drugs to prevent HIV acquisition. Susceptibility to HIV acquisition may be 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 counseling about PrEP

for HIV prevention and offering PrEP (or referred for PrEP services) to prevent HIV acquisition and potential perinatal HIV transmission when patients without HIV are planning to have a child or are pregnant, postpartum, or breastfeeding.[3]

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 long-acting injectable cabotegravir (CAB-LA) as PrEP was approved in 2021. When taken as prescribed, TDF/FTC provides greater than 90% protection against HIV acquisition. Of the FDA-approved PrEP agents for receptive vaginal exposure, TDF/FTC is currently the only option with published safety data in pregnancy and during early postpartum and breastfeeding.

The HIV Prevention Trials Network (HPTN) 084 study compared CAB-LA to TDF/FTC and found HIV infection risk was 88% lower in the CAB-LA group, demonstrating superiority over TDF/FTC in preventing HIV.[4-6] Data in pregnancy are still preliminary. The PURPOSE-1 study, a Phase 3, double-blind, randomized controlled trial evaluated the effectiveness of tenofovir alafenamide (TAF)/FTC among cisgender women aged 16 to 25 in South Africa and Uganda, and demonstrated an HIV incidence rate similar to the background HIV incidence; of note, adherence to oral TAF/FTC was low.[7] TAF/FTC is not recommended for HIV prevention for potential receptive vaginal exposure to HIV, including during pregnancy and postpartum.[8,9] Lenacapavir (LEN) was also evaluated in the PURPOSE-1 study and was found to be highly effective among women, including in pregnancy; FDA approval for use as HIV PrEP is pending. The guidance in the subsequent three sections focuses on the use of TDF/FTC as PrEP during periconception, antepartum, and postpartum periods (through 6 months postpartum and/or throughout breastfeeding). More information about other PrEP agents is included below in "What Is Known About Other PrEP Agents During Periconception, Antepartum, and Postpartum Periods?"

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] To address underutilization of PrEP and disparities in PrEP use among women,[10] it is important for clinicians and clinical programs to consider strategies such as health care professional education, standard protocols, clinic champions, and resource tools to optimize implementation and reduce barriers to accessing PrEP.[11-14] PrEP can be prescribed to individuals 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[15,16];
- Have a partner with HIV with unknown or inconsistent virologic suppression;
- Have infrequent condom use with one or more partners of unknown HIV status;
- Are taking nonoccupational post-exposure prophylaxis (nPEP) and anticipate ongoing indications for prevention or have used multiple courses of nPEP[17];
- Engage in transactional sex;

- Have substance use disorder and/or substance use associated with sex;
- Have a history of experiencing intimate partner violence[18]; *or*
- Have a partner with any of the factors listed above.

When prescribing PrEP, clinicians should—

- Confirm that no acute, potential exposure to HIV has occurred in the past 72 hours. In such cases, nPEP should be administered for 28 days prior to initiating PrEP.[19]
- Counsel 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). If pregnancy occurs while using TDF/FTC PrEP, PrEP use can continue throughout pregnancy.
- Explain that condomless sex with a partner who has sustained viral suppression is associated with no risk of HIV sexual transmission (see Reproductive Options When One or Both Partners Have HIV).[20-23]
- 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 determining full protection 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 protection against vaginal exposure to HIV and is not recommended.
- When PrEP is used, counsel about the symptoms associated with acute HIV infection and recommend contacting a health care professional immediately for HIV testing and further evaluation if symptoms occur (see Early [Acute and Recent] HIV Infection). If symptoms of acute HIV infection occur, advise 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]
- If pregnancy occurs while receiving PrEP, clinicians are encouraged strongly to register the pregnancy 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 used during pregnancy, including ARV drugs used for PrEP.

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 when receiving PrEP during all stages of pregnancy (e.g., preconception, antepartum, postpartum, breastfeeding) includes—

- HIV diagnostic testing with an antigen/antibody combination immunoassay at baseline. For exposure to antiretrovirals as PrEP, delays can be seen in antigen/antibody detection during acute infection.[24] 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, while using PrEP regimens.
- HIV testing (i.e., antigen/antibody combination immunoassay, as well as HIV-RNA testing) in the context of PrEP use 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 antiretroviral therapy are recommended (see Recommendations for Use of Antiretroviral Drugs During Pregnancy). During pregnancy, appropriate care to prevent perinatal transmission should also be provided. See Early (Acute and Recent) HIV Infection and Previous Experience With Antiretroviral Medications but Not on Antiretroviral Therapy During Current Pregnancy.
- Renal function testing at baseline and every 12 months thereafter if <50 years of age and/or if estimated creatinine clearance (CrCl) is over 90 mL/min. Otherwise, renal function should be monitored every 6 months. TDF/FTC as PrEP should not be initiated when there is a confirmed calculated CrCl <60 mL/min. Clinicians should discontinue daily TDF/FTC as PrEP if a confirmed calculated CrCl <50 mL/min develops.
- For those accessing PrEP with activity against hepatitis B (TDF/FTC), testing for hepatitis B virus (HBV) infection is indicated for patients initiating PrEP, but PrEP initiation need not be delayed while awaiting results. If there is no prior HBV infection and lack of HBV immunity, HBV vaccination should be provided if HBV vaccination has not occurred or reimmunization should be considered if vaccination was previously provided but immunity is still lacking. In the context of chronic HBV, counseling should be provided regarding the risk of possible hepatitis flares when tenofovir-based PrEP is stopped.[25]
- Pregnancy testing at baseline and then as indicated.
- Testing for STIs (e.g., 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.[26-28] Although pharmacokinetic (PK) data are limited in pregnant women, they suggest that pregnant women taking daily PrEP experience lower tenofovir drug levels.[29,30] 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. When PrEP has been initiated and protective drug levels have not yet been reached or there is a struggle to achieve daily adherence, other strategies (e.g., condoms) should be used to prevent HIV.

When there are plans to discontinue daily oral PrEP, ongoing use for 7 to 28 days after last potential vaginal HIV exposure is recommended. This time frame aligns with recommendations for post-exposure prophylaxis.[31]

Adherence Support

Among 6,296 cisgender women participants from 11 post-approval studies of TDF/FTC PrEP, a pooled analysis[32] found no incident HIV infections among women with consistent daily adherence to oral TDF/FTC. For women taking PrEP four to six times per week, the HIV incidence rate per 100 person-years was 0.13. Based on these findings among nonpregnant women, the Panel continues to recommend daily adherence but acknowledges that four to six doses per week achieves a high level of protection. Before initiating PrEP, health care professionals 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.[33-35] Based on barriers, health care professionals can discuss strategies tailored to individual 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 PrEP webpages and a Compendium of Best Practices for PrEP provision.

Contraception

Contraception is an important component of reproductive health care when PrEP is used and pregnancy is not desired.[20] No known significant drug–drug interactions exist between TDF and different modes of hormonal contraception.[36-38] For additional information, refer to CDC's U.S. Medical Eligibility Criteria for Contraceptive Use, 2024 and U.S. Medical Eligibility Criteria for Contraceptive Use, 2024.

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.[39,40] PrEP is recommended for all people with potential exposure to HIV.[3,41] Although data about the use of PrEP during periconception, pregnant, and postpartum are less robust than for nonpregnant people,[42] 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.[43-46]

Susceptibility to HIV acquisition may be greater during periconception, antepartum, and early postpartum periods through 6 months. Data suggest that there is a higher risk for HIV acquisition while trying to conceive, likely due to increased condomless sex.[47-51] 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.[52-54] HIV incidence among women during pregnancy and postpartum is two to six times greater than HIV incidence outside of pregnancy.[50,54-57] 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).[58] In addition, when HIV is acquired while pregnant or breastfeeding, there is a greater likelihood of transmitting HIV to infants.[49,59,60]

If pregnancy occurs while PrEP is used, including drugs not yet approved for PrEP during pregnancy (e.g., CAB-LA, TAF/FTC, LEN), clinicians are strongly encouraged to register the pregnancy 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 randomized controlled trials that enrolled men and women in heterosexual relationships demonstrated the efficacy of TDF/FTC PrEP to be 63% to 75%. In women with detectable drug levels (or taking PrEP), PrEP protected against 90% of incident transmissions.[32,61] Newer observational data from implementation studies suggest a dose-response curve with zero HIV incidence when taking seven doses per week, and lower but still high levels of protection when taking four to six doses per week.[32] Although participants planning for pregnancy were not enrolled in these clinical trials, subsequent data suggest that PrEP uptake and adherence are high during periconception periods.[62-65]

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.[43,66] 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?

TAF/FTC is not approved by the FDA for HIV prevention in the context of vaginal exposure, and the Panel does not recommend TAF/FTC as PrEP for this population, including during pregnancy and postpartum.[67] In the PURPOSE 1 study, adherence was low among participants on oral TAF/FTC, and the associated HIV incidence rate was not significantly different from the background HIV incidence.[7-9]

CAB-LA is FDA-approved for use as PrEP in adults and adolescents. Safety and PK of CAB-LA injections continued during pregnancy[68-74] are limited to preliminary data from the HIV Prevention Trials Network 084 Protocol Open Label Extension (OLE), in which, upon diagnosis of pregnancy, HIV-negative pregnant women were given the choice of continuing their current regimen (either CAB-LA or TDF/FTC) or switching to the regimen of their choosing (CAB-LA or TDF/FTC) for HIV PrEP. In the OLE, a total of 351 pregnancies were confirmed across all groups. Pregnancy-related maternal adverse event and adverse pregnancy outcome rates were similar across groups and similar to background rates.[6] Monthly PK sampling was performed among a subset of 75 participants; preliminary PK data from the first 50 participants, all of whom were continuing on CAB-LA from prior to pregnancy, found that concentrations decreased in pregnancy but were largely maintained above the protocol-defined exposure target.[5] No PK data were reported regarding initiation of CAB-LA in pregnancy (see Cabotegravir section).[74,75]

CDC guidance notes that CAB-LA for PrEP may be initiated or continued if pregnancy occurs while receiving injections when anticipated benefits outweigh the risks. When there are PrEP indications in pregnancy, as CAB-LA dosing, efficacy, and other details are still unknown, TDF/FTC is preferred for initiation during pregnancy given the more robust safety and efficacy data.[43,46,76,77] If pregnancy occurs while on CAB-LA for PrEP, the limited available safety data and long half-life of CAB-LA should be discussed, and the patient and health care professionals should engage in shared decision-making about whether to continue CAB-LA or switch to TDF/FTC. Expert consultation may be beneficial to make the best decision about continuing or discontinuing CAB-LA for PrEP in light of evolving data and knowledge. Important considerations include the following:

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

In the PURPOSE 1 study, no incident cases of HIV were reported among participants on LEN. At the time of the interim analysis, 510 pregnancies were reported among 487 participants. Pregnancy

outcomes were similar to those expected for the population (see Lenacapavir). LEN is not yet FDA-approved for HIV PrEP.[7]

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.[78]

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Prepregnancy Counseling and Care

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Panel's Recommendations
• When there is childbearing potential, HIV care should include discussions about reproductive desires and plans on an ongoing basis throughout the course of care (AIII). • Provide information about effective and appropriate contraceptive methods when pregnancy is not currently desired (AI). Offer all contraceptive methods or refer for contraceptive services. All available contraceptive methods (e.g., pill, patch, ring, injection, implant) can be used with HIV; 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 when pregnancy is not currently desired. • Assess knowledge about partner HIV status and the need to screen partner(s) for HIV and sexually transmitted infections; provide testing or refer for services as needed (AII). Discuss whether HIV status has been disclosed to sexual partner(s); discuss options for pre-exposure prophylaxis when indicated (AII) (see Reproductive Options When One or Both Partners Have HIV and Pre-exposure Prophylaxis to Prevent HIV During Periconception, Antepartum, and Postpartum Periods). • Provide education and counseling about interventions to prevent perinatal HIV transmission, including antiretroviral therapy (ART). Explain that maximum viral suppression of HIV should be attained before attempting conception for personal 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%). • When pregnancy with HIV is being considered or planned, begin to provide patient-centered, evidence-based counseling to support shared decision-making about infant feeding (AIII) (see Preventing HIV Transmission During Infant Feeding). Information and plans for infant feeding should be reviewed throughout pregnancy and again after delivery. • When selecting or evaluating an ARV regimen and there is the potential for pregnancy, consider a regimen's effectiveness, changes in ARV pharmacokinetics in the second and third trimesters of pregnancy, hepatitis B status, possible drug–drug interactions with other needed medications, and the possible adverse outcomes for maternal and fetal health (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 treating 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 comprehensive family planning and the opportunity to receive prepregnancy counseling and care as a component of routine primary medical care when there is the potential for pregnancy. The purpose of prepregnancy care is to improve health before conception by identifying risk factors for maternal and fetal adverse outcomes, 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 needs during the different stages of reproductive life. Integrating comprehensive family planning and prepregnancy care into routine HIV health care visits can help patients 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.[7-12]

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, being younger than 30, being married or cohabitating, having a secondary education or higher, and being childless.[13] 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.[14] 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 HIV care, the delivery of comprehensive reproductive counseling often falls short of the current guidelines.[15-17]

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 and in ACOG's Prepregnancy Counseling guidance. 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.[18-21]

- Discuss reproductive options; routinely assess pregnancy intentions 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.
- When pregnancy is not currently desired, offer a full range of contraceptive methods to help achieve fertility goals. In the context of HIV, all available contraceptive methods, including hormonal contraception (e.g., pill, patch, ring, injection, implant) and intrauterine devices (IUDs) can be used; see Medical Eligibility Criteria for Contraceptive Use.[22] 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.[23] 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.[24,25] 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).

- When pregnancy is being contemplated, use the prepregnancy period to modify the ARV regimen to optimize virologic suppression and minimize potential adverse effects (see Recommendations for the Use of Antiretroviral Drugs During Pregnancy and Table 7). In the context of perinatally acquired HIV, there may be more difficulty maintaining viral suppression, a greater likelihood of multidrug-resistant virus, and there may be a benefit to providing additional psychosocial and/or adherence support[26] (see Prenatal Care, Antiretroviral Therapy, and HIV Management When HIV Was Perinatally Acquired).
- Recognize that patients whose self-expression is less common may have special needs.[27] For example, the use of testosterone may induce hypothalamic–pituitary–gonadal axis suppression, leading to decreased ovulation.[28]
- Recognize that the primary HIV treatment goal when pregnancy is being planned should include sustained suppression of plasma HIV viral load below the limit of detection before conception for personal 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). When pregnancy is being considered or planned, counseling should include that with ART started before pregnancy and an undetectable viral load maintained throughout pregnancy and delivery, the risk of HIV transmission to the infant is extremely low (<1%).[29,30]
- 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 disclosure of HIV status to partners or co-parents 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 Prevent 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 on how to manage health risks (e.g., access to a syringe services program). A 2019 analysis[31] 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.[32]

- Counsel on maintaining a healthy diet and healthy weight before and during pregnancy.
- When pregnancy is being contemplated, counsel to take a daily multivitamin that contains 400 mcg of folic acid to help prevent neural tube defects (NTDs). When there is a history of having a child with NTDs, there is a family history of NTDs, or when certain anti-epileptic medications, especially when using valproic acid, a higher dose (1,000–4,000 mcg) of folic acid can be prescribed. 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 in the Adult and Adolescent Opportunistic Guidelines.
- 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; consider switching to safer medications; encourage cessation of tobacco, alcohol, and other substances; optimize management of chronic health conditions).
- 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 maternal and fetal health outcomes.
- Support shared decision-making about ART. Educate and counsel on the factors that affect the selection of ARVs when trying to conceive, during pregnancy, or during postpartum. For more information, see Recommendations for Use of Antiretroviral Drugs During Pregnancy: Overview.
- Consider the following factors when prescribing ART and there is the possibility of pregnancy: the regimen's effectiveness, changes in ARV pharmacokinetics (PK) in the second and third trimesters of pregnancy, hepatitis B virus (HBV) status, possible adverse maternal and fetal health outcomes,, and the likelihood of developing drug resistance.[33-35]
- Provide patient-centered, evidence-based counseling to support shared decision-making about infant feeding (see Preventing HIV Transmission During Infant Feeding). 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 maternal and fetal health outcomes.
- Administer all vaccines as indicated (see CDC's Recommended Immunization Schedule and ACOG's Maternal Immunization Practice Advisory, 2022), which includes vaccination for influenza, pneumococcus, HBV, tetanus, and SARS-CoV-2.[36] Tdap (tetanus, diphtheria, and pertussis) vaccination should be performed during each pregnancy, including pregnancies impacted by HIV, typically between 27 and 36 weeks of gestation but preferably as early in this time window as possible.
- Ask about safety at home and offer assistance or referrals to those experiencing intimate partner violence 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.[37-39] 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 the context of 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. When using darunavir/ritonavir-based ART, an alternative or additional contraception may be considered because the area under the curve (AUC) for oral contraceptive hormones may be decreased.[40] Cobicistat-boosted protease inhibitors are contraindicated with drosperinone-containing hormonal contraceptives due to the potential for hyperkalemia.[41] 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.[42-45]

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 when using ARVs, both PK and clinical data suggest that these implants have decreased efficacy when used with EFV-based regimens.[46-49] 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.[50]

Tuberculosis Treatment, Antiretrovirals, and Contraception

Other medications, such as concomitant tuberculosis (TB) treatment with EFV, may also have drug–drug interactions with contraceptives. PK studies of HIV/TB coinfection when using EFV-based HIV treatment and rifampicin-based TB treatment show increased metabolism of DMPA and levonorgestrel emergency contraception, suggesting that redosing DMPA more frequently or doubling the dose of emergency contraception may be required for effective contraception.[25,51-54]

Vaginal Ring

For the ENG/EE contraceptive vaginal ring (NuvaRing), PK evaluation showed that ENG levels were 79% lower and EE levels were 59% lower in participants on EFV-based ART regimens compared with the control group.[56] A newer contraceptive vaginal ring containing segesterone/EE (Annovera) also is approved by the U.S. Food and Drug Administration, but no drug–drug interaction studies with this contraceptive ring and ARVs have been reported to date. The segesterone and EE in the Annovera vaginal ring may be metabolized in the same way as ENG and EE in the NuvaRing (see Table 3 below).[56]

Table 3. Drug Interactions Between Antiretroviral Agents and Hormonal Contraceptives

Table 3 provides a summary of drug interactions between antiretroviral (ARV) agents and hormonal contraceptives, with recommendations for contraceptive dosing and additional contraceptive protection. Because data are limited on pregnancy rates when using 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 pharmacokinetic interactions between ARVs and combined hormonal methods, depot medroxyprogesterone acetate, and levonorgestrel and etonogestrel implants.

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.[57]

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 the Contraceptive's Effects on ART and HIV	COC • No effect on EE concentrations • ↓ active metabolites of norgestimate; LNG AUC ↓ 83% and norelgestromin AUC ↓ 64%[58] • ENG (in COC) C_{24h} ↓ 61%[59] • ENG ↓ 79%; EE ↓ 59%[56] DMPA • No effect on DMPA levels[42,43] • DMPA AUC ↓ 33% to 35% when coadministered with EFV, rifampin, and INH. More frequent DMPA dosing may be appropriate.[54] ENG Implant • ENG ↓ below the level necessary to prevent pregnancy (90 pg/mL) in 60% receiving EFV[60] • ↓ 49% ENG concentration[61] • ENG AUC ↓ 63% to 82%[49,62] LNG Implant • ↓ 61% LNG concentration[61] • LNG AUC ↓ 47%[50] • ↑ pregnancy incidence rate among women using LNG or ENG implants, more among ENG users[63]

Table 3. Drug Interactions Between Antiretroviral Agents and Hormonal Contraception

	• LNG AUC ↓ 40% to 73% over 30 months of use[64] • Doubling the dose of LNG implant from 150 mg to 300 mg did not overcome the decrease in LNG concentration.[65] LNG Emergency Contraception (Oral Dosing) • LNG (emergency contraception) AUC ↓ 58%[23] • C_{max} was 51% higher with 3 mg LNG (24.9 ng/mL) than with 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.[24] Vaginally Administered ENG/EE (Vaginal Ring) • ENG ↓ 93% in CYP2B6 slow metabolizers and ↓ 75% in normal and intermediate metabolizers[66] • EE ↓ 75% in slow metabolizers and ↓ 41% in normal and intermediate metabolizers[66] Changes in ARV Levels and/or Effects on HIV *COC* • No effect on EFV concentrations[58] • EFV C_{12h} ↓ 22%; under therapeutic threshold in 3 of 16 participants[59] *DMPA* • No effect on HIV disease progression[42,67,68] • No effect on EFV concentrations[42] LNG Implant • No effect on HIV disease progression[50]
Clinical Studies	COC • No difference in pregnancy rates[69] • Pregnancy rate was 13% higher in women using COCs and EFV than in women using COCs alone.[48,70] • Progesterone >3 ng/mL (a surrogate for ovulation) in 3 of 16 women[71] • No ovulations[58] DMPA • No increase in pregnancies[42,48,68,69] • Low endogenous progesterone, consistent with no ovulation[42,43,68] ENG Implant • Pregnancy rate was higher with EFV compared with no ART but still lower with implants than with other hormonal methods of contraception.[48] • Presumptive ovulation in 5%[62]

Table 3. Drug Interactions Between Antiretroviral Agents and Hormonal Contraception

	LNG Implant • 12% pregnancy rate[47] • 15% pregnancy rate[50] • Pregnancy rate was higher with EFV compared with no ART but still lower with implants than with other hormonal methods of contraception.[48] • No increase in pregnancy rate[69]
Justification/Evidence for Recommendation	For COCs, some studies suggest higher pregnancy rate and ovulation rate and decreased progestin levels. EFV levels 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.[56]
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 the Contraceptive's Effects on ART and HIV	EE AUC ↑ 22%[72] No significant effect on NE[72]
Clinical Studies	COC • No ovulations[72]
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 the Contraceptive's Effects on ART and HIV	EE AUC ↓ 29%[73]; no change in EE AUC[74] NE AUC ↓ 18%[73] ENG (in COC) C_{24h} ↓ 22%[59] DMPA • No significant change[42]

Table 3. Drug Interactions Between Antiretroviral Agents and Hormonal Contraception

	LNG Implant • LNG AUC ↑ 35%[50] • ↑ pregnancy incidence rate among women using LNG or ENG implants, more among ENG users[63] Changes in ARV Levels and/or Effects on HIV *COC* • No significant effect on NVP levels[71,73,75] *DMPA* • No effect on HIV disease progression[42,67,68,76] *LNG Implant* • No effect on HIV disease progression[50,77]
Clinical Studies	COC • No increase in pregnancy rate[48,69,70,78,79] • No ovulations[71,74,79] DMPA • No increase in pregnancy rates[48,68,69,78] • Low serum progesterone, consistent with no ovulation[42] ENG Implant • No increase in pregnancy rate[48] LNG Implant • No increase in pregnancy rate[47,48,50,69,77]
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[b] RPV)	
Dosing Recommendation/Clinical Comment for COC/P/R, POPs, DMPA[a], ENG or LNG Implants	No additional contraceptive protection is needed.
Effect on Contraceptive Drug Levels and the Contraceptive's Effects on ART and HIV	EE AUC ↑ 14%[80] No significant change on NE[80]

Table 3. Drug Interactions Between Antiretroviral Agents and Hormonal Contraception

	Changes in ARV Levels and/or Effects on HIV *COC* • No change in RPV levels compared with historical controls[80] ENG or LNG Implants • ENG and LNG concentrations not altered with RPV-based ART[38]
Clinical Studies	COC • No change in progesterone[80]
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 the Contraceptive's Effects on ART and HIV	No clinically significant interaction with EE and LNG[81]
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 the Contraceptive's Effects on ART and HIV	EE AUC ↓ 19%[82] Norgestimate AUC ↑ 85%[82] POP • NE AUC ↑ 50%[83] Vaginally Administered ENG/EE • ENG ↑ 71% • EE ↓ 38%[56]
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.

Table 3. Drug Interactions Between Antiretroviral Agents and Hormonal Contraception

Darunavir/Ritonavir (DRV/r)	
Dosing Recommendation/Clinical Comment for COC/P/R, POPs, and ENG or LNG 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.
Effect on Contraceptive Drug Levels and the Contraceptive's Effects on ART and HIV	EE AUC ↓ 44%[40] NE AUC ↓ 14%[40] ENG or LNG Implants • Progestin concentrations higher with DRV/r-based ART but no related adverse effects[38]
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 the Contraceptive's Effects on ART and HIV	EE AUC ↓ 55%[84] NE AUC ↓ 17% Patch • EE AUC ↓ 45%[84] • Norelgestromin AUC ↑ 83%[84] DMPA • DMPA AUC ↑ 46%[44] ENG Implant • ENG AUC ↑ 52%[62] Changes in ARV Levels and/or Effects on HIV *Patch* • LPV/r ↓ 19%[84] *DMPA* • No effect on HIV disease progression[44] • No change in LPV/r levels[44]
Clinical Studies	COC • Trend of increased pregnancy rate, but CIs overlap[48]

Table 3. Drug Interactions Between Antiretroviral Agents and Hormonal Contraception

	Patch • Low serum progesterone[84] consistent with no ovulations (n = 8) DMPA • No pregnancies and no ovulations[44] • Trend of increased pregnancy rate, but CIs overlap[48] ENG Implant • No increase in pregnancy rate[48] LNG Implant • No increase in pregnancy rate[47,48]
Justification/Evidence for Recommendation	For COCs, nonsignificant increase in pregnancy rate and 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 the Contraceptive's Effects on ART and HIV	Drospirenone AUC ↑ 2.3-fold[41] No change in LNG concentration 25% decrease in EE C24[85]
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.

Table 3. Drug Interactions Between Antiretroviral Agents and Hormonal Contraception

Effect on Contraceptive Drug Levels and the Contraceptive's Effects on ART and HIV	Drospirenone AUC ↑ 1.6-fold EE AUC ↓ 30%[41]
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.
Dosing Recommendation/Clinical Comment for POPs, DMPA[a], ENG Implants	No additional contraceptive protection is needed.
Effect on Contraceptive Drug Levels and the Contraceptive's Effects on ART and HIV	COC • EE AUC ↑ 48%[86] • NE AUC ↑ 110%[86]
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 the Contraceptive's Effects on ART and HIV	COC • No significant effect on EE or LN[87]
Clinical Studies	N/A
Justification/Evidence for Recommendation	For COCs, no change in EE or progestin concentrations. 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 the Contraceptive's Effects on ART and HIV	No significant drug interactions with EE or norgestimate

Table 3. Drug Interactions Between Antiretroviral Agents and Hormonal Contraception

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 the Contraceptive's Effects on ART and HIV	COC • No significant effect on ENG implants[60] • No significant effect on norgestimate or EE • No change in DTG AUC[88]
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 the Contraceptive's Effects on ART and HIV	COC • Norgestimate AUC ↑ 126% • EE AUC ↓ 25%[89,90]
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 the Contraceptive's Effects on ART and HIV	COC • No change in EE • Norgestimate AUC ↑ 14%[91]
Clinical Studies	N/A
Justification/Evidence for Recommendation	For COCs, no change in EE concentrations and a small increase in progestin concentrations. No clinical data. No data on POPs.

Table 3. Drug Interactions Between Antiretroviral Agents and Hormonal Contraception

Long-Acting Cabotegravir (CAB-LA)	
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 the Contraceptive's Effects on ART and HIV	Oral contraceptive use was associated with lower CAB-LA C_{max} than for 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 differences in other PK parameters were observed, suggesting that the association is not likely to be clinically significant.
Entry and Attachment Inhibitors	
Fostemsavir (FTR)	
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 the Contraceptive's Effects on ART and HIV	Temsavir (the active moiety of FTR) increased EE concentrations by 40% but had no effect on NE concentrations. EE dose should not exceed 30 µg or equivalent.[92] FTR did not impact progestin. Progestin-only and nonhormonal contraceptives will not be affected by FTR.
Clinical Studies	N/A
Justification/Evidence for Recommendation	No clinical data

[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.

[b] No data are available for long-acting RPV.

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; $C_{max;}$ = maximum 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; FTR = fostemsavir; 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; Adult and Adolescent Antiretroviral Guidelines; 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
When Pregnancy is Desired and One or Both Partners Have HIV • When trying to conceive with HIV, viral suppression should be sustained (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 personal health, prevent HIV sexual transmission (AI), and minimize the risk of HIV transmission to 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 when 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 variety of parenting desires within people whose sexual orientations or self-expression are less common, 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 with all varieties of sexual orientation and self-expression may seek options to build families, including adoption, and should be supported to do so.[3]

When conception is desired and 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 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 when 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 when 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; however, this combination is not approved for preventing HIV transmission through receptive vaginal sex. The use of long-acting injectable cabotegravir (CAB-LA) for PrEP was approved in 2021 for men and women. When planning to become pregnant, there are limited safety data or pharmacokinetic data to inform efficacy or safety of CAB-LA for personal or fetal health. If cabotegravir (CAB) PrEP is used when pregnancy occurs, 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 and there are plans become pregnant, the Panel recommends TDF/FTC whenever possible. Adherence is critical.

When pregnancy is desired 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 pregnancy occurs also can further reduce the risk of perinatal transmission (see Antiretroviral Therapy When 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 Pregnancy Without HIV When Partners Have HIV

In instances of pregnancy without HIV, when partners have HIV, providers should notify patients that HIV screening is recommended during all pregnancies and that an HIV test will be provided as part of the routine panel of prenatal tests unless declined (this is the opt-out strategy; see Pregnancy and Postpartum HIV Testing and Identification of Perinatal and Postnatal HIV Exposure). In instances of HIV seronegative tests during pregnancy, 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. For pregnancy without HIV, PrEP may be considered 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). For cases of pregnancy without HIV, counseling should be provided 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 such symptoms develop. Acute HIV infection during pregnancy or lactation involves high risk of transmitting HIV to 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 pregnancy when initial HIV testing was negative but there is an increased risk of acquiring HIV (see Pregnancy and Postpartum HIV Testing and Identification of Perinatal and Postnatal HIV Exposure). More frequent testing is indicated during pregnancy when a partner has HIV; testing should be performed every trimester during these pregnancies.

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 **HIV** Care

Updated: January 31, 2024
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Panel's Recommendations
In addition to the standard antepartum assessments during pregnancy, the initial evaluation 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. HIV-Related Antepartum Screenings and Assessments During Pregnancy for the recommended schedule of HIV-related laboratory tests during pregnancy. If clinically indicated, amniocentesis may be performed during pregnancy with HIV after thorough patient-centered counseling on potential risks, benefits, and alternatives. o An effective ARV regimen should be used during pregnancy, ideally ensuring undetectable HIV RNA levels (BIII). o For pregnancies where HIV RNA levels are detectable and amniocentesis is required, consultation with an expert in HIV care 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. Counseling for HIV care during pregnancy and postpartum should address the known benefits and potential risks of all medications, including ARV drugs. 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 during pregnancy, intitial evaluations in the context of 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 during pregnancy with HIV should include the following items (see Table 4. HIV-Related Antepartum Screenings and Assessments During Pregnancy):

- 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 during all pregnancies, and specifically during pregnancies 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 Pregnancy: 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 testosterone or other hormonal medications[10,11];
- 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 for all pregnancies, 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).

When there isdesire for diagnostic testing or indications for diagnostic testing during pregnancy (e.g., abnormal ultrasound or aneuploidy screening), counseling should be provided about the potential risk of perinatal HIV transmission, along with other risks of the procedure, so that informed decisions can be made 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, effective ART should be recommended during pregnancy 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 HIV Care).

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 managing HIV care during pregnancy and infancy.

ART Adherence Support During Pregnancy

In general, the recommendations for the use of ART during pregnancy are the same as for nonpregnant adults. 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 When Antiretroviral Therapy Has Never Been Received and Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs During Pregnancy and When Trying to Conceive and Recommendations for Use of Antiretroviral Drugs During Pregnancy: Overview).

Clinicians should discuss the substantial benefits of ARV drugs for optimal health during pregnancy and for reducing the risk of perinatal HIV transmission; this helps put the potential risks of using these drugs into perspective (see Table 14. Antiretroviral Drug Use in Pregnancy: 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 about ARV drug use during pregnancy 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 on maternal health during pregnancy[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 risks and adverse effects of ARV drugs during pregnancy, their impact on fetuses and infants, and possible interactions with existing medications (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 comprehensive support for HIV care during all stages of pregnancy and the postpartum period. Medical care during pregnancy with HIV requires coordination and communication between HIV specialists and obstetric providers.

Anticipatory guidance provided during pregnancy in the context of HIV is generally similar to counseling that is recommended 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 maternal and fetal health, 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 support planned disclosure of HIV status during pregnancy and postpartum,[39,40] and to ensure privacy during health care encounters (including telemedicine visits and in-person care) when HIV status has not yet been disclosed.[41] The use of medications such as testosterone or less common forms of self-expression may present specific concerns and needs for added support when receiving services in settings designed for pregnancy care.

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 Preventing HIV Transmission During Infant Feeding). 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. HIV-Related Antepartum Screenings and Assessments During Pregnancy[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 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).

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

Updated: June 12, 2025
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Panel's Recommendations
• The plasma HIV RNA levels during pregnancies impacted by 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, the need for intrapartum intravenous zidovudine administration (see Intrapartum HIV Care), and to inform decisions about optimal management for the newborn (see Antiretroviral Management of Infants With *In Utero*, Intrapartum, or Breastfeeding Exposure to HIV) (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 pregnancy when ARV drugs have never been taken previously and testing for ARV drug resistance was not previously conducted (AII); o Initiating ART in pregnancy when ARV drugs have previously been taken (including those who have received pre-exposure prophylaxis) (AIII); *or* o Modifying ARV regimens for pregnancy that occurs while receiving ARV drugs or for suboptimal virologic response to ARV drugs that were started during pregnancy (AII). See Antiretroviral Drug Resistance and Resistance Testing in Pregnancy. • ART should be initiated in pregnancy 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 being taken (AIII). • When ART is taken during pregnancies impacted by HIV, standard gestational diabetes screening should be conducted (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*

Viral Load and CD4 Cell Count Testing and Monitoring

Viral loads should be monitored more frequently during pregnancy 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). When there is adherence to antiretroviral

therapy (ART) and resistance mutations to the prescribed drugs are not present, viral suppression should generally be achieved within 3 to 12 weeks on preferred regimens, such as integrase inhibitor–based ART, depending on the initial viral load.[1-4] Higher viral loads and lower CD4 T lymphocyte (CD4) cell counts are more likely to cause more time to achieve viral suppression[5,6] than 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 during pregnancies impacted by 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 Antiretroviral Therapy Use During Prepregnancy and Early Pregnancy).

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, the need for intrapartum intravenous zidovudine administration, and optimal treatment for newborns (see Intrapartum HIV Care).

For pregnancies impacted by HIV, CD4 count should be measured at the initial clinic visit with a review of prior CD4 counts (see Table 5 below). There is a physiologic decrease in CD4 counts during pregnancy.[15,16] 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.[10,17,18] 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.[19]

HIV Drug–Resistance Testing

HIV drug–resistance testing should be reviewed in conjunction with ARV history if prior results are available and performed during pregnancies impacted by 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

when there is treatment experience with suspected multidrug resistance and failing regimens are currently being taken, 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 Lack of Viral Suppression While on Antiretroviral Therapy in Pregnancy 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.[20-24] 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.[25-27]

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.[28,29] The majority of studies in pregnant women have not demonstrated an association between HIV infection and gestational diabetes.[30-32] However, other studies did show an increased risk of gestational diabetes.[33-35] 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.[36-40] When ART is being taken during a pregnancy impacted by HIV, the standard screening for gestational diabetes that is recommended during all pregnancies should be conducted (see Table 5 below).[41]

In addition to gestational diabetes risk, risk for weight gain and obesity both during pregnancy and postpartum may be present with INSTIs, although existing evidence is somewhat inconclusive[42-47] (see Maternal Health Outcomes in Recommendations for the Use of Antiretroviral Drugs During Pregnancy: Overview). Most published data about weight gain associated with specific ARV drugs has been collected in nonpregnant populations (see Considerations for Antiretroviral Use in Special Populations in the Adult and Adolescent Antiretroviral Guidelines and Maternal Health Outcomes in Recommendations for the Use of Antiretroviral Drugs During Pregnancy: Overview). One study in pregnant women with HIV observed higher weight gain with the combined use of tenofovir

alafenamide and INSTIs.[48,49] 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.[50-52]

Table 5. HIV-Related Laboratory Monitoring Schedule During Pregnancy[a]

Laboratory Test	Timepoint or Frequency of Testing						
	Entry Into Antenatal Care[b]	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
HIV RNA Levels[c]	✓[b]	✓ If a result is not available within 2 weeks of ART initiation or modification	✓	✓ Until HIV RNA levels are undetectable	✓ At least every 3 months[d]		✓
CD4 Count[e]	✓[b]				✓ 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.[e]		

Table 5. HIV-Related Laboratory Monitoring Schedule During Pregnancy

Laboratory Test	Timepoint or Frequency of Testing						
	Entry Into Antenatal Care[b]	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
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					
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.						

Table 5. HIV-Related Laboratory Monitoring Schedule During Pregnancy

[a] For additional information, see Laboratory Testing in the Adult and Adolescent Antiretroviral Guidelines.

[b] Prior HIV-related illnesses and past plasma HIV RNA levels and CD4 counts should be reviewed at entry into antenatal care.

[c] The plasma HIV RNA levels of pregnancies impacted by 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) 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.

[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 Antiretroviral Therapy Use During Prepregnancy and Early Pregnancy).

[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 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 pregnancy when ARV drugs were never taken previously and testing for ARV drug resistance was not previously conducted (AII);
- Initiating ART in pregnancy when ARV drugs were previously being taken (AIII); *or*
- Modifying ARV regimens for pregnancy that occurs while receiving ARV drugs or for suboptimal virologic response to ARV drugs that were started during pregnancy (AII).

ART should be initiated in pregnancy 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).

[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 being taken (e.g., hematologic monitoring for those receiving ART regimens containing zidovudine, serum creatinine monitoring for those receiving ART regimens containing tenofovir) (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 in the presence of virologic failure and with 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). When HIV RNA levels are >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) during pregnancy when there is no history of prior antiretroviral (ARV) use or prior ARV resistance testing results (AII), o Initiating ART during pregnancy with prior exposure to ARVs, including pre-exposure prophylaxis (AIII), *or* o Modifying ARV regimens during a new pregnancy or when virologic response to ARV drugs during pregnancy is suboptimal (AII). • ART should be initiated during pregnancy 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 when multidrug resistance is suspected due to previous ARV exposure (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 HIV Care) (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 (Antiretroviral Management of Infants With *In Utero*, Intrapartum, or Breastfeeding Exposure to HIV) (BIII). • ART should be given during pregnancy to maximally suppress viral replication, which is the most effective strategy for preventing development of resistance and minimizing risk of perinatal transmission (AII). • Prenatal and postpartum counseling should address the importance of ART adherence to reduce the risk of acquired drug 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 During Pregnancy 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) during pregnancy when there is no history of prior antiretroviral (ARV) use or prior ARV resistance testing results,
- Initiating ART during pregnancy with prior exposure to ARVs, including pre-exposure prophylaxis (PrEP), *or*
- Modifying ARV regimens during a new pregnancy or when virologic response to ARV drugs during pregnancy is suboptimal.

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 as soon as possible during pregnancy, regardless of prior ARV exposure or the availability of resistance testing results, because earlier viral suppression reduces the 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 during pregnancy,[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 during pregnancy. 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 perinatally acquired HIV during pregnancy warrant consultation with an expert in HIV.[15] See Prenatal Care, Antiretroviral Therapy, and HIV Management When HIV Was Perinatally Acquired 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 HIV during pregnancy with prior ART or ARV prophylaxis use, including drug resistance testing, is discussed in Previous Experience With Antiretroviral Medications but Not on Antiretroviral Therapy During Current Pregnancy. Inadequate adherence and viral resistance should be considered when there is a suboptimal virologic response or viral rebound to an ARV regimen (see Lack of Viral Suppression While on Antiretroviral Therapy in Pregnancy). 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 HIV Management and Follow-Up).

The optimal prophylactic regimen for newborns perinatally exposed to drug-resistant HIV is unknown. Therefore, ARV prophylaxis for infants with known or suspected perinatal exposure to drug-resistant HIV should be determined with the help of a pediatric HIV specialist, preferably before delivery (see Antiretroviral Management of Infants With *In Utero*, Intrapartum, or Breastfeeding Exposure to HIV). 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 HIV Care). 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 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

Pregnancy often results in exclusion from clinical trials of antiretroviral (ARV) drugs, resulting in limited data on pharmacokinetics (PK), drug safety, and the 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).

- In most cases of HIV, when antiretroviral therapy (ART) is being used at the time of presentation for pregnancy care, the current ART should be continued if 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 Antiretroviral Therapy Use During Prepregnancy and Early Pregnancy).
- If ART is not already being used during pregnancies impacted by HIV, ART should be initiated as early in pregnancy as possible, regardless of HIV RNA level or CD4 T lymphocyte cell count, to maximize health and prevent perinatal HIV transmission and sexual transmission (AI). In addition to benefiting personal 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 to reduce the risk of perinatal transmission and maximize health during pregnancy (AI).
- 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 When Antiretroviral Therapy Has Never Been Received, and Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs During Pregnancy and When 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 When Antiretroviral Therapy Has Never Been Received and Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs During Pregnancy and When Trying to Conceive for a variety of clinical scenarios.
    - When selecting ARV drugs for use in pregnancy or when trying to conceive, the Panel recommends the 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 During Pregnancy and When Trying to Conceive.

When choosing an ARV drug regimen and weighing the benefits and risks of specific ARVs for use during pregnancy or in when trying to conceive, providers and patients 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 during pregnancy if data are available), and the patient's resistance test results and comorbidities (AIII).

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 intrapartum and delivery management (see Table 9 in Intrapartum HIV Care). Patients 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 Antiretroviral Therapy Use During Prepregnancy and Early Pregnancy).

- 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 and Postpartum HIV Management and Follow-Up for more information.
- Clinicians are encouraged to submit to the Antiretroviral Pregnancy Registry data any time ARV drugs are being used during pregnancy or when conception occurs (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

Selection of Antiretroviral Drugs During Pregnancy

Selection of antiretroviral (ARV) drugs **should be individualized** for HIV during pregnancy or when 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 during all pregnancies, 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 maternal health, especially those that may be exacerbated during pregnancy.

Individual-level factors, if applicable, should be considered when selecting ARVs. Factors to consider include potential ARV drug interactions with other medications; results of resistance testing and prior exposure to ARV drugs; comorbidities; ability of the patient to tolerate and adhere to a regimen; and convenience and individual preference. A preference for antiretroviral therapy (ART) during pregnancy may require 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 ART for HIV is usually being used when pregnancy occurs and often *Preferred* or *Alternative* ARV drugs are being used.[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 During Pregnancy
- Antiretroviral Therapy When Trying to Conceive
- Lack of Experience With Antiretroviral Drugs During Pregnancy and Prior to Pregnancy (Antiretroviral-Naïve)
- Antiretroviral Therapy Use During Prepregnancy and Early Pregnancy
- Previous Experience With Antiretroviral Medications but Not on Antiretroviral Therapy During Current Pregnancy
- Lack of Viral Suppression While on Antiretroviral Therapy in Pregnancy
- Discontinuation of ART (see Discontinuation of ART below)

Table 6. What to Start: Initial Antiretroviral Regimens During Pregnancy When Antiretroviral Therapy Has Never Been Received provides advantages and disadvantages of specific ARV drugs and drug combinations in pregnancy, focusing primarily on considerations when ARV drugs have never been used, with additional information about other clinical scenarios.

Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs During Pregnancy and When Trying to Conceive for a variety of clinical scenarios consolidates these scenario-specific recommendations for the use of ARV drugs for HIV when trying to conceive or during pregnancy into a single table for ease of reference.

Table 14. Antiretroviral Drug Use in Pregnancy: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy and Appendix B: 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 when there is childbearing potential but pregnancy is not currently desired, see the Adult and Adolescent Antiretroviral Guidelines.

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 patient and the health care provider following comprehensive discussion of the known benefits, as well as potential risks to maternal and fetal health[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: 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, some regimens that could not be used during pregnancy due to insufficient or problematic safety and/or PK data may be able to be used. 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 the Adult and Adolescent Antiretroviral Guidelines and Postpartum HIV Management and Follow-Up).

Pregnancy often results in exclusion 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 HIV in pregnancy can be extrapolated from evidence of efficacy in nonpregnant adults, as long as direct PK evaluation in pregnancy 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 perinatal 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. There is a median delay of 6 years between the registration of new ARVs and the first published PK data in pregnancy.[5] In addition, clinical trials should carefully evaluate the safety of ARV drugs in the setting of childbearing potential, and measurement of efficacy should be included as a secondary endpoint in pregnancy.[6]

Drugs with known benefits to people who are not pregnant should not be withheld during pregnancy unless they have known adverse effects for maternal, fetal, or infant health and these adverse effects outweigh the maternal benefits 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 for providers to counsel about 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.[7] 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 During Pregnancy. Overall, data are limited on the risks associated with using *Preferred* and *Alternative* ARV drugs other than tenofovir disoproxil fumarate, emtricitabine, lamivudine, efavirenz (EFV), and dolutegravir (DTG) 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: Safety and Toxicity of Individual Antiretroviral Agents in 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 (PIs), 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.[8-10]

Maternal Health Outcomes

Data on maternal health outcomes (e.g., gestational hypertension, weight gain) with ART use during pregnancy, particularly with newer ART regimens, are needed (see Antiretroviral Drug Regimens and Pregnancy Outcomes).[11-14]

Data on the association between ART and hypertensive disorders in pregnancy are limited; some studies demonstrated an elevated incidence in pregnant people with HIV, but other studies have shown no difference.[14] A U.S.-based cohort of pregnant people with HIV who were on ART found

that nearly 20% had hypertensive disorders of pregnancy, composed of about 50% chronic and 50% new-onset hypertension.[15] The incidence of new-onset hypertension was higher among pregnant people initiating ART on or after 20 weeks of gestation compared to those starting ART before conception and in those with low CD4 T lymphocyte cell count. Meanwhile, ARV class was not associated with hypertensive disorders.

Substantial weight gain on DTG-based regimens has been observed in nonpregnant populations, especially among women and people also receiving tenofovir alafenamide (see Dolutegravir and Tenofovir Alafenamide).[16, 17] 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). Data on weight gain during pregnancy with DTG-based ART are mixed. Some data from African studies suggest that there may be more weight gain with DTG-based ART than with EFV-based ART during pregnancy[18, 19]; however, the weight gain observed with DTG was less than the weight gain observed in pregnant people without HIV and less than the recommended weight gain in pregnancy for the general population.[19, 20] A study in the United States found that gestational weight gain was not associated with ARV class, but weekly weight gain in the second and third trimesters was greater in pregnant people who were overweight or obese when entering pregnancy and received integrase strand transfer inhibitors (INSTIs).[20]

Pharmacokinetic Considerations for ARV Drugs

Physiologic changes in pregnancy can affect drug absorption, distribution, biotransformation, and elimination, thereby affecting requirements for drug dosing and potentially increasing the risk for virologic failure or drug toxicity.[21-23] During pregnancy, gastrointestinal transit time is prolonged, and body water and fat increase throughout gestation. These changes are accompanied by increases in cardiac output, ventilation rate, and liver and renal perfusion. 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 pregnancy.

In general, the PK of nucleoside reverse transcriptase inhibitors and non-nucleoside reverse transcriptase inhibitors (NNRTIs) are similar in pregnancy and in nonpregnant people (although PK data for some drugs are limited or not available). The PK of PIs 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: Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy and Table 14. Antiretroviral Drug Use in Pregnancy: 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 When Antiretroviral Therapy Has Never Been Received, and Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs During Pregnancy and When Trying to Conceive).

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 pregnancy. Table 6. What to Start: Initial Antiretroviral Regimens During Pregnancy When Antiretroviral Therapy Has Never Been Received lists all ARV drugs and drug combinations and summarizes advantages and disadvantages of each. Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs During Pregnancy and When 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 When Trying to Conceive, Antiretroviral Therapy Use During Prepregnancy and Early Pregnancy, Previous Experience With Antiretroviral Medications but Not on Antiretroviral Therapy During Current Pregnancy, and Lack of Viral Suppression While on Antiretroviral Therapy in Pregnancy. It is important for health care providers to read all the information on each drug in the Perinatal Guidelines before administering any of these HIV medications during pregnancy (see Appendix B: Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy) and provide appropriate 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 pregnancy 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 maternal, fetal, and infant health. Some *Preferred* drugs or regimens may have minimal toxicity or incompletely evaluated teratogenicity risks that are offset by other advantages during pregnancy or when trying to conceive.
- **Alternative:** Drugs or drug combinations are designated as *Alternative* options for therapy in pregnancy when clinical trial data in adults show efficacy and the data in pregnancy are limited but generally favorable. 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 during pregnancy or when 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 pregnancy. In some cases, it may be appropriate to continue using these drugs or drug combinations when ART that has been well tolerated is used when pregnancy occurs.
- **Not Recommended Except in Special Circumstances:** Although some drugs are not recommended for initial ART when ART has never been used because of specific safety concerns or very limited safety and efficacy data in pregnancy, there may be circumstances in the context of ART experienced when initiation or continuation of specific drugs is needed 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 maternal or fetal safety concerns. 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 occurs during pregnancy.

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* when fully suppressive ART that has been well tolerated is used when pregnancy occurs, although viral load monitoring and, in some cases, safety monitoring should be performed more frequently in these instances. See Antiretroviral Therapy Use During Prepregnancy and Early Pregnancy and Initial Evaluation and Continued Monitoring of HIV During Pregnancy.

In assigning these categories, the Panel uses information from several sources to develop recommendations on specific drugs or regimens for use during pregnancy. 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 people with PK (drug exposure) data in pregnancy demonstrating exposures similar to those in nonpregnant people;
- PK (drug exposure) data during pregnancy;
- Data from animal teratogenicity studies; *and*
- Antiretroviral Pregnancy Registry data and other postmarketing surveillance data.[24]

Discontinuation of ART

The Panel strongly recommends against discontinuing ART during pregnancy. 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 same regimen is restarted or a new regimen is initiated during pregnancy. 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 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).[25]

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 oral medications from being used. Possible toxicity or intolerance to a single ARV agent should prompt discussion about options for modifying rather than stopping an entire ARV regimen (see Antiretroviral Therapy Use During Prepregnancy and Early Pregnancy).[25]

Discontinuation of therapy could lead to an increase in viral load, with possible disease progression and decline in immune status during the pregnancy 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.[26] 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; $P = 0.002$).[26]

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Use of Antiretroviral Drugs to Prevent Perinatal HIV Transmission and Improve Health During Pregnancy

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

Panel's Recommendations
• Antiretroviral therapy (ART) should be initiated as early in pregnancy as possible, regardless of HIV RNA level or CD4 T lymphocyte count, to maximize health outcomes and to prevent perinatal HIV transmission and secondary sexual transmission (AI). • When initiating ART, any necessary support should be provided to achieve viral suppression to undetectable levels as rapidly as possible, and to maintain an undetectable viral load prior to conception, during pregnancy, postpartum, and thereafter (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 Infants With *In Utero*, Intrapartum, or Breastfeeding Exposure to 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*

Antiretroviral therapy (ART) should be initiated early in pregnancy, preferably prior to conception, regardless of HIV viral load or CD4 T lymphocyte (CD4) cell count, to maximize health benefits 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 pregnancy, regardless of CD4 count and HIV RNA level, 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 during pregnancy. Prompt initiation of ART is particularly important during pregnancies with acute HIV infection or 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 Pregnancy: 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 Infants With *In Utero*, Intrapartum, or Breastfeeding Exposure to HIV).[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 When 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) (AIII). • Use of contraception, regardless of type, should never be a requirement to initiate or continue ARV regimens, even if data are limited on use of 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. Information about the benefits and risks of initiating specific antiretroviral (ARV) regimens when trying to conceive should be provided so they informed decisions about care can be made (see Appendix C: Antiretroviral Counseling Guide for Health Care Providers). Prevention of perinatal HIV transmission is maximized when fully suppressive ART is being used prior to conception and suppression remains consistent during pregnancy and through delivery.[1] For more information, see Prepregnancy Counseling and Care.

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 both during pregnancy and when trying to conceive and initiating treatment (see Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs During Pregnancy and When 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. When long-acting (LA) injectable ARVs are being used and switching regimens prior to conceiving is being considered 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 LA drugs are fully eliminated. Additionally, when LA injectable cabotegravir (CAB) and rilpivirine (RPV) are being used and there is a history of poor adherence to oral medications, switching from LA CAB/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, when pregnancy is not desired but there is childbearing potential, ARV regimens that are not designated as *Preferred* when trying to conceive may be chosen. 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., LA CAB/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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Lack of Experience With Antiretroviral Drugs During Pregnancy and Prior to Pregnancy (Antiretroviral-Naive)

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Panel's Recommendations
• During pregnancy, when there is a lack of experience with 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). • During pregnancy, when there is a lack of experience with ART and no previous use of long-acting cabotegravir (CAB-LA) as pre-exposure prophylaxis (PrEP), *Preferred* regimens consist of the integrase strand transfer inhibitors (INSTIs) dolutegravir (DTG) or bictegravir (BIC) plus a tenofovir-containing dual–nucleoside reverse transcriptase inhibitor combination (see Table 6. What to Start: Initial Antiretroviral Regimens During Pregnancy When Antiretroviral Therapy Has Never Been Received and Early (Acute and Recent) HIV Infection) (AIII). *Preferred* regimens include: o DTG plus (tenofovir disoproxil fumarate [TDF] or tenofovir alafenamide [TAF]) plus (emtricitabine [FTC] or lamivudine [3TC]) *or* o BIC plus TAF plus FTC (available as the fixed-dose combination BIC/TAF/FTC) • In the context of HIV during pregnancy, when CAB-LA has previously been used as PrEP, genotype testing should be performed before the start of ART and should include screening for INSTI-resistance mutations (AIII). ART should be started as soon as possible, before the results of genotype testing are available. o *Preferred* regimens for those who have received CAB-LA as PrEP should consist of the ritonavir-boosted protease inhibitor darunavir/ritonavir, rather than an INSTI, with (TAF or TDF) plus (FTC or 3TC) (see Previous Experience With Antiretroviral Medications but Not on Antiretroviral Therapy During Current Pregnancy) (AIII). • *Alternative* ARVs for the treatment of HIV during pregnancy when ARV drugs have never been used are shown in Table 6. What to Start: Initial Antiretroviral Regimens During Pregnancy When Antiretroviral Therapy Has Never Been Received. • 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 therapy (ART) regimens designated by the Panel on Treatment of HIV During Pregnancy and Prevention of Perinatal Transmission (the Panel) as *Preferred* regimens for pregnancy when antiretroviral therapy has never been used (i.e., are ART-naive) and long-acting cabotegravir (CAB-LA) has not previously been used as pre-exposure prophylaxis (PrEP) consist of the integrase strand transfer inhibitors (INSTIs) dolutegravir (DTG) or bictegravir (BIC) plus a tenofovir-

containing dual–nucleoside reverse transcriptase inhibitor (NRTI) combination. *Preferred* regimens for the treatment of pregnancy when antiretroviral (ARV) drugs have never been used include:

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

The NRTI components listed above 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, less toxicity than zidovudine plus 3TC, and are active against hepatitis B virus (HBV).[1-3]

DTG is a *Preferred* INSTI for use in pregnancy because it has been studied extensively in pregnancy and 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 birth.[7,8] Higher rates of viral suppression did not translate into statistically significantly lower rates of observed perinatal 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 during pregnancy with early (acute or recent) HIV infection without prior use of long-acting injectable cabotegravir (CAB-LA) as PrEP (see Early [Acute and Recent] HIV Infection).

BIC is also classified as a *Preferred* INSTI for use in pregnancy because it is associated with high rates of viral suppression and has high tolerability; has a high genetic barrier to drug resistance; and is coformulated with a *Preferred* dual-NRTI backbone (TAF/FTC) as a single, once-daily pill. In two separate PK studies, BIC exposure was lower in pregnant women who were in the second and third trimester than in nonpregnant or postpartum patients; however, BIC levels remained above the effective concentration to cause 95% inhibition during pregnancy, and participants demonstrated high levels of viral suppression.[12] Therefore, BIC is anticipated to suppress viral load without the need for dose adjustment. In a cohort of 144 infants born in the United States to people with HIV who received BIC during pregnancy, birth outcomes were reassuring about the safety of BIC use in pregnancy and maternal viral suppression was high.[13] In another multicenter cohort of 147 pregnancies in the United States, BIC use during pregnancy was associated with high levels of viral suppression and perinatal outcomes that were similar to those in the published literature.[14]

Ritonavir-boosted darunavir (DRV/r) is *Preferred* (rather than an INSTI-based regimen) for pregnancy when there is a history of CAB-LA PrEP use, pending results of genotypic resistance testing for INSTI mutations (see Early [Acute and Recent] HIV Infection and Previous Experience With Antiretroviral Medications but Not on Antiretroviral Therapy During Current Pregnancy). For pregnancies when CAB-LA has not previously been used, DRV/r is 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.[15] 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[16]; therefore, twice-daily dosing is recommended (see Darunavir).

Abacavir (ABC) is also classified as an *Alternative* ARV drug for use in pregnancy. Despite documented efficacy and safety in pregnancy, the use of ABC requires testing for the HLA-B*5701 gene variant before initiating therapy to avoid ABC-associated hypersensitivity reactions. For this reason, providers may choose to use TDF or TAF rather than ABC to avoid delays in ART initiation while awaiting HLA-B*5701 test results. In addition, some data suggest an increased risk of cardiovascular events associated with ABC. Moreover, ABC is not active against HBV; therefore, ARV drugs that are active against HBV—TDF or TAF with either 3TC or FTC—should be used for chronic HBV coinfection.

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 When Antiretroviral Therapy Has Never Been Received.

Recommendations for Regimens Other Than Combination (Three-Drug) Antiretroviral Therapy

Although the Adult and Adolescent Antiretroviral Guidelines recommend some two-drug ARV regimens for nonpregnant people without ARV experience in certain clinical circumstances, two-drug ARV regimens **are not recommended** for initiation of ART in pregnancy when there is a lack of ARV experience because of a lack of data in pregnancy.

Antiretroviral Therapy–Naivete With Presentation in the Third Trimester

INSTIs have an important role when ART is initiated late in pregnancy, particularly when viral loads are high, because of the documented ability of INSTIs to suppress viral load rapidly (a decrease of approximately 2 $\log_{10}$ copies/mL occurs by Week 2 of therapy with these drugs).[17-21]

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 birth, 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 of gestation) to receive raltegravir (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 birth (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.[22]

RAL and DTG are likely to be similarly effective in rapidly reducing viral load in instances of presentation in the third trimester. DTG is *Preferred* and RAL is *Alternative* when initiating ART when ARV drugs have never been used 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 a *Preferred* INSTI-based regimen when initiating ART during pregnancy, but data are not available for its use when initiated during the third trimester. BIC is also likely to be effective in rapidly reducing viral load and may be considered in instances of presentation in the third trimester if a single tablet, once-daily regimen is needed to support adherence. 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). DRV/r is *Preferred* for pregnancy when there is a history of CAB-LA PrEP use, including instances of presentation in the third trimester, pending results of genotypic resistance testing for INSTI mutations. For more information, see Table 6. What to Start: Initial Antiretroviral Regimens During Pregnancy When Antiretroviral Therapy Has Never Been Received.

Presentation after early (acute or recent) HIV infection at any time in pregnancy is discussed in Early (Acute and Recent) HIV Infection.

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Antiretroviral Therapy Use During Prepregnancy and Early Pregnancy

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Panel's Recommendations
• In most cases, when antiretroviral therapy (ART) is used at the time of presentation for pregnancy care, ART regimens should be continued 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. If DTG/3TC or DTG/RPV is used during pregnancy at the time of presentation and viral suppression has been successfully maintained, the two-drug regimen can be continued (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 limited and insufficient to make a recommendation for or against use in pregnancy. When this regimen is used during pregnancy at the time of presentation, counseling about limited data should be provided. In conjunction with an HIV expert, a shared decision should be reached 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 (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 one of these regimens is used during pregnancy at the time of presentation, a shared decision should be reached 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 When Antiretroviral Therapy Has Never Been Received 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). In these instances, viral load should be monitored more frequently (i.e., every 1–2 months) (CIII). • When a regimen that is not fully suppressive is used during pregnancy at presentation, adherence barriers, drug–drug and drug–food interactions, and HIV drug resistance should be carefully evaluated to determine whether a change in ART regimen is indicated. See Lack of Viral Suppression While on Antiretroviral Therapy in Pregnancy for additional guidance. • If an ARV regimen is altered during pregnancy, 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 When Antiretroviral Therapy Has Never Been Received and Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs), and more frequent virologic monitoring is warranted until stable viral suppression is observed (CIII). • If ART is used during pregnancy, ARV drug-resistance testing should be performed prior to changing an ARV regimen when 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 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.

Please see Intrapartum HIV Care for guidance about use of intrapartum intravenous zidovudine prophylaxis and scheduled cesarean birth for instances when viral suppression on ART has not been achieved at birth.
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*

Management on Fully Suppressive Antiretroviral Therapy

In general, **when a fully suppressive antiretroviral regimen is used when pregnancy occurs, the antiretroviral therapy (ART) regimen should be continued.** 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.

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 or c]-boosted regimens, oral rilpivirine [RPV]) or regimens with insufficient data about dosing and/or safety in pregnancy (e.g., doravirine [DOR], oral two-drug regimens, long-acting injectables for HIV treatment [cabotegravir (CAB), RPV, and lenacapavir]), 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 When Antiretroviral Therapy Has Never Been Received and Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs During Pregnancy and When Trying to Conceive).

For regimens with PK concerns or those with insufficient data about dosing in pregnancy, a shared decision may be reached 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 birth), 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 when virologic suppression is already achieved, clinicians should closely monitor tolerability of the new regimen, evaluate for

adverse effects, and perform more frequent viral load monitoring (i.e., every 1–2 months). For additional information, see Appendix C: Antiretroviral Counseling Guide for Health Care Providers.

Cobicistat-Boosted Regimens

Clinicians and patients should be aware that the use of atazanavir/cobicistat, darunavir/cobicistat, 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 one of these regimens is used during pregnancy at the time of presentation, 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 Antiretroviral Regimens During Pregnancy When Antiretroviral Therapy Has Never Been Received and Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs During Pregnancy and When Trying to Conceive.[3-5] A multicenter, retrospective study of 134 pregnant women with HIV who received EVG/c-containing ART at any time during pregnancy reported that 81.3% of study participants had viral suppression at birth (HIV RNA <40 copies/mL); among 68 women who initiated EVG/c before pregnancy and continued receiving EVG/c through birth, the rate of viral suppression at birth was 88.2%. The perinatal HIV transmission rate was 0.8% in this study.[6] 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 if used with EVG/c).

Doravirine

Data on DOR use during pregnancy are extremely limited and insufficient to make a recommendation for or against use in pregnancy. PK data on DOR in human pregnancy are available only from PK modeling data based on *ex vivo* studies of placental transfer.[7,8] If pregnancy occurs with viral suppression while receiving regimens with DOR, counseling should be provided about limited available data; see Doravirine. A shared decision should be reached 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., dolutegravir (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.[9,10] 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 there should be adequate exposure during most pregnancies. A recent observational study of 188 pregnant people on oral RPV as part of a three-drug regimen at birth found that 182 (96.8%) had viral load <200 copies/mL.[11] 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 When Antiretroviral Therapy Has Never Been Received, and Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs During Pregnancy and When Trying to Conceive).

Long-Acting Injectable Cabotegravir and Rilpivirine

Data on long-acting injectable CAB plus RPV (LA CAB/RPV) are currently limited. A small number of patients without HIV who became pregnant while enrolled in the initial trials of long-acting injectable CAB for pre-exposure prophylaxis (PrEP) stopped the medication once pregnancy was recognized, usually in the first trimester. In these patients, the pharmacologic washout was similar in pregnant and nonpregnant adults.[12,13] A case report describing bimonthly LA CAB/RPV prior to and during a single pregnancy found that CAB concentrations during pregnancy were comparable to those for nonpregnant individuals; however, RPV was 70% to 75% lower. The mother's HIV viral load remained undetectable throughout pregnancy, and the infant's HIV RNA test was negative.[14] In the HPTN 084 open-label extension PK sub-study of 50 participants who took long-acting injectable CAB (CAB-LA) for PrEP before and during pregnancy, CAB-LA concentrations declined over the course of the pregnancy; however, drug levels remained above protocol-specific target levels.[15] While data in nonpregnant adults suggest slower washout (and thus potentially higher CAB levels) with intramuscular CAB among people with obesity,[16] 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. Prior data have shown concern for lower concentrations of oral RPV in the third trimester,[17] as above. Some patients who have achieved virologic suppression on LA CAB/RPV experienced previous challenges with oral ART, such that switching back to oral ART could increase the risk of virologic rebound. A shared decision should be reached 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 LA CAB/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 or longer.[18] When LA CAB/RPV injections are stopped, the Panel recommends initiating an alternative fully suppressive ARV regimen no later than 1 month after the final LA CAB/RPV injection.[19] Dosing recommendations, including guidance for switching to an oral regimen, can be found in the prescribing information.[18,20] 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.

When Full Suppression With ART is Not Achieved When Pregnancy Occurs

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 Lack of Viral Suppression While on Antiretroviral Therapy in Pregnancy).

When ART is used during pregnancy, ARV drug-resistance testing should be performed prior to changing an ARV regimen if HIV RNA levels are >200 copies/mL. If there has been any prior CAB-LA exposure (as part of ART or PrEP), the Panel recommends also performing an integrase strand transfer inhibitor genotype test. For 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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Previous Experience With Antiretroviral Medications but Not Currently on Antiretroviral Therapy During Current Pregnancy

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Panel's Recommendations
• In choosing an antiretroviral therapy (ART) regimen for pregnancy when antiretroviral (ARV) medications have been used previously, 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 (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*

Initiating Antiretroviral Therapy After Previous Exposure to Antiretroviral Medications

The choice may be made to discontinue antiretroviral therapy (ART) for a variety of reasons, and the length of time off treatment before pregnancy may vary. HIV treatment history and all prior drug resistance test results should be considered when choosing ART for pregnancy when antiretroviral (ARV) medications have been used previously, even when the results of drug-resistance testing performed during the current pregnancy are not yet available.

When ARV medications have been discontinued, interpreting resistance testing results can be complex because resistance testing is most accurate when performed while ART is still being used 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 when ARVs have been used previously (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.[1,2] 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 During Pregnancy.

A previous ART regimen that successfully suppressed viral load may be restarted 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 When Antiretroviral Therapy Has Never Been Received and Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs During Pregnancy and When 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 selecting appropriate ART in 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 instances. Consultation is also available through the National HIV Perinatal Hotline (1888448-8765).

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 integrase strand transfer inhibitors (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 Lack of Viral Suppression While on Antiretroviral Therapy in Pregnancy).

History of Intermittent or Time-Limited Use of Antiretroviral Therapy

History of limited used could have occurred in some pregnancies when medication was used for personal health (i.e., ART) or to prevent HIV transmission to the infant (i.e., perinatal prevention) or the sexual partner. They may also have received ARVs as post-exposure prophylaxis or as pre-exposure prophylaxis (PrEP) for preventing HIV acquisition.[3,4]

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 medications are used as a part of subsequent ART.[5-9] 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–based therapy,[10-12] but not in those who previously received protease inhibitor (PI)–based therapies.[10] To date, there are no data on the risk of developing resistance when long-acting ART (e.g., long-acting cabotegravir [CAB-LA] and long-acting rilpivirine) is discontinued without starting alternative ART.

Antiretroviral Therapy After Pre-Exposure Prophylaxis

In contrast to time-limited exposure to ART for HIV, recent studies suggest that there may be risk for selection of integrase inhibitor mutations if HIV is acquired while receiving CAB-LA for PrEP.[13] Therefore, when there is a history of using CAB-LA as PrEP, genotypic resistance testing performed before starting ART should also include screening for INSTI-resistance mutations.[14] 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 with (tenofovir alafenamide or tenofovir disoproxil fumarate) plus (emtricitabine or lamivudine), rather than the INSTI dolutegravir, as the *Preferred* ARV in the context of prior CAB-LA exposure and 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 When Antiretroviral Therapy Has Never Been Received, and Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs During Pregnancy and When Trying to Conceive for more information.

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Lack of Viral Suppression While on Antiretroviral Therapy in Pregnancy

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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 During Pregnancy. • To detect problems with viral suppression early, more frequent viral load monitoring (every 1–2 months) is recommended when regimens associated with lower drug levels in the third trimester or drugs with limited or no pharmacokinetic (PK) data about use in pregnancy are used (AII). See Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs During Pregnancy and When 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 Antiretroviral Drug Resistance and Resistance Testing in Pregnancy and 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 (ARV) 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 antiretroviral therapy (ART) due to inadequate viral suppression (BIII). Consultation is also available through the National Perinatal HIV/AIDS 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, the development of resistance mutations, and an increase in the risk of perinatal HIV transmission and clinical progression. Therefore, this strategy is not recommended (AI). Please see Intrapartum HIV Care for guidance about use of intrapartum intravenous zidovudine prophylaxis and scheduled cesarean birth for pregnancy when viral suppression has not been achieved 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 both during pregnancy and in 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 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 lack of viral suppression early, more frequent viral load monitoring (every 1–2 months) is recommended when regimens associated with lower drug levels in the third trimester or drugs with limited or no pharmacokinetic (PK) data about use in pregnancy are used (see Table 7. Situation-Specific

Recommendations for Use of Antiretroviral Drugs During Pregnancy and When Trying to Conceive). **During pregnancy or breastfeeding, the definition of viral suppression (i.e., viral load ≤50 copies/mL) differs from thresholds used for nonpregnant individuals (**Adult and Adolescent Antiretroviral Guidelines**).**

For people initiating or changing antiretroviral therapy (ART), HIV RNA is expected to decline fairly quickly, ideally achieving at least a tenfold (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 of gestation or within 4 weeks of planned birth.[8] In a retrospective cohort of 604 pregnant patients on either a protease inhibitor (PI)–based regimen (n = 411, 68%) or an INSTI-based regimen (n = 193, 32%) at birth, viral suppression was more frequent in those on the INSTI-based regimen (147/193, 76%) compared to those on the PI-based regimen (275/411, 67%; odds ratio 1.59; 95% confidence interval [CI], 1.08–2.33).[9] In a separate pregnancy cohort (n = 315 mother–infant pairs), no significant differences were observed in undetectable viral load at birth by ART regimen (INSTI vs. non-INSTI, $P = 0.11$).[10] Acute HIV during pregnancy generally involves high viral loads which may take longer to be suppressed than viral loads seen in nonpregnant people with HIV (see Early [Acute and Recent] HIV Infection).

Situations in which virologic suppression is not achieved (i.e., viral load is detectable) remain a common problem during pregnancies 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.[11] Additionally, in 230 pregnancies in the United States, rates of optimal virologic control at birth did not significantly differ among mothers receiving dolutegravir (DTG, 93.1%), rilpivirine (RPV, 92.1%), boosted darunavir (DRV, 82.6%), or efavirenz (76.9%) but were significantly lower among mothers receiving atazanavir (49.0%) or lopinavir (40.9%). Overall, 73.5% of the cohort had an undetectable viral load at birth.[12]

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., RPV, DRV) that affect adequate drug absorption; concomitant administration or inadequate spacing of vitamins or foods containing calcium or iron (e.g., DTG, bictegravir, raltegravir, elvitegravir; see Appendix B: 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.[13] 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.[14-16] 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.[17-19]

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 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 birth; 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.[20] Viral load testing is currently recommended at 34 to 36 weeks of gestation for birth planning; providers may consider repeat testing subsequently in selected instances when there is increased risk for viral rebound. Risk for viral rebound may be greater when regimens with PK concerns for lower drug levels in late pregnancy are used (e.g., cobicistat-boosted regimens and RPV) (see Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs During Pregnancy and When Trying to Conceive and Antiretroviral Therapy Use During Prepregnancy and Early Pregnancy).

The lack of virologic suppression by late pregnancy may indicate virologic failure, but it may also represent inadequate time on ART when ART was initiated 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 of gestation (with a PI- or non-nucleoside reverse transcriptase inhibitor–based regimen or a nucleoside reverse transcriptase inhibitor–only regimen) also was associated with a significantly higher risk of having a viral load >400 copies/mL at birth.[21] 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.[22] In the French Perinatal Cohort of 14,630 women with HIV and giving birth from 2000 to 2017, both HIV RNA level at birth and timing of ART initiation were independently associated with risk of perinatal transmission of HIV.[1]

For pregnancies with perinatally acquired HIV, there may be additional barriers to adherence and virologic suppression. Several studies from the United States and Europe have demonstrated that during pregnancy, perinatally acquired HIV is a risk factor for detectable viral load near the time of birth, increased resistance mutations, and a higher perinatal transmission rate than non–perinatally acquired HIV.[23,24] 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 When HIV Was Perinatally Acquired).

Managing Lack of Viral Suppression

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. A three-pronged approach is indicated for evaluating and managing pregnancy when ART is being used and suppression of HIV RNA has not been achieved, 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,[25,26] lack of attention to food requirements); ordering ARV drug–resistance tests should be considered before changing regimens if plasma HIV RNA levels are >200 copies/mL while on the current regimen. For instances of confirmed HIV with 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 Antiretroviral Therapy Use During Prepregnancy and Early Pregnancy, Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs During Pregnancy and When 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. Prepregnancy 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.[18] 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 birth (adjusted odds ratio 2.29; 95% CI, 0.94–5.55; $P = 0.068$).[27] 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 Pregnancy: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy) and directly observing drug administration in the home or hospital setting.[28]

When considering altering an ARV regimen because viral suppression targets have not been reached, resistance testing should be performed during pregnancy while the current regimen is still being used (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 instances of 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 viral load has rebounded (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.

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.[29-31] 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 When Antiretroviral Therapy Has Never Been Received

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Recommendations for initial antiretroviral therapy (ART) during pregnancy are intended when there **has never been prior receipt of ART or antiretroviral (ARV) drugs for prophylaxis** (i.e., ARV-naive) and there is no evidence of significant resistance to regimen components (see Lack of Experience With Antiretroviral Drugs During Pregnancy and Prior to Pregnancy [Antiretroviral-Naïve]). Recommendations about the use of ARVs in other scenarios are detailed in Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs During Pregnancy and When Trying to Conceive.

In general, the Panel on Treatment of HIV During Pregnancy and Prevention of Perinatal Transmission (the Panel) recommends that **pre-pregnancy regimens should be continued when pregnancy occurs on fully suppressive ARV regimens,** unless these regimens include 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 Antiretroviral Therapy Use During Prepregnancy and Early Pregnancy). Clinicians may need to consider additional factors when initiating ART in patients who previously received ART or ARV drugs for prophylaxis (see Previous Experience With Antiretroviral Medications but Not on Antiretroviral Therapy During Current Pregnancy and Table 7).

Whenever possible, changes in ARV regimens should be timed so that viral suppression can be achieved before attempts at becoming pregnant begin (see Table 7).

Regimens are listed alphabetically within each drug class and recommendation category for initial therapy when there has never been prior ART or ARV exposure (ARV-naïve), 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 health risks during pregnancy and risks to fetuses and infants (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 Pregnancy: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy.

Table 6. What to Start: Initial Antiretroviral Regimens During Pregnancy When Antiretroviral Therapy Has Never Been Received

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 health during pregnancy as well as the health of the fetus and infant. Some *Preferred* drugs or regimens may have minimal toxicity or teratogenicity risks that are offset by other advantages during pregnancy or when 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
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 in pregnancy 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.)
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 in pregnancy 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.

Table 6. What to Start: Initial Antiretroviral Regimens During Pregnancy When Antiretroviral Therapy Has Never Been Received

Preferred INSTI Regimens	Advantages	Disadvantages
BIC/TAF/FTC (FDC)	• Co-formulated as a single, once-daily pill; for this reason, may be preferred over DTG to support adherence • High barrier to resistance • No food requirement • No dose adjustment required in pregnancy • No safety concerns observed • High rates of viral suppression • BIC/TAF/FTC is a Preferred regimen for initial treatment in people with early (acute or recent) HIV infection without a history of CAB exposure for PrEP; see Early (Acute or Recent) HIV Infection and the Adult and Adolescent Antiretroviral Guidelines.	• PK and safety data in pregnancy suggest sufficient efficacy and safety of BIC for its use as a *Preferred* initial agent in pregnancy when there has not been prior ARV or ART experience (ARV-naïve). Drug levels are lower in the second and third trimester of pregnancy than in nonpregnant or postpartum patients and are reduced in later pregnancy to a greater degree for BIC than for DTG, but BIC levels remained above the protein-adjusted EC_{95} during pregnancy and therefore are anticipated to suppress viral load. • Potential concerns about excess 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). • BIC/TAF/FTC is not *Preferred* for initial treatment in people with early (acute or recent) HIV infection *and* a history of CAB-LA exposure for PrEP due to concerns about INSTI resistance mutations, unless genotype testing has demonstrated an absence of INSTI resistance mutations; DRV/r is *Preferred* in this situation; see the Adult and Adolescent Antiretroviral Guidelines.
DTG Plus a *Preferred* Dual-NRTI Backbone	• Once-daily dosing • 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 birth with a PI-based regimen are a concern. • DTG has been shown to rapidly decrease viral load in pregnancy when presentation to care is late in pregnancy and there is no prior experience with ART or ARVs (ARV-naïve). 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 in scenarios of presentation to care late in pregnancy.	• Potential concerns about excess weight gain • Do not use DTG/3TC in the setting of HBV coinfection without another HBV agent. • 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-LA exposure for PrEP due to concerns about INSTI resistance mutations unless genotype testing has demonstrated an absence of INSTI resistance mutations; DRV/r is *Preferred* in this situation; see the Adult and Adolescent Antiretroviral Guidelines. • In the U.S., not available as an FDC

Table 6. What to Start: Initial Antiretroviral Regimens During Pregnancy When Antiretroviral Therapy Has Never Been Received

	• DTG with a NRTI backbone of TAF or TDF with 3TC or FTC is a *Preferred* regimen for initial treatment in people with early (acute or recent) HIV infection without a history of CAB exposure for PrEP; see Early (Acute or Recent) HIV Infection and the Adult and Adolescent Antiretroviral Guidelines.	
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 when genotype testing is unavailable or demonstrates INSTI resistance mutations). 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 When Antiretroviral Therapy Has Never Been Received

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 pregnancy 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 during pregnancy or when 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
DTG/ABC/3TC (FDC)	• Once-daily dosing • DTG/ABC/3TC is available as an FDC. • See above section about DTG for other details.	• Potential concerns about excess weight gain • DTG/ABC/3TC requires HLA-B*5701 testing before use (see ABC/3TC below). • Do not use DTG/ABC/3TC or DTG/3TC in the setting of HBV coinfection without another HBV agent. • See above section about DTG for other 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 birth 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 pregnancy when presentation to care is late in pregnancy and there is no prior experience with ART or ARVs (ARV-naïve). 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).
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.

Table 6. What to Start: Initial Antiretroviral Regimens During Pregnancy When Antiretroviral Therapy Has Never Been Received

		• 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 and the Adult and Adolescent Antiretroviral Guidelines.	• 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
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. • Now classified as an *Alternative* ARV drug due to inability to start without HLA-B*5701 testing and concerns over cardiac safety. • 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.

Table 6. What to Start: Initial Antiretroviral Regimens During Pregnancy When Antiretroviral Therapy Has Never Been Received

		• 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.
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.
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 co-formulated, 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 co-formulated, 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. • 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 When Antiretroviral Therapy Has Never Been Received

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 pregnancy. When virologic suppression on one of these drugs or drug combinations is present when pregnancy occurs, providers and patients should consider whether to continue the current regimen or switch to a *Preferred* ARV regimen (see Antiretroviral Therapy Use During Prepregnancy and Early Pregnancy 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	• Co-formulated 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 When Antiretroviral Therapy Has Never Been Received

Not Recommended for Use as Initial Regimens in Pregnancy		
Drugs and drug combinations listed in this category are *Not Recommended* for initial use in pregnancy because of inferior virologic efficacy or potentially serious safety concerns for during pregnancy or for the 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 occurs (see Table 7 and Table 14). Note: When virologic suppression on one of these drugs or drug combinations is present when pregnancy occurs, providers and patients should consider whether to continue the current regimen or switch to a *Preferred* ARV regimen (see Antiretroviral Therapy Use During Prepregnancy and Early Pregnancy 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 adults or adolescents (pregnant or nonpregnant) who have never received ARV drugs • 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 People With HIV and Antiretroviral Therapy Experience in the Adult and Adolescent Antiretroviral Guidelines).
DRV/c (FDC) *or* DRV/c/FTC/TAF (FDC)	• DRV/c/FTC/TAF is co-formulated as a single-tablet, once-daily regimen.	• Limited existing data suggest insufficient levels of COBI 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)	• Co-formulated 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 birth 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).
Not Recommended for Initial Use in Pregnancy, but May Be Used in Special Circumstances of Substantial Prior ART Experience		

Table 6. What to Start: Initial Antiretroviral Regimens During Pregnancy When Antiretroviral Therapy Has Never Been Received

These drugs are *Not Recommended* for initial use in pregnancy when there has never been prior receipt of ART or antiretroviral (ARV) drugs for prophylaxis (i.e., ARV-naive). 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 of Substantial Prior ART Experience	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)
MVC	• Limited data suggest standard adult dose is appropriate during pregnancy in the special circumstance where MVC is used.	• Not recommended in nonpregnant individuals who are ART-naive • Limited PK, toxicity, and efficacy data during pregnancy • Requires tropism testing before use

Table 6. What to Start: Initial Antiretroviral Regimens During Pregnancy When Antiretroviral Therapy Has Never Been Received

NVP	• Standard adult dosing is appropriate during 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 pregnant people 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; if pregnancy occurs while taking any of these medications, medications should be switched 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 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; H2 blocker = histamine H2-receptor antagonist; 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 During Pregnancy and When Trying to Conceive

Updated: June 12, 2025
Reviewed: June 12, 2025

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	Initiating ART in Pregnancy When ARV Drugs Have Never Previously Been Used	Continuing ART When Pregnancy Occurs on a Fully Suppressive, Well-Tolerated Regimen	Starting or restarting ART During Pregnancy When ARV Drugs Have Been Used in the Past[a]	Switching to a New ART Regimen During Pregnancy When Current Regimen Is Not Well Tolerated and/or Is Not Fully Suppressive	Starting ART When 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[a]	Preferred[a]
BIC[a,e]	Preferred[a,e]	Continue	Preferred[a,e]	Preferred[e]	Preferred[a,e]
RAL	Alternative	Continue	Alternative	Alternative	Alternative
CAB[d] Oral (lead-in) Long-acting (IM)	Not recommended[d]	Continue with frequent viral load monitoring or consider switching due to insufficient data.[d]	Insufficient data[d]	Insufficient data[d]	Insufficient data[d]

Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs During Pregnancy and When Trying to Conceive

ART Regimen Component	Initiating ART in Pregnancy When ARV Drugs Have Never Previously Been Used	Continuing ART When Pregnancy Occurs on a Fully Suppressive, Well-Tolerated Regimen	Starting or restarting ART During Pregnancy When ARV Drugs Have Been Used in the Past[a]	Switching to a New ART Regimen During Pregnancy When Current Regimen Is Not Well Tolerated and/or Is Not Fully Suppressive	Starting ART When Trying to Conceive[b]
EVG/c[f]	Not recommended[f]	Continue with frequent viral load monitoring or consider switching.[f]	Not recommended[f]	Not recommended[f]	Not recommended[f]
Protease Inhibitor (PI) Drugs Used in combination with a dual-NRTI backbone[c]					
ATV/r[g]	Alternative[g]	Continue	Alternative[g]	Alternative[g]	Alternative[g]
DRV/r[a,g]	Alternative[a,g]	Continue	Alternative[a,g]	Alternative[g]	Alternative[a,g]
LPV/r[g]	Not recommended, except in special circumstances[g]	Continue	Not recommended, except in special circumstances[g]	Not recommended, except in special circumstances[g]	Not recommended except in special circumstances[g]
ATV/c[f]	Not recommended[f]	Continue with frequent viral load monitoring or consider switching.[f]	Not recommended[f]	Not recommended[f]	Not recommended[f]
DRV/c[f]	Not recommended[f]	Continue with frequent viral load monitoring or consider switching.[f]	Not recommended[f]	Not recommended[f]	Not recommended[f]

Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs During Pregnancy and When Trying to Conceive

ART Regimen Component	Initiating ART in Pregnancy When ARV Drugs Have Never Previously Been Used	Continuing ART When Pregnancy Occurs on a Fully Suppressive, Well-Tolerated Regimen	Starting or restarting ART During Pregnancy When ARV Drugs Have Been Used in the Past[a]	Switching to a New ART Regimen During Pregnancy When Current Regimen Is Not Well Tolerated and/or Is Not Fully Suppressive	Starting ART When 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[h]	Continue[h]	Alternative[h]	Alternative[h]	Alternative[h]
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[i]	Continue with frequent viral load monitoring or consider switching due to insufficient data.[i]	Insufficient data[i]	Insufficient data[i]	Insufficient data[i]
ETR[j]	Not recommended[j]	Continue[j]	Not recommended, except in special circumstances[j]	Not recommended, except in special circumstances[j]	Not recommended, except in special circumstances[j]
NVP[j]	Not recommended[j]	Continue[j]	Not recommended[j]	Not recommended[j]	Not recommended
NRTI Drugs[c,k]					
FTC	Preferred	Continue	Preferred	Preferred	Preferred
3TC	Preferred	Continue	Preferred	Preferred	Preferred
TDF[c]	Preferred[c]	Continue	Preferred	Preferred	Preferred

Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs During Pregnancy and When Trying to Conceive

ART Regimen Component	Initiating ART in Pregnancy When ARV Drugs Have Never Previously Been Used	Continuing ART When Pregnancy Occurs on a Fully Suppressive, Well-Tolerated Regimen	Starting or restarting ART During Pregnancy When ARV Drugs Have Been Used in the Past[a]	Switching to a New ART Regimen During Pregnancy When Current Regimen Is Not Well Tolerated and/or Is Not Fully Suppressive	Starting ART When Trying to Conceive[b]
TAF[c]	Preferred[c]	Continue	Preferred	Preferred	Preferred
ABC[c,k]	Alternative[c,k]	Continue	Alternative[c,k]	Alternative[c,k]	Alternative[c,k]
ZDV	Alternative	Continue	Alternative	Alternative	Alternative
Entry, Attachment, Fusion, and Capsid Inhibitor Drugs					
FTR[j]	Not recommended	Continue[j]	Not recommended, except in special circumstances[j]	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
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.					
BIC/FTC/TAF[e]	Preferred[e]	Continue	Preferred[e]	Preferred[e]	Preferred[e]

Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs During Pregnancy and When Trying to Conceive

ART Regimen Component	Initiating ART in Pregnancy When ARV Drugs Have Never Previously Been Used	Continuing ART When Pregnancy Occurs on a Fully Suppressive, Well-Tolerated Regimen	Starting or restarting ART During Pregnancy When ARV Drugs Have Been Used in the Past[a]	Switching to a New ART Regimen During Pregnancy When Current Regimen Is Not Well Tolerated and/or Is Not Fully Suppressive	Starting ART When Trying to Conceive[b]
DTG/ABC/3TC[a,c,k]	Alternative (ABC)[a,c,k]	Continue	Alternative (ABC)[a,c,k]	Alternative (ABC)[a,c,k]	Alternative (ABC)[a,c,k]
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)[h]	Continue (RPV)[h]	Alternative (RPV)[h]	Alternative (RPV)[h]	Alternative (RPV)[h]
RPV/TAF/FTC[h]	Alternative[h]	Continue	Alternative[h]	Alternative[h]	Alternative[h]
DOR/3TC/TDF[i]	Insufficient data (DOR)[i]	Continue with frequent viral load monitoring or consider switching due to insufficient data (DOR).	Insufficient data (DOR)[i]	Insufficient data (DOR)[i]	Insufficient data (DOR)[i]
IM CAB and RPV[d] As a complete regimen	Not recommended[d]	Continue with frequent viral load monitoring or consider switching due to insufficient data.[d]	Insufficient data[d]	Insufficient data[d]	Insufficient data[d]
DRV/c/FTC/TAF[f]	Not recommended (DRV/c)[f]	Continue with frequent viral load monitoring or consider switching (DRV/c).[f]	Not recommended (DRV/c)[f]	Not recommended (DRV/c)[f]	Not recommended (DRV/c)[f]
EVG/c/FTC/TDF[f]	Not recommended (EVG/c)[f]	Continue with frequent viral load monitoring or consider switching (EVG/c).[f]	Not recommended (EVG/c)[f]	Not recommended (EVG/c)[f]	Not recommended (EVG/c)[f]
EVG/c/FTC/TAF[f]	Not recommended (EVG/c)[f]	Continue with frequent viral load monitoring or consider switching (EVG/c).[f]	Not recommended (EVG/c)[f]	Not recommended (EVG/c)[f]	Not recommended (EVG/c)[f]

Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs During Pregnancy and When Trying to Conceive

ART Regimen Component	Initiating ART in Pregnancy When ARV Drugs Have Never Previously Been Used	Continuing ART When Pregnancy Occurs on a Fully Suppressive, Well-Tolerated Regimen	Starting or restarting ART During Pregnancy When ARV Drugs Have Been Used in the Past[a]	Switching to a New ART Regimen During Pregnancy When Current Regimen Is Not Well Tolerated and/or Is Not Fully Suppressive	Starting ART When Trying to Conceive[b]
DTG/3TC As a complete regimen[m]	Not recommended[m]	Continue with frequent viral load monitoring.[m]	Not recommended[m]	Not recommended[m]	Not recommended[m]
DTG/RPV As a complete regimen[m]	Not recommended[m]	Continue with frequent viral load monitoring.[m]	Not recommended[m]	Not recommended[m]	Not recommended[m]

[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 if CAB has been taken in the past 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 only when actively trying to conceive in the context of starting ART for the first time or currently receiving ART. For ART recommendations where the possibility exists for unintended pregnancy, please see Adult and Adolescent Antiretroviral Guidelines.

[c] TDF plus FTC, TAF plus FTC, and TDF plus 3TC are *Preferred* dual-NRTI backbones; ZDV plus 3TC and ABC plus 3TC are *Alternative* dual-NRTI backbones for ARV regimens due to more frequent dosing and mild adverse events (ZDV) and the need for HLA-B*5701 testing and concerns over cardiac safety (ABC).

[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, if conception occurs 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 injections monthly or every 2 months, change to an oral regimen should occur within 1 month (+/- 7 days) after the last CAB IM injection or 2 months after the last RPV IM injection. 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] Available data for BIC during pregnancy suggest sufficient PK, efficacy, and safety of this medication to support its use as a *Preferred* agent in those who are pregnant or trying to conceive. No safety concerns have been observed. Drug levels are lower in the second and third trimester of pregnancy 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 protein-adjusted 95% 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 suppression on regimens that include these drugs is present at the time of presentation to prenatal HIV care, 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 Antiretroviral Therapy Use During Prepregnancy and Early Pregnancy. 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 pregnancy when ARV drugs have never previously been used, in special circumstances of substantial prior ART experience, it may be necessary 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 T20 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 NVP-containing regimen is well tolerated and associated with effective viral suppression when pregnancy occurs, it is likely that NVP will be safe and effective during pregnancy. See Table 6. What to Start: Initial Antiretroviral Regimens During Pregnancy When Antiretroviral Therapy Has Never Been Received 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 Pregnancy: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy and the drug sections in Appendix B: 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.

[m] Two-drug oral ARV regimens **are not recommended** for initial use in pregnancy because of the lack of available data about use in pregnancy. However, if an oral two drug regimen with DTG/3TC or DTG/RPV is well tolerated and associated with effective viral suppression when pregnancy occurs, this regimen can be continued with more frequent viral load monitoring (every 1–2 months) throughout pregnancy because the component drugs are recommended for use in pregnancy.

Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs During Pregnancy and When Trying to Conceive

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 pregnancy occurs while taking any of these medications, medications should be switched to a recommended regimen. See Archived Drugs in the Perinatal Guidelines for individual ARV drugs, ARV combinations, and ARV 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 When Antiretroviral Therapy Has Never Been Received 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, prenatal counseling should include that ARV drugs generally do not increase the risk of birth defects during pregnancy (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). • Antiretroviral therapy (ART) should be initiated as early as possible in all pregnancies with HIV (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 before, during, and after pregnancy (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, Introduction to the Selection of Antiretroviral Drugs In Pregnancy, Antiretroviral Therapy When Trying to Conceive, and Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs During Pregnancy and When 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

Reporting to the Antiretroviral Pregnancy Registry about all instances of prenatal exposure to antiretroviral (ARV) drugs (either single-drug exposure or exposure to a combination of ARV drugs) is strongly recommended 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 during pregnancy. 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 ARV exposure during pregnancy depends on multiple factors, including the drug itself, dosage, gestational age at exposure, duration of exposure, interactions with other substances, and, to an unknown extent, genetic factors. 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 during pregnancy or before a planned pregnancy. 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 assessing whether to continue an effective antiretroviral regimen in early pregnancy, the potential risk of viral rebound when switching regimens must be considered alongside known or unknown risks for birth defects associated with the current drug regimen and gestational stage.[1] For additional information, see Antiretroviral Therapy Use During Prepregnancy and Early Pregnancy.

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 women, 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
• Given the clear and proven benefits of HIV treatment in pregnancy, antiretroviral therapy (ART) should not be withheld due to concern for possible associations with adverse neonatal and pregnancy outcomes (AII). • ART use should not be avoided or withheld before conception or in early pregnancy for the purpose of preventing preterm birth (AII). • ART should not be avoided or withheld to prevent hypertensive disorders of pregnancy (HDP) or stopped if HDP develop (AIII). • Enhanced antenatal surveillance of fetal growth in the third trimester may be considered for pregnancy in the setting of HIV, especially those who are prescribed ART with boosted protease inhibitors, due to the increased risk for low birth weight or small-for-gestational-age infants (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*

In this section, the Panel on Treatment of HIV During Pregnancy and Prevention of Perinatal Transmission (the Panel) provides a summary of data published in the preceding 10 years on antiretroviral therapy (ART) and adverse pregnancy outcomes. Regardless of antiretroviral (ARV) drug use, there may be increased risk for adverse neonatal outcomes for pregnancy with HIV. 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 between ≥20 weeks and ≥28 weeks. Limited data suggest a potential association between HIV infection and hypertensive disorders of pregnancy (HDP) (i.e., chronic hypertension, gestational hypertension, preeclampsia, and eclampsia). As a result of variable study periods, 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 Pregnancy: 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). Pregnancies impacted by HIV during which ART is not used are not an appropriate comparator for pregnancies during which ART is used because of an increased risk of adverse outcomes due to immunocompromised status. Comparing ART use during pregnancy to pregnancies that are not impacted by HIV is confounded by HIV status. In the setting of limited data, the Panel may reference studies with these comparators.

Some evidence suggests that the risk of adverse outcomes varies by ARV drug—even within ARV drug classes—and 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. Studies evaluating the safety of newer ART, specifically integrase strand transfer inhibitors (INSTIs), on pregnancy outcomes are reassuring.[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, and most have not demonstrated a significant association between ARV 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 were observational studies, and most were older studies that do not include ARV drugs currently used.[2-7] A large meta-analysis of 61 observational studies (n = 409,781) compared the risk of PTB in ART-naive women and women with HIV who were prescribed zidovudine (ZDV) single-drug therapy or ART. Although the risk of any PTB in women with HIV who were prescribed ART compared with ART-naive women with HIV was not significantly different, women who were prescribed ART were less likely to experience spontaneous PTB (relative risk 0.46; 95% confidence interval [CI], 0.32–0.67).[5] Another meta-analysis compared pregnancy outcomes between women with HIV 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]

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 comprehensively controlled for all factors that may be associated with PTB. An 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. Women with HIV on any ART were less likely than women with HIV not on ART 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 nor first-trimester ARV use was associated with PTB.[20]

Antiretroviral Therapy and Preterm Birth

Integrase Strand Transfer Inhibitor–Based Regimens

INSTIs are a preferred class of ARV drug for HIV treatment in pregnancy. Compared to other ARV drug classes, INSTI use does not appear to be associated with an increased risk of PTB. In the VESTED International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) randomized controlled trial (RCT) comparing pregnant participants receiving efavirenz (EFV)/TDF/emtricitabine (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.[21]

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.[16] Very limited data suggest no association between the use of long-acting injectable cabotegravir in combination with rilpivirine during pregnancy and PTB.[22] However, this dataset was too small to make definitive conclusions regarding adverse neonatal and pregnancy outcomes. In conclusion, INSTI use in pregnancy has not been associated with an increased risk of PTB compared to other ARVs.

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

Data regarding an association between NRTI and non-nucleoside reverse transcriptase inhibitor (NNRTI)–based ART and PTB are inconclusive. 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 (relative risk 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, but there are conflicting reports.[23]

Protease Inhibitor–Based Regimens

The association between the use of protease inhibitor (PI)–based ART and PTB has been investigated in multiple studies across Europe, North America, and Africa.[8,10,12,13,15,24-28] Not all the studies reviewed for this section have identified an association between PI use and an increased risk of PTB.[10,20,24,29,30]

A meta-analysis of 10 studies (8 prospective cohort studies, 1 RCT, and 1 surveillance study) demonstrated that the use of PI-based ART is associated with an increased risk of PTB, with an adjusted odds ratio 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.[31] A network meta-analysis of seven 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/ritonavir (LPV/r) had an increased risk of spontaneous PTB (n = 991; relative risk 1.81; 95% CI, 1.21–2.71).[26] 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-based ART.[32] 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 (relative risk 1.33; 95% CI, 1.03–1.72; I^2=0%; four studies; n = 1,937 women). Compared with women prescribed non-boosted PI-based ART, women prescribed boosted PIs were more likely to experience PTB (relative risk 1.36; 95% CI, 1.12–1.65; I^2=0%; five studies; n = 3,333).[32] These authors performed a subsequent systematic review and meta-analysis of 18 studies (n = 32,883) and reported that PI-based ART was not more likely to be associated with PTB when compared to NNRTI-based ART (relative risk 1.08; 95% CI, 0.93–1.25). In a subanalysis of these data, LPV/r-based ART was associated with an increased risk of PTB before 32 weeks of gestation compared to EFV (relative risk 1.66; 95% CI, 1.1–2.5).[7]

ART that includes PIs boosted with ritonavir may be associated with an increased risk of PTB compared with non-boosted PI regimens.[33] Despite this potential association between the use of PI-based ART and PTB, PI-based regimens may be required during some pregnancies. In these cases, the Panel recommends the use of darunavir/ritonavir over LPV/r.[34]

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 (relative risk 1.16; 95% CI, 1.03–1.31; I^2 = 81%).[6] Additional studies have described an association between initiating ART before pregnancy and an increased risk of PTB.[13-15,18,23,27,28,35,36] These studies were conducted in Asia, Europe, Latin America, Africa, and North America and included various ART regimens (including no ART and single-drug, two-drug, and multidrug regimens). The association between PTB and ARV drug use prior to conception is attenuated in some multivariate analyses.[9,13,27,37-39] 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 birth LBW infants than women with HIV not on ART.[5] A secondary analysis of the MOTIVATE study reported that women prescribed ART before conception and after conception birthed a similar percentage of LBW infants (3.3% and 4.4%, respectively).[39] Although multiple observational studies have reported associations between ARV drug exposure and LBW, these studies are heterogeneous in population, design, and comparison groups.[3,9,11,13,14,16,24,25,28,30,37,40-45] 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 born to women with HIV may be at risk for SGA.[9,11,14-17,21,23,29,30,37,44,46,47] In a meta-analysis of five studies (n = 6,818), women prescribed ART were more likely to birth SGA infants than women with HIV not on ART (relative risk 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 birth SGA infants than women with HIV prescribed non-PI ART (relative risk 1.24; 95% CI, 1.08–1.43; I^2 = 67%; 11 studies; n = 25,893).[32] A subsequent meta-analysis of 11 studies (n = 24,255) by these authors reported that PI-based ART was associated with SGA when compared to NNRTI-based ART (relative risk 1.28; 95% CI, 1.09–1.51).[7]A systematic review and meta-analysis of 28 studies from 1997 to 2020 reported that PI-based ART was not significantly associated with an increased risk of SGA (pooled odds ratio 1.09; 95% CI, 0.76–1.55).[48] In an RCT, the percentage of SGA infants was similar among women with HIV who were randomized to DTG-based ART (TAF/FTC or TDF/FTC) or EFV-based ART (16%, 23%, and 21%, respectively).[21] In a subsequent analysis of these data, women prescribed DTG/TAF/FTC were more likely to gain weight in accordance with the National Academy of Medicine—formerly the Institute of Medicine—recommendations for pregnancy and were less likely to experience PTB or birth SGA infants.[49] Observational data are mixed regarding an association with SGA infants and ARV exposure.[28,50,51] Data on the risk of SGA in infants exposed to HIV and/or ARVs, even when considering PI-boosted ART, are mixed.

In summary, data are mixed regarding the effect of ARV drug use on birth weight. Given the potential for LBW or SGA infants, especially in cases where ART was initiated preconception, providers may consider additional monitoring for fetal growth abnormalities during pregnancy.

Stillbirth

Stillbirth is a relatively rare outcome in resource-rich settings, and data related to stillbirth and ARV drug use are limited. In a meta-analysis of 17 studies that included 37,877 women with HIV who were on ART, 3 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 relative risk 0.6; 95% CI, 0.43–0.84; I^2 = 72%).[2] In another meta-analysis evaluating the difference in stillbirth between PI-based and non-PI-based ART, data from a single study (n = 6,952) reported that PI-based ART was not associated with an increased risk of stillbirth (relative risk 1.04; 95% CI, 0.06–1.79).[32] 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%).[21]

Some studies have reported an association between HIV infection and stillbirth,[9,16,24,28,35,36,40,42,44,52,53] and other studies do not report an association.[54] 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.[53]

Outcomes During Pregnancy

Hypertensive Disorders of Pregnancy

Limited data suggest that women with HIV may have an increased risk of HDP. A single meta-analysis did not reveal a clear association between HIV and HDP.[55] Observational data evaluating an

association with HDP and HIV infection, ART use during pregnancy, and timing of ART initiation reported conflicting findings.[56]

Two observational studies have reported a potential association between INSTIs and HDP.[57] Pregestational diabetes has been associated with an increased risk of HDP in two observational studies of women with HIV who were prescribed INSTIs.[58] Although these limited data may suggest an association between HDP and HIV, no known interventions reduce this risk of developing HDP. Providers should not withhold ART in the setting of HDP. Low-dose aspirin to prevent or delay the onset of HDP may be of benefit during some pregnancies with HIV. For more information, please refer to U.S. Preventive Services Task Force recommendations.[59]

Summary

Given that ART has clear benefits for health during pregnancy and reduces the risk of perinatal HIV transmission, ART or specific ARVs should not be withheld due to concern for increased risk of adverse outcomes. Clinicians should monitor for potential pregnancy complications, including PTB, LBW and SGA infants, and HDP.

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Special Populations: Hepatitis B Virus/HIV Coinfection

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Reviewed: January 31, 2024

Panel's Recommendations
Screening for HBV infection should be performed during each pregnancy impacted with HIV unless HBV/HIV coinfection has been confirmed or HBV immunity has been documented via serologic testing (AIII). A negative screening for HBV infection and lack of HBV immunity (i.e., HBV surface antigen negative, HBV core antibody negative, and HBV surface antibody negative) warrants administration of the HBV vaccine series (AII). • In the context of chronic HBV infection during pregnancy, if the hepatitis A virus (HAV) vaccine series has not been previously administered, screening for immunity to HAV infection should occur. 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, treatment of HBV/HIV coinfection with antiretroviral regimens that include drugs with anti-HBV activity (tenofovir disoproxil fumarate or tenofovir alafenamide plus lamivudine or emtricitabine) should be continued (AII). • Counseling about signs and symptoms of liver toxicity should be given when ART is administered during pregnancy with HBV/HIV coinfection, and liver transaminases should be assessed 1 month after initiating ART and at least every 3 months thereafter during pregnancy (BIII). • If medications with anti-HBV activity are discontinued during pregnancy with HBV/HIV coinfection, 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 with perinatal HBV exposure 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. Screening for HBV should be performed during each pregnancy impacted with HIV unless HBV/HIV coinfection has been confirmed or HBV immunity has been documented via serologic testing. 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.

A negative screening for HBV (i.e., HBsAg negative, anti-HBc negative, and anti-HBs negative) or a lack of HBV immunity (i.e., anti-HBs negative) warrants prompt administration of 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] During pregnancy with HBV/HIV coinfection, assessment of anti-HBs titers 1 to 2 months after the vaccine series and management of nonresponders should be conducted the same way as recommended for others with HBV/HIV 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 other adults with HIV 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 other adults with HIV and 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 HBV viremia is identified during pregnancy with isolated anti-HBc, ART should be adjusted to assure control of both HBV and HIV. Isolated anti-HBc and occult HBV infection are typically associated with very low levels of HBV DNA and therefore extremely low risk of transmitting HBV perinatally.[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]

During pregnancy, screening for HAV using antibody testing for immunoglobulin G (IgG) should be carried out in those with HBV infection who have not already received the hepatitis A virus (HAV) vaccine series (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. The HAV vaccine series should be administered during pregnancy to those have not already received the HAV vaccine series and are not immune to HAV. 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. HAV revaccination during pregnancy is not needed if the original HAV vaccine series was administered at CD4 counts ≥200 cells/mm^3, as protection against HAV has likely been conferred (even if 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 during pregnancy (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 in the context of HBV mono-infection lowers HBV viremia and lowers the risk of HBV transmission to the infant. For HBV/HIV coinfection during pregnancy, an ART regimen that includes tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF), and either lamivudine (3TC) or emtricitabine (FTC), should be administered 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]

When providing care during pregnancy with HBV/HIV coinfection, consultation with an expert in HIV and HBV is strongly recommended for those 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 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 during pregnancy with HBV/HIV coinfection—particularly in 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. Counseling about signs and symptoms of liver toxicity should be given when ART is administered during pregnancy with HBV/HIV coinfection, 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 at risk of perinatal HBV/HIV acquisition 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 at risk of perinatal HBV acquisition, including 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
• Hepatitis C virus (HCV) screening should be performed during each pregnancy, 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 may be repeated later in pregnancy if the initial test is negative but persistent or new risk factors for HCV are identified (e.g., new or ongoing injection or intranasal substance use) (AIII). • For those known to be HCV antibody-positive, HCV RNA and liver function tests should be checked at the beginning of prenatal care to determine the risk of perinatal transmission and the severity of liver disease (AIII). • Hepatitis B surface antigen testing is advised during each pregnancy, ideally in the first trimester, including for HIV/HCV coinfection cases. If results are negative and there is no immunity, the hepatitis B virus vaccine series should be initiated (see Hepatitis B Virus/HIV Coinfection) (AIII). • For pregnancies with HCV infection where the hepatitis A virus (HAV) vaccine series has not been received, HAV immunity should be assessed (AIII). If testing is negative for HAV antibodies (either immunoglobulin G [IgG] or total antibody [IgG and immunoglobulin M]), the HAV vaccine series should be provided (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 during pregnancy. If considering initiating HCV treatment during a pregnancy with HCV/HIV coinfection, consultation with an expert in HIV and HCV is strongly recommended (AIII). • Recommendations for antiretroviral therapy (ART) are the same for all pregnancies with HIV, including in the context of HCV coinfection (AIII). • For pregnancies with HCV/HIV coinfection and ART use, counseling on the signs and symptoms of liver toxicity should be provided, and hepatic transaminases should be assessed 1 month after initiating ART and at least every 3 months during pregnancy (BIII). • Postpartum HCV treatment with direct-acting antiviral agents should be recommended and offered (AI). • Post-delivery evaluation of HCV RNA is advised for HCV infection to check for spontaneous clearance, particularly if initiation of postpartum HCV therapy is under consideration (BII). • HCV/HIV coinfection is not an independent indication for cesarean delivery (see Intrapartum HIV Care) (AIII). • Infants exposed to HCV/HIV coinfection during pregnancy or delivery 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 pregnancy; 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

HCV screening should be performed at entry into general HIV care and during each pregnancy, ideally at initiation of prenatal care. For those known to be HCV antibody–positive, HCV RNA and liver function tests should be checked at the beginning of prenatal care to assess risk of perinatal transmission of HCV and the 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 HCV/HIV coinfection during pregnancy while engaged with the health care system so that HCV treatment can be offered postpartum, 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 when initial screening is negative but ongoing or new risk factors for HCV are identified (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).

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 during pregnancy, 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 during pregnancy. In the United States, HCV screening should occur in 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. HCV RNA testing is recommended during pregnancy when serologic results for HCV are indeterminate or negative, but elevated aminotransaminase levels or risk behaviors, such as a history of injection drug use, suggest potential infection.[23] At the initial prenatal visit, quantitative plasma HCV RNA testing and liver function assessments are recommended when HCV antibody positivity is confirmed 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. During pregnancy, individuals with chronic HCV typically have favorable outcomes as long as decompensated cirrhosis has not developed.[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 the context of HCV/HIV coinfection during pregnancy 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 HCV/HIV coinfection in pregnancy. 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 HIV Care). 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]

In the context of HCV/HIV coinfection, HCV treatment with DAAs should be initiated 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.

HCV/HIV Coinfection Monitoring 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 in the context of HCV/HIV coinfection than 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 in the context of 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—in the context of pregnancy with HCV infection—no obstetric guidelines currently suggest more frequent monitoring 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 pregnancies with HCV/HIV coinfection as for those with HIV infection alone (see Intrapartum HIV Care).

Evaluation of Infants Exposed to HCV

Infants exposed to HCV/HIV coinfection during pregnancy or delivery 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, see Preventing HIV Transmission During Infant Feeding

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HIV-2 and Pregnancy

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Panel's Recommendations
• HIV-2 infection should be considered in pregnancy when the virus is endemic in the country of origin or the partner's country of origin (AII). • When pregnant or trying to conceive with HIV-2 infection, treatment should be based on the guidelines for HIV-1 infection but using antiretroviral (ARV) drugs that are active against HIV-2 (AIII). • ARV regimens for use during pregnancy (and when trying to conceive) with HIV-2 mono-infection or HIV-1/HIV-2 coinfection should include an integrase strand transfer inhibitor (INSTI) recommended for use in pregnancy (bictegravir or dolutegravir) plus two nucleoside reverse transcriptase inhibitors (NRTIs) (AII). A recommended alternative regimen is ritonavir-boosted darunavir plus two NRTIs (BII). See Recommended Antiretroviral Therapy for Treating HIV-2 Infection During Pregnancy below and Recommendations for the Use of Antiretroviral Drugs During Pregnancy: Overview. • During pregnancy (and when trying to conceive) with HIV-2 mono-infection or HIV-1/HIV-2 coinfection, immediate antiretroviral therapy (ART) is recommended (AII). • If ART is already being used during pregnancy with drugs that are active against HIV-2, treatment should be continued (AIII). • As with HIV-1, the possibility of hepatitis B virus coinfection should be considered when choosing an ARV regimen to treat HIV-2 (AI) (see Hepatitis B Virus/HIV Coinfection). • HIV-2 RNA, CD4 T lymphocyte (CD4) cell counts, and clinical status should be monitored for response to treatment (AII). In the context of HIV-2, regular CD4 testing should be continued even with below detectable HIV RNA levels (viral load) because disease progression can occur even with undetectable viral load (AIII). However, monitoring HIV-2 plasma viral loads in pregnancy 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. • HIV-2 resistance may occur with INSTIs, NRTIs, or protease inhibitors. However, no validated HIV-2 genotypic or phenotypic resistance assays are approved for clinical use. • During pregnancy and when trying to conceive with virologic or immunologic failure, a new ART regimen should be considered in consultation with an HIV expert. For multidrug-resistant virus, ibalizumab and lenacapavir demonstrate *in vitro* activity against HIV-2 but are not recommended except in special circumstances due to insufficient efficacy, pharmacokinetic, and safety data in pregnancy. Shared decision-making should be used when selecting a new ART regimen. • ARV management of infants perinatally exposed to HIV-2 mono-infection or HIV-1/HIV-2 coinfection should follow recommendations for infants perinatally exposed to HIV-1 infection (see Antiretroviral Management of Infants With *In Utero*, Intrapartum, or Breastfeeding Exposure to HIV, Table 11, and Table 12) using drugs that are active against HIV-2 (AIII) (see Care of Infants With *In Utero*, Intrapartum, or Breastfeeding Exposure to HIV-2 below). Nevirapine (NVP) should not be used because it lacks activity against HIV-2. In the context of HIV-2, the same patient-centered, evidence-based counseling should be provided according to the guidance for HIV-1 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 Preventing HIV Transmission During Infant Feeding). • For infants perinatally exposed to HIV-2 infection, ARV prophylaxis during breastfeeding should follow recommendations for infants perinatally exposed to HIV-1 infection (see Antiretroviral Prophylaxis for Breastfeeding Infants in Antiretroviral Management of Infants With *In Utero*, Intrapartum, or Breastfeeding Exposure to HIV, Table 12, and Table 12.1). If extended ARV prophylaxis is used, infants should receive lamivudine since NVP lacks activity against HIV-2 (CIII).

- If maternal HIV-2 infection is suspected or confirmed, infant diagnostic testing for HIV-2 can follow the same schedule as for infants perinatally exposed to HIV-1 using virologic assays to diagnose HIV-2 infection. See Diagnosis of HIV Infection in Infants and Children and Table 13. Recommended Virologic Testing Schedules for Infants With Perinatal and Breastfeeding Exposure to HIV for guidance about infant testing.

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. HIV-2 is also endemic in Angola, Mozambique, and parts of India.[1]

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 mono-infection, n = 102; dual HIV-1 and HIV-2, n = 11; probable but unconfirmed HIV-2, n = 85).[2] 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 pregnancy when the disease is endemic in the country of origin or the partner's country of origin.

Using the currently recommended HIV testing algorithm,[3] people with HIV-2 infection will have positive results on a standard HIV-1/HIV-2 antibody or HIV-1/HIV-2 antigen/antibody immunoassay, which will prompt testing with a supplemental HIV-1/HIV-2 antibody differentiation immunoassay. Individuals with HIV-2 mono-infection will test negative for HIV-1 antibodies and positive for HIV-2 antibodies, whereas both tests will be positive for individuals with HIV-1/HIV-2 coinfection.

The first step in the Centers for Disease Control and Prevention (CDC) HIV testing 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).[3,4] 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[5] and the New York State Department of Health Wadsworth Center[6] 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.[7] 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 a French resistance tool.[8,9]

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.[10] The most common mode of HIV-2 transmission is through sex. HIV-2 infection does not protect against HIV-1, and dual infection—which carries the same prognosis as HIV-1 mono-infection—can occur.[11] HIV-2 is less infectious than HIV-1, with a fivefold lower rate of sexual transmission and a 20-fold to 30-fold lower rate of perinatal transmission.[12-14]

Several studies confirm that rates of HIV-2 perinatal transmission 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. In a systematic review and 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.[15] The review found that the perinatal transmission rate of HIV-2 is influenced by higher viral load and lower CD4 count of the mother. In general, mothers with HIV-2 had lower viral loads and higher CD4 counts than those with HIV-1. HIV-2 can also be transmitted through breastfeeding.[16]

Recommended Antiretroviral Therapy for Treating HIV-2 Infection During Pregnancy

Pregnancy with HIV-2 infection should be treated according to the guidelines for HIV-1 mono-infection, 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 HIV-1. The integrase strand transfer inhibitors (INSTIs) raltegravir (RAL), elvitegravir, dolutegravir (DTG), bictegravir (BIC), and cabotegravir (CAB) are effective against HIV-2.[17,18] HIV-2 has variable susceptibility to protease inhibitors (PIs), with lopinavir (LPV) and darunavir having the most activity.

Pregnancy care with HIV-2 infection alone has been based on expert opinion and extrapolation from both HIV-1 treatment and treatment of HIV-2 in nonpregnant adults.[19] An ART regimen containing two nucleoside reverse transcriptase inhibitors (NRTIs) and a *Preferred* INSTI (i.e., DTG or BIC) is currently recommended for use in pregnancy; a regimen of two NRTIs and ritonavir-boosted darunavir (DRV/r) is recommended as an *Alternative*. See Recommendations for the Use of Antiretroviral Drugs During Pregnancy: Overview, Table 6. What to Start: Initial Antiretroviral Regimens During Pregnancy When Antiretroviral Therapy Has Never Been Received, Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs During Pregnancy and When Trying to Conceive, and Appendix C: Antiretroviral Counseling Guide for Health Care Providers.

The following regimens can be used to treat HIV-2, based on the available efficacy and safety data on the use of these drugs during pregnancy from clinical trials in the setting of HIV-1 infection:

- BIC or DTG (with two NRTIs) are *Preferred* regimens for HIV-2 when pregnant or trying to conceive as well as in the context of HIV-1. RAL (with two NRTIs) is an *Alternative* INSTI regimen for treating HIV-2 as well as HIV-1. See Table 6 and Table 7.
- DRV/r (with two NRTIs) is an *Alternative*, PI-based regimen in the context of HIV-2 when pregnant or trying to conceive as well as in the context of HIV-1. Ritonavir-boosted lopinavir (with two NRTIs) is active against HIV-2 and can be used in special circumstances for treating HIV-2 as well as HIV-1. See Table 6 and Table 7.

- *Preferred* NRTIs recommended as part of a full ART regimen for HIV-2 when pregnant or trying to conceive are the same as those recommended for treatment of HIV-1 during pregnancy: tenofovir disoproxil fumarate or tenofovir alafenamide plus emtricitabine (FTC) or lamivudine (3TC). Abacavir (ABC) plus 3TC or FTC is an *Alternative* NRTI backbone for use during pregnancy or when trying to conceive. See Table 6 and Table 7 for considerations on the use of ABC. Zidovudine (ZDV) plus 3TC can be used as an *Alternative* dual-NRTI backbone.
- If ART is already being used during pregnancy with drugs that are active against HIV-2, treatment should be continued.
- ART regimens containing non-nucleoside reverse transcriptase inhibitors (including long-acting injectable rilpivirine given with the INSTI CAB), enfuvirtide, and fostemsavir are not recommended and **should not be used** because they are not active against HIV-2 (see HIV-2 Infection in the Adults and Adolescent Antiretroviral Guidelines).

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.[20] 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.[21,22] HIV-2 drug resistance has been documented with various ARV drugs.[23,24] 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 NRTIs of 7.9% (95% CI, 0.0% to 16.5%). No RAM above the 20% detection threshold was found for PIs or INSTIs.[25] For multidrug-resistant virus, ibalizumab[26] and Lenacapavir[27] demonstrate *in vitro* potency against HIV-2 and may be considered; these drugs are not recommended except in special circumstances for use in pregnancy.

When monitoring the plasma viral loads and CD4 counts during pregnancy with HIV-2 infection, clinicians should follow the guidelines outlined for HIV-1 infection (see Initial Evaluation and Continued Monitoring of HIV During Pregnancy). However, disease progression can occur in the setting of undetectable HIV-2 plasma viral load. When HIV-2 plasma viral loads are below the limits of detection, routine CD4 counts and clinical monitoring should still be performed (see Plasma HIV-1 RNA [Viral Load] and CD4 Count Monitoring in the Adult and Adolescent Antiretroviral Guidelines).

No data exist on the impact of scheduled cesarean delivery on HIV-2 perinatal transmission. No evidence supports a recommendation to schedule cesarean delivery for the purpose of reducing HIV-2 perinatal transmission. In addition, data are not available to address whether treatment should be continued after pregnancy with HIV-2 mono-infection. 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 HIV-2 infection should be treated using the guidelines provided for HIV-1 infection (see HIV-2 Infection).

Care of Infants With *In Utero*, Intrapartum, and Breastfeeding Exposure to HIV-2

As noted above, rates of perinatal (*in utero* and intrapartum) transmission of HIV-2 are low with and without interventions, and it is unclear whether infants perinatally exposed to undetectable HIV-2 viral loads will benefit from ARV prophylaxis.[19] However, monitoring HIV-2 plasma viral loads in pregnancy 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 in Pregnancy and Prevention of Perinatal Transmission (the Panel) recommends that all infants perinatally exposed to HIV-2 mono-infection or HIV-1/HIV-2 coinfection receive ARV prophylaxis following recommendations for infants perinatally exposed to HIV-1 infection (see Antiretroviral Management of Infants With *In Utero*, Intrapartum, or Breastfeeding Exposure to HIV, Table 11, and Table 12) using drugs that are active against HIV-2 as summarized below. The Panel recognizes that data about *in utero* and intrapartum transmission risk according to maternal HIV-2 RNA levels and receipt of infant ARV prophylaxis are limited, and there may be fewer viral load test results in instances of HIV-2 mono-infection during pregnancy than for HIV-1 during pregnancy. Therefore, maternal receipt of and adherence to an ART regimen that is active against HIV-2 and the lower risk of perinatal transmission of HIV-2 infection are factors to consider when making decisions about the use of ZDV prophylaxis alone or a three-drug presumptive HIV therapy regimen for infants perinatally exposed to HIV-2 mono-infection.

- Infants at low risk of *in utero* and intrapartum HIV acquisition, defined as perinatal exposure to HIV-2 (and HIV-1) RNA levels <50 copies/mL from 20 weeks of gestation through delivery, should receive ZDV alone for 2 weeks.
- Infants at high risk of HIV infection from *in utero* or intrapartum exposure, defined as perinatal exposure to viremia (HIV-2 and/or HIV-1 RNA levels ≥50 copies/mL) in the 4 weeks prior to delivery, should be provided a three-drug ARV regimen administered from birth for 2 weeks to 6 weeks that serves as presumptive HIV therapy or enhanced prophylaxis. Infants with exposure to HIV-2 should receive a regimen of RAL plus ZDV plus 3TC; nevirapine (NVP) should not be used because it lacks activity against HIV-2. If the duration of the three-drug regimen is shorter than 6 weeks, ZDV should be continued alone to complete a total of 6 weeks of prophylaxis.
- Infants not meeting criteria for high or low risk should receive ARV regimens and durations based on case-specific factors related to the level and timing of viremia during the pregnancy (i.e., 2 to 6 weeks of ZDV prophylaxis **or** a three-ARV presumptive HIV therapy regimen of ZDV plus 3TC plus RAL). See Table 11 in Antiretroviral Management of Infants With *In Utero*, Intrapartum, or Breastfeeding Exposure to HIV. Examples of case-specific factors can include viremia in the first 20 weeks of pregnancy, diagnosis of HIV at delivery or immediately postpartum, etc.

In the context of HIV, patient-centered, evidence-based counseling should be provided during all pregnancies to support shared decision-making about infant feeding. The risk of infant HIV-2 infection from breastfeeding is lower for HIV-2 than for HIV-1, but the risk is not zero.[16] 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 Preventing HIV Transmission During Infant Feeding). For infants perinatally exposed to HIV-2 infection, ARV prophylaxis during breastfeeding should follow recommendations for infants perinatally exposed to HIV-1 infection (see Antiretroviral Prophylaxis for Breastfeeding Infants in Antiretroviral Management of Infants With *In Utero*, Intrapartum, or Breastfeeding Exposure to HIV, Table 12, and Table 12.1). If extended ARV prophylaxis is used, infants should receive 3TC since NVP lacks activity against HIV-2.

Infants born to mothers with HIV-2 should be tested for HIV-2 infection with HIV-2-specific virologic assays at the same time points as those used for HIV-1 testing; see Diagnosis of HIV Infection in Infants and Children and Table 13. Recommended Virologic Testing Schedules for Infants With Perinatal and Breastfeeding Exposure to HIV.[28] Quantitative HIV-2 plasma RNA viral load testing for clinical care is available from the University of Washington[5] and the New York State

Department of Health.[6] Antibody testing of infants (e.g., with the Bio-Rad Laboratories Multispot HIV-1/HIV-2 test) can also be performed after age 18 months to confirm clearance of HIV-2 antibodies if infant HIV-2 nucleic acid testing has been incomplete.

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Prenatal Care, Antiretroviral Therapy, and HIV Management When HIV Was Perinatally Acquired

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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 perinatally acquired HIV (PHIV) or non-perinatally acquired HIV during pregnancy (AII). • PHIV is often associated with extensive ART experience, and multidrug antiretroviral (ARV) resistance may be a factor at the onset of pregnancy due to long-term HIV exposure and prior adherence difficulties. 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). • Managing PHIV during pregnancy necessitates 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). Pregnancy with PHIV is becoming more frequent in the United States as childbearing age is reached. 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 pregnancies associated with PHIV and those with non–perinatally acquired HIV (NPHIV), in which HIV was acquired through other routes of transmission. However, the prevention of perinatal transmission in the context of PHIV can pose unique challenges related to lifelong HIV management and the use of 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 with PHIV. 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 During Pregnancy and When 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 pregnancies 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 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 during pregnancy and postpartum.[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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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 during pregnancy when initial HIV test results are negative and there is increased risk of acquiring HIV, including instances when care is received in facilities that have an HIV incidence of ≥1 case per 1,000 women experiencing pregnancy screened per year, the jurisdiction of residence (state or county) has an elevated HIV incidence among females aged 15 to 45 years (>17 per 100,000 females aged 15–45 years), or the state or territory of residence requires 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 Tuberculosis Prevention AtlasPlus webpage. • Antiretroviral therapy (ART) should be initiated as soon as possible after HIV diagnosis (AII). The goals of ART are to suppress HIV RNA to undetectable levels (AI), prevent perinatal and horizontal HIV transmission (AI), and preserve immune function (AIII). • A blood sample for genotypic resistance testing should be sent to the laboratory before initiating ART (AIII). o Standard genotypic drug-resistance testing should be performed for mutations in the reverse transcriptase and protease genes in the setting of early HIV (AIII). o Genotype testing for integrase strand transfer inhibitor (INSTI) resistance should be performed in the following situations: ▪ For those who acquire HIV during or after the use of long-acting cabotegravir (CAB-LA) as pre-exposure prophylaxis (PrEP), *or* ▪ If transmitted INSTI resistance is suspected, *or* ▪ If HIV diagnosis occurs after receiving an INSTI-based regimen for post-exposure prophylaxis (AIII). • ART should be initiated before drug-resistance test results are available. The regimen can be adjusted when results are available to optimize virologic response. In early (acute and recent) HIV infection when there is no history of using CAB-LA as PrEP, one of the following *Preferred* antiretroviral (ARV) regimens are recommended for initial ART[b] (AIII): o Dolutegravir (DTG) with (tenofovir alafenamide fumarate [TAF] or tenofovir disoproxil fumarate [TDF])[c] plus (emtricitabine [FTC] or lamivudine [3TC]), *or* o Bictegravir (BIC)/TAF/FTC In early (acute and recent) HIV infection and a history of CAB-LA use as PrEP, a regimen of ritonavir-boosted darunavir (DRV/r) with (TAF or TDF) plus (FTC or 3TC) is recommended for initial ART (AIII). o Use of an empiric INSTI-containing regimen is not recommended unless genotype testing shows no evidence of INSTI resistance (AIII). This is because INSTI resistance may be present in those who acquire HIV during and possibly after the use of CAB-LA as PrEP. o If baseline drug-resistance tests show no evidence of INSTI resistance, a switch to one of the *Preferred* INSTI-based regimens with DTG or BIC (listed above) should be considered. o See Table 6. What to Start: Initial Antiretroviral Regimens During Pregnancy When Antiretroviral Therapy Has Never Been Received, Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs During Pregnancy and

When 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.

- When early HIV infection is diagnosed during the postpartum period, decisions on HIV drug-resistance testing and ARV regimens should be guided by recommendations outlined in the Early (Acute and Recent) HIV Infection section of the Adult and Adolescent Antiretroviral Guidelines.
- 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 HIV (AIII).
- When ART is initiated, providers should counsel on the importance of strict adherence to rapidly achieve and maintain viral suppression (AIII).
- When HIV is diagnosed during breastfeeding, counseling should be provided about the Panel's recommendation to discontinue breastfeeding immediately to reduce the risk of postnatal HIV transmission to the infant (see Preventing HIV Transmission During Infant Feeding) (AII).
- Infants perinatally exposed to early HIV that was diagnosed during pregnancy or breastfeeding should receive immediate diagnostic testing and an ARV regimen. The ARV regimen will vary based on when parental infection occurred, treatment response, and viral load at delivery (see Table 11. Antiretroviral Management of Infants With *In Utero* or Intrapartum Exposure to HIV and Table 12.1. Antiretroviral Prophylaxis Dosing for Infants Who Are Breastfed in Antiretroviral Management of Infants With *In Utero*, Intrapartum, or Breastfeeding Exposure to HIV and Diagnosis of HIV Infection in Infants and Children) (AII). Consulting a pediatric HIV specialist regarding appropriate infant management is strongly recommended.

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

[b] *Because of the current low rates of transmitted INSTI resistance in the United States, even when there is suspicion that HIV was acquired from a partner with virologic failure while on an INSTI, an INSTI-based regimen can be started while awaiting the results of the INSTI genotype.*

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

Susceptibility to HIV acquisition may be greater during the periconception period, throughout pregnancy, and through 6 months postpartum.[1-3] When there is risk for acquiring HIV during pregnancy and the postpartum period, interventions that prevent HIV acquisition, such as oral daily or long-acting injectable antiretroviral (ARV) formulations for pre-exposure prophylaxis (PrEP) should be considered.[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 During Pregnancy or Breastfeeding

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 have been 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 with acute infection is likely related to the high viral loads in plasma, breast milk, and the genital tract that are present during acute infection.[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 the Early [Acute and Recent] HIV Infection section of the Adult and Adolescent Antiretroviral Guidelines). 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 during pregnancy or breastfeeding when clinical signs and symptoms are compatible with acute infection. Even when high-risk behaviors are not reported, it is still possible that sexual partners are practicing high-risk behaviors privately or it is not understood that such behaviors involve high risk for HIV acquisition. An estimated 40% to 90% of people 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 Pregnancy and Postpartum HIV Testing and Identification of Perinatal and Postnatal 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 pregnancy when there is increased risk of acquiring HIV, including instances when care is received in facilities that have an HIV incidence of ≥1 case per 1,000 women experiencing pregnancy screened per year, the jurisdiction of residence (state and county) has an elevated HIV incidence among females aged 15 to 45 years (>17 per 100,000 females aged 15–45 years), or the state or territory of residence requires 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 Tuberculosis 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 Pregnancy and Postpartum HIV Testing and Identification of Perinatal and Postnatal 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 99% after implementing measures to comply with the state's third-trimester testing mandate.[24]

Antiretroviral Therapy for 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 perinatal HIV transmission.[1,5] Therefore, when there is acute or recent HIV infection during pregnancy, antiretroviral therapy (ART) should be started as soon as possible to rapidly achieve and sustain plasma viral suppression, both for personal health and to prevent perinatal and horizontal HIV 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 among individuals who are ART naive, 6% to 19% have one or more transmitted drug-resistance mutations.[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 ARV 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 ever using long-acting cabotegravir (CAB-LA) as PrEP, if transmitted INSTI resistance is suspected or if HIV diagnosis occurs after receiving an INSTI-based regimen for post-exposure prophylaxis (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 pregnancies with early infection when sexual partners are on INSTI-based ART with unsuppressed or unknown viral loads.

In pregnancies when CAB-LA has never been used prior to diagnosis of acute/recent HIV infection, a regimen that includes dolutegravir (DTG) with tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF) plus emtricitabine (FTC) or lamivudine (3TC), or a regimen of the fixed-dose combination of bictegravir (BIC)/TAF/FTC should be initiated (see Table 6. What to Start: Initial Antiretroviral Regimens During Pregnancy When Antiretroviral Therapy Has Never Been Received, Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs During Pregnancy and When 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 and BIC are associated with high rates of viral suppression, fast rates of viral load decline, and a high genetic barrier to drug resistance. Both DTG plus (TDF or TAF) plus (FTC or 3TC) and the fixed dose combination of BIC/TAF/FTC are recommended ARV regimens for treatment of acute and early infection in nonpregnant adults as well as *Preferred* regimens for treatment during pregnancy. In pregnancies where an INSTI-based regimen cannot be used (e.g., intolerance, potential transmitted resistance), ritonavir-boosted darunavir (DRV/r) plus (TDF or TAF) plus (FTC or 3TC) should be administered. The combination of (TDF or TAF) plus (FTC or

3TC) is a *Preferred* nucleoside reverse transcriptase inhibitor backbone for the treatment of early HIV infection. To avoid delays in initiating therapy, abacavir (ABC) **should not be used** for empiric treatment of acute infection unless the person 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.

For pregnancies 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 DRV/r (administered twice daily during pregnancy) plus (TDF or TAF) plus (FTC or 3TC) should be initiated (see Table 6. What to Start: Initial Antiretroviral Regimens During Pregnancy When Antiretroviral Therapy Has Never Been Received and Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs During Pregnancy and When Trying to Conceive). The regimen can be adjusted once drug-resistance results are available.

Several studies have demonstrated that the use of INSTI-based regimens are associated with a 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 (DTG in pregnant mothers with HIV 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 nucleoside reverse transcriptase inhibitors (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 1.64 [95% confidence interval, 1.3–2.1]; $P < 0.0001$).[32] In the IMPAACT 2010 trial, 643 pregnant women at 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.[31]

When acute or recent HIV is diagnosed postpartum, ART should be started as soon as possible. HIV drug-resistance testing as well as 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 or DTG with (TAF or TDF) plus (FTC or 3TC) for individuals with no prior history of using CAB-LA as PrEP. Boosted DRV with (TAF or TDF) plus (FTC or 3TC) is recommended for individuals with a history of using CAB-LA as PrEP.

Obstetrical and Neonatal Considerations

When early HIV 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 viral load (see Intrapartum HIV Care). Infants perinatally exposed to early HIV that was diagnosed during pregnancy or breastfeeding should receive immediate diagnostic testing and an ARV regimen. The ARV regimen will vary based on when parental infection occurred, treatment response, and viral load at delivery (see Table 11. Antiretroviral Management of Infants With *In Utero* or Intrapartum Exposure to HIV and Table 12.1. Antiretroviral Prophylaxis Dosing for Infants Who Are Breastfed in Antiretroviral Management of Infants With *In Utero*, Intrapartum, or Breastfeeding Exposure to

HIV and Diagnosis of HIV Infection in Infants and Children). Consulting a pediatric HIV specialist regarding appropriate infant management is strongly recommended.

When HIV infection is suspected during breastfeeding, parents should be counseled about the Panel's recommendation to discontinue breastfeeding immediately.[34] Breast milk can be expressed and stored appropriately while HIV diagnostic testing is completed. Expressed breast milk should not be used for infant feeding until all supplemental HIV test results are reviewed and determined to be negative. It is recommended that breastfeeding not be resumed if HIV infection is confirmed (see Situations to Consider Stopping or Modifying Breastfeeding in Preventing HIV Transmission During Infant Feeding). Because of the high risk of postnatal transmission associated with early HIV infection in pregnancy and during breastfeeding, this guidance is more directive than the shared decision-making recommended in the context of suppressive ART.

All HIV diagnoses should prompt a discussion about whether the HIV status of their partners is known. When positive HIV test during pregnancy occurs, HIV testing of the sexual partners should be encouraged, and PrEP should be offered to partners who test negative for HIV.

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Intrapartum HIV Care

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Panel's Recommendations
HIV Testing When Maternal HIV Status is Unknown in Labor • Expedited antigen/antibody HIV testing should be performed when HIV status is unknown during labor and when there is increased risk of HIV infection but retesting was not performed in the third trimester (AII). See Pregnancy and Postpartum HIV Testing and Identification of Perinatal and Postnatal HIV Exposure for more information. o 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). o If acute or recent HIV infection is suspected or if recent HIV exposure has occurred, 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 in the Context of HIV During Pregnancy • See Table 9. Intrapartum Care and Recommended Interventions to Prevent Perinatal HIV Transmission below. • Patients should continue taking their antepartum antiretroviral therapy (ART) on schedule during labor and before scheduled cesarean birth (AIII). • Based on laboratory and clinical information near the time of birth, intrapartum IV ZDV should be administered in the following situations if— o HIV RNA >1,000 copies/mL, o Unknown HIV RNA, o Known or suspected lack of adherence since the last HIV RNA result, *or* o 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 birth (AII). • When HIV RNA is >1,000 copies/mL or is unknown near the time of birth, scheduled cesarean birth at 38 weeks gestation is recommended to minimize perinatal HIV transmission, irrespective of administration of antepartum ART (AII). Given the potential for rapid decreases in viral load with current ART options, individualized birth plans to extend these pregnancies beyond 38 weeks to avoid the need for a cesarean birth can be considered with expert consultation and shared decision-making. Expert guidance from the National Perinatal HIV/AIDS Clinical Consultation Center (1-888-448-8765) may be helpful when choosing to develop an individualized birth plan. o Management of patients originally scheduled for cesarean birth 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 birth 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 [1-888-448-8765]) may be helpful for rapidly developing an individualized birth plan. When ART is used and HIV RNA levels are ≤1,000 copies/mL near the time of birth (within 4 weeks of birth): o IV ZDV **is not required** when ALL of the following criteria are met: (1) ART is being taken, (2) HIV RNA levels are <50 copies/mL within 4 weeks of birth, and (3) adherence to the ARV regimen is achieved (BII).

- IV ZDV may be considered when HIV RNA levels are ≥50 copies/mL and ≤1,000 copies/mL within 4 weeks of birth (BII). Data are insufficient to determine whether administration of IV ZDV when HIV RNA levels are 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 birth performed solely for prevention of perinatal HIV transmission in those receiving ART with HIV RNA ≤1,000 copies/mL near the time of birth is not recommended (AII).
- When HIV RNA levels are ≤1,000 copies/mL during pregnancy, if scheduled cesarean birth 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.
- When ART is being taken and HIV RNA levels are ≤1,000 copies/mL during pregnancy, longer duration of ruptured membranes is not associated with an increased risk of perinatal transmission and is not an indication for cesarean birth to prevent HIV transmission (BII).

Other Intrapartum Management Considerations (See Table 9 Below)

- Fetal scalp electrodes should be avoided in pregnancies impacted by HIV when viral suppression is achieved and should not be used in pregnancies when viral suppression (≥50 copies/mL) is not achieved (BIII).
- Artificial rupture of membranes and operative vaginal birth 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 HIV Care During Intrapartum

Specialized HIV care during labor and birth is required to optimize health outcomes and to prevent perinatal HIV transmission. Documentation of HIV status should always be assessed during labor, and HIV testing should be offered when HIV status is unknown or undocumented, there has been recent HIV exposure, and/or there are 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 birth), to inform decisions about intrapartum care. The risk of perinatal HIV transmission is reduced to very low levels (1% or less) when antiretroviral therapy (ART) is being taken during pregnancy and documented viral suppression (<50 copies/mL) is achieved near birth.[1-3] The Panel's recommendations about

intrapartum care to prevent HIV transmission are based on maternal HIV RNA levels and encompass continuation of ART during pregnancy, intrapartum intravenous (IV) zidovudine (ZDV) during labor and birth, scheduled cesarean birth, and other intrapartum management considerations. Table 9 provides an overview of the Panel's recommendations for intrapartum care based on maternal HIV RNA. These recommendations are discussed in the following sections.

Presenting in Labor Without Documentation of HIV Status

All instances where documentation of HIV status is lacking at the time of labor should prompt screening for HIV with expedited testing unless declined (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 acquisition and were not retested in the third trimester.[4,5] Factors that may increase the risk of HIV acquisition include having a sexually transmitted 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 acquisition 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 Preventing HIV Transmission During Infant Feeding). For additional information, see Postpartum HIV Management and Follow-Up, Antiretroviral Management of Infants With *In Utero*, Intrapartum, or Breastfeeding Exposure to HIV, and Table 11.1. Drug Dosing Recommendations for Antiretroviral Prophylaxis and Presumptive HIV Therapy in Infants With *In Utero* or Intrapartum Exposure to HIV. 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 birth, please see the HIV Testing During Labor When HIV Status is Unknown 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 pregnancies impacted by HIV, regardless of CD4 T lymphocyte cell count and HIV RNA (viral load). Antepartum antiretroviral (ARV) regimens should be continued on schedule during the intrapartum period to maintain virologic suppression and to minimize the chance of developing drug resistance. When cesarean birth 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 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 maternal blood and body fluids. Although the PACTG 076 ZDV regimen included a continuous IV infusion of ZDV during labor for all women, decisions regarding the use of IV ZDV during labor are now based on the maternal HIV RNA level and adherence considerations (see Table 9). IV ZDV also is recommended when an initial diagnosis of HIV is determined during labor and when HIV is confirmed but HIV RNA level is unknown during pregnancy.

Intrapartum IV ZDV reduces perinatal HIV transmission when HIV RNA levels are >1,000 copies/mL and ART is being taken, but the benefits when HIV RNA levels are ≤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 birth, transmission rates did not differ significantly between those who received IV ZDV (0.6%, 47 of 8,132 infants) and those who did not (0 of 369 infants, $P > 0.20$).

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

Based on available data, the Panel recommends that IV ZDV continue to be administered during pregnancy when HIV RNA levels are >1,000 copies/mL within 4 weeks of birth (or when HIV is confirmed but HIV RNA levels are unknown within 4 weeks of birth), regardless of their antepartum ARV regimen. Administration of intrapartum IV ZDV may be considered when HIV RNA levels are ≥50 copies/mL and ≤1,000 copies/mL or when there are concerns about adherence to or tolerance of 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. Some experts think the data are insufficient to determine whether administration of intrapartum IV ZDV during pregnancy when HIV RNA levels are between 50 and 1,000 copies/mL provides any additional protection against perinatal transmission. However, based on studies of women initiated therapy in the third trimester, the transmission risk is slightly higher (approximately 1% to 2%) when HIV RNA is in the range of 50 to 999 copies/mL than when it is <50 copies/mL (transmission risk is ≤1%).[1,6,9,10]

The Panel does not recommend IV ZDV when **all** of the following criteria are met: (1) ART is being taken, (2) HIV RNA levels are <50 copies/mL within 4 weeks of birth, and (3) adherence to the ARV regimen is achieved. However, a study showing that 6% of women with suppressed HIV RNA levels during pregnancy had viral load rebound near birth[11] highlights the importance of using clinical judgment when making the decision to use intrapartum IV ZDV, regardless of the patient's viral load within 4 weeks prior to birth. The additional benefit of IV ZDV in pregnancy when ART is being taken and viral suppression (HIV RNA <50 copies/mL) is achieved 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 birth 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 in the context of maternal resistance to the drug (see Antiretroviral Drug Resistance and Resistance Testing in Pregnancy).

Administration of Intrapartum Intravenous Zidovudine

Intrapartum IV ZDV is recommended when HIV RNA levels are >1,000 copies/mL or unknown HIV RNA within 4 weeks prior to birth. In those with HIV RNA >1,000 copies/mL who are undergoing a scheduled cesarean birth for prevention of perinatal HIV transmission, IV ZDV administration should begin at least 3 hours before the scheduled cesarean birth; **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) is recommended.** 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 birth. 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 birth is being performed for other indications and the maternal viral load is ≤1,000 copies/mL near the time of birth, administering IV ZDV is not required.

When an urgent unscheduled cesarean birth 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 birth. For example, some experts recommend administering the 1-hour loading dose of IV ZDV and not waiting to complete additional administration before proceeding with birth when an expedited birth 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 when HIV RNA levels are >1,000 copies/mL near birth. Prompt administration of combination ART during pregnancy is preferred to single therapy with oral ZDV. Consultation with a person experienced in HIV management during labor and birth is recommended and is available through the National Perinatal HIV/AIDS Clinical Consultation Center (1-888-448-8765).

Transmission and Mode of Delivery

Current Recommendations on Mode of Delivery

Scheduled cesarean birth, defined as cesarean birth performed before the onset of labor and before rupture of membranes (ROM), is recommended at 38 weeks gestation for prevention of perinatal HIV transmission when HIV RNA levels are >1,000 copies/mL near birth and when HIV RNA levels are unknown. Although most studies do not specify the exact time that the HIV RNA levels closest to birth were measured, the Panel recommends viral load testing at approximately 36 weeks gestation or within 4 weeks of anticipated birth to inform decisions about mode of birth and optimal treatment of the newborn. The American College of Obstetricians and Gynecologists (ACOG) recommends counseling about the potential benefits of scheduled cesarean birth when HIV RNA levels are >1,000 copies/mL during pregnancy.[15]

Recommendations for cesarean birth 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 either no ARV drugs or ZDV as a single drug were prescribed during most pregnancies impacted by HIV. The HIV RNA threshold of 1,000 copies/mL for decisions about mode of birth 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 birth in an era when ART is recommended during all pregnancies 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 birth (13 of 3,544 women; 0.3%) were not significantly different from those who had a planned vaginal birth (6 of 2,238 women; 0.3%).[9] Similarly, data from the French Perinatal Cohort showed no difference in transmission rates between vaginal birth and planned cesarean birth 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 birthing 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 ART is taken during pregnancy, the benefit of scheduled cesarean birth is difficult to evaluate in the context of viral suppression. It is unclear whether scheduled cesarean birth confers any additional benefit in reducing transmission, and there are harms associated with unindicated cesarean birth. No evidence to date suggests any benefit from scheduled cesarean birth when ART has been taken for several weeks and viral suppression has been achieved at or near birth. 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 birth for pregnancies when ART is being taken and HIV RNA levels are ≤1,000 copies/mL should be individualized based on discussion between an obstetrician and a patient. Counseling should be provided explaining that no evidence indicates that a scheduled

cesarean birth performed solely for prevention of perinatal HIV transmission is of any benefit when ART is being taken and HIV RNA levels are ≤1,000 copies/mL and, therefore, **is not routinely recommended** in these situations.

Timing of Delivery

ACOG recommends against nonmedically indicated cesarean birth prior to 39 0/7 weeks gestation because of the risk of iatrogenic prematurity.[22,23] However, when the maternal viral load is >1,000 copies/mL, earlier birth is indicated. When cesarean birth is indicated to prevent transmission of HIV, ACOG recommends scheduling cesarean birth at 38 0/7 weeks gestation to decrease the likelihood of onset of labor or ROM before scheduled cesarean birth.[5] However, recent evidence indicates that integrase strand transfer inhibitors (INSTIs) cause a rapid reduction in HIV viral loads when there is adherence to therapy, with the DolPHIN-2 trial reporting a median time of 7 days for patients taking dolutegravir to achieve a viral load <1,000 copies/mL.[24] When INSTI-based ART was recently started, adherence to therapy is known, and viral loads are trending down and approaching the threshold of <1,000 copies/mL near term, it is reasonable to consider shared decision-making regarding mode and timing of birth while providing increased adherence support (possibly including directly observed therapy). When attempting to avoid a cesarean birth in the setting of a rapidly decreasing viral load, providers must balance the risks of ROM and spontaneous labor while simultaneously mitigating the reason for lack of viral suppression. For providers considering an individualized birth plan, consultation with the National Perinatal HIV/AIDS Clinical Consultation Center (1-888-448-8765) may be helpful. 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 instances of suboptimal pregnancy dating, amniocentesis to document lung maturity should be avoided in pregnancies impacted by HIV[25] See Early Labor or Ruptured Membranes at Presentation 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 birth and infant RDS in an adjusted model that included infant gestational age and birth weight.[26] Although newborn complications may be increased with planned cesarean birth at <39 weeks gestation, the benefits of planned cesarean birth at 38 weeks generally are thought to outweigh the risks if the procedure is performed to prevent HIV transmission.

In pregnancies when HIV RNA levels are ≤1,000 copies/mL, cesarean birth is not recommended to prevent perinatal HIV transmission. The Panel recommends delivering according to standard obstetric indications; **labor should not be induced at 38 weeks for prevention of perinatal HIV transmission.** When scheduled cesarean birth is performed during pregnancies when HIV RNA levels are ≤1,000 copies/mL for an indication other than preventing HIV transmission, cesarean birth should be scheduled based on ACOG guidelines for pregnancies that are not impacted by HIV. Among women with HIV RNA levels <1,000 copies/mL, a comparison of 613 women 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 birth; these findings suggest that when there is no indication for scheduled cesarean birth for prevention of perinatal HIV transmission, providers should deliver according to standard obstetric indications.[27]

Cesarean Delivery When Presenting Late in Pregnancy

When pregnancy is near term at the time of presentation and ARV drugs are not being taken, HIV RNA results may not be available before birth. 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 Lack of Viral Suppression While on Antiretroviral Therapy in Pregnancy).[24,28-31] In this instance, scheduled cesarean birth 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 birth when virologic suppression has been achieved for a brief period (e.g., <2 weeks), given this scenario, many others would support a vaginal birth as long as the plasma HIV RNA level was <1,000 copies/mL by the day of birth. In these situations, patient-centered counseling and shared decision-making should be used in planning for birth. Regardless of mode of birth, presumptive HIV therapy should be considered for the neonate in these circumstances (see Antiretroviral Management of Infants With *In Utero*, Intrapartum, or Breastfeeding Exposure to HIV. 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 birth would be reasonable **(CIII).**

Risk of Complications With Cesarean Delivery

Administration of perioperative antimicrobial prophylaxis is recommended during all pregnancies to decrease infectious morbidity associated with cesarean birth. 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.[32-37] A Cochrane review of six studies in women with HIV concluded that urgent cesarean birth was associated with the highest risk of postpartum morbidity, scheduled cesarean birth was intermediate in risk, and vaginal birth had the lowest risk of morbidity.[38,39] Complication rates in women with HIV in most studies[16,40-44] 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 birth 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 birth than with vaginal birth (odds ratio 3.12) and no reduction in perinatal HIV transmission among the mothers on ART.[45] Therefore, during pregnancies impacted by HIV, counseling should be provided regarding the specific risks associated with undergoing cesarean birth in the setting of HIV infection.

In addition, caution should be exercised in proceeding with a cesarean birth in circumstances without clear evidence of benefit, especially in instances of younger maternal age when additional pregnancies and perhaps multiple cesarean deliveries are likely. The risks of abnormal placentation

(e.g., placenta previa, placenta accreta spectrum), bowel and bladder injury, and intrapartum hemorrhage increase with the number of reoccurring cesarean deliveries. These risks should be considered and discussed with the patient before proceeding with a cesarean birth.[46,47]

Early Labor or Ruptured Membranes at Presentation

Most studies have shown a similar risk of perinatal HIV transmission for cesarean birth performed for obstetric indications after labor and membrane rupture as for vaginal birth. In one study, the HIV transmission rate was similar in women undergoing emergency cesarean birth 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,[48] it is not clear how soon after the onset of labor or ROM that the benefit of cesarean birth is lost for women with HIV RNA >1,000 copies/mL.[49] Later data are reassuring on the association between the duration of ROM and perinatal HIV transmission in the era of ART and viral load measurement. 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 birth—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.[50]

Because it is not clear whether cesarean birth after onset of labor reduces the risk of perinatal HIV transmission when HIV RNA levels are >1,000 copies/mL, management of patients originally scheduled for cesarean birth 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 and HIV RNA levels are ≤1,000 copies/mL, interventions to decrease the interval to birth (e.g., administration of oxytocin) should be considered based on obstetric considerations. When membrane rupture occurs before 34 weeks gestation, decisions about timing of birth should be based on best obstetric practices, considering infant risks of prematurity and 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 pregnancy in the context of HIV.

In these circumstances, where there is a paucity of data, consultation with an expert in perinatal HIV may be helpful. Because the birth plan in the setting of labor must be made quickly, telephone consultation via a 24-hour, 7-day-a-week hotline (e.g., the National Perinatal HIV/AIDS Clinical

Consultation Center [1-888-448-8765]) may provide assistance in rapidly developing an individualized plan.

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.[51-54] 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. Fetal scalp electrodes should be avoided in pregnancies impacted by HIV when viral suppression is achieved and should not be used in pregnancy when viral suppression (≥50 copies/mL) is not achieved. Consider consultation with the National Perinatal HIV/AIDS Clinical Consultation Center (1888-448-8765) for infant management when a scalp electrode is used in the setting of HIV infection. See Antiretroviral Management of Infants With *In Utero*, Intrapartum, or Breastfeeding Exposure to HIV.

Based on data discussed in the previous section (see Early Labor or Ruptured Membranes at Presentation, above), artificial ROM can be performed for standard obstetric indications when HIV RNA levels are <50 copies/mL and ART is being taken. Artificial ROM should be avoided when HIV RNA levels are ≥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.[55-57] 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.[58]

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.[59] 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 birth with forceps or a 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 on whether forceps or a vacuum device were used, 249 (8.2%) involved operative birth (5.6% using forceps, 2.4% using a vacuum device, 0.1% using both forceps and a 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 birth is a safe option for women who are virally suppressed.[60] Based on these data, the Panel recommends that operative birth 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 (e.g., a need for expedited vaginal birth, shoulder dystocia) should be the same as they are for pregnancies not impacted by HIV.

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.[61,62] 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 Based on HIV RNA Levels at the Time of Delivery

Antiretroviral therapy (ART) should always be taken or initiated 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 Prior to Birth				
	<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	Prescribed ART should be taken on schedule during labor and before scheduled cesarean birth (CIII). In general, ARV regimens are initiated postpartum when HIV is diagnosed during labor.			
Intrapartum IV ZDV	Not required (BII)	Not required but may be considered (CII); some 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	Vaginal birth[c] (AII)	Vaginal birth[c] (AII)	Scheduled cesarean birth at 38 weeks gestation[d] (AII)	Individualized care[d]
Artificial Rupture of Membranes[e]	Per standard obstetric indications (BII)	Avoid if possible (BIII).	Not applicable; cesarean birth recommended	Avoid, if possible, when viral load is detectable or unknown and a cesarean birth is not being performed (BIII).
Induction of Labor	Per standard obstetric indications, including use of oxytocin. When HIV RNA levels are ≤1,000 copies/mL, routine induction at 38 weeks gestation should NOT be performed.		Not applicable; scheduled cesarean birth at 38 weeks is recommended.	Avoid if possible (BIII).
IUPC	Data not available for pregnancies impacted with HIV; use IUPC with caution and only if clear obstetric indications exist.			
Fetal Scalp Electrodes for Fetal Monitoring	Avoid—particularly when maternal viral load is not suppressed (≥50 copies/mL) or is unknown—because of the potential risk of HIV transmission (BIII). See Antiretroviral Management of Infants With *In Utero*, Intrapartum, or Breastfeeding Exposure to HIV.			
Operative Delivery With Forceps or a Vacuum Extractor	Per standard obstetric indications (BIII)	Avoid during pregnancy 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 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 Prior to Birth				
	<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 ARV Drugs and Infant Feeding	See Antiretroviral Management of Infants With *In Utero*, Intrapartum, or Breastfeeding Exposure to HIV, Table 11, Table 11.1, Postpartum HIV Management and Follow-Up, and Preventing HIV Transmission During Infant Feeding.			

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 birth.

[b] Begin IV ZDV when patients present in labor or at least 3 hours before a cesarean birth 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 birth performed solely for prevention of perinatal HIV transmission when ART is being taken and HIV RNA levels are ≤1,000 copies/mL is not recommended given the low rate of perinatal transmission in this group (AII). When HIV RNA levels are ≤1,000 copies/mL, if scheduled cesarean birth 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 birth reduces the risk of perinatal HIV transmission when spontaneous labor or rupture of membranes have occurred. When cesarean birth was originally scheduled because of HIV and labor is ongoing, management 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 [1-888-448-8765]) may be helpful in rapidly developing an individualized plan.

[e] In pregnancies when ART is being taken and suppressed viral load (HIV RNA <50 copies/mL) is achieved, duration of ruptured membranes is not associated with an increased risk of perinatal transmission and is not an indication for cesarean birth to prevent HIV transmission (BII).

[f] Consider drug interactions with ART when treating postpartum bleeding caused by uterine atony. When a cytochrome P450 3A4 (CYP3A4) enzyme inhibitor (e.g., a protease inhibitor, cobicistat) is being taken, 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). When a CYP3A4 enzyme inducer—such as nevirapine, efavirenz, or etravirine—is being taken, 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 HIV Management and Follow-Up

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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). Confirmatory testing should follow a positive HIV test during labor; see Pregnancy and Postpartum HIV Testing and Identification of Perinatal and Postnatal HIV Exposure. If testing confirms HIV infection, ART should be offered, and a supply of ART should be provided before postpartum hospital discharge to prevent treatment interruption (AII). Immediate linkage to HIV care and comprehensive follow-up also is needed (AII). When HIV is newly diagnosed in the intrapartum period, infants should begin presumptive HIV therapy, and ART should be provided before postpartum hospital discharge (AII) (see Antiretroviral Management of Infants with Perinatal HIV Exposure or HIV Infection). • In the context of HIV during pregnancy, evidence-based counseling should be provided 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 Preventing HIV Transmission During Infant Feeding). • 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). 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 patients 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).

Tailored supportive services 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.

Postpartum care should include immediate linkage to care, thorough medical assessment, counseling, and follow-up, with particular attention to new HIV diagnoses during labor or 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 contact with obstetrician-gynecologists within 3 weeks postpartum and that postpartum care be provided as an ongoing process based on individual needs rather than as a single postpartum visit.[3] A follow-up appointment within 2 to 4 weeks of postpartum discharge is recommended with the health care provider managing HIV care, whether an obstetrician or an HIV specialist, particularly in the context of ART adherence challenges. Telemedicine visits should be considered when in-person appointment attendance is a concern.[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. Case management improves the likelihood of achieving viral suppression and maintaining continuity of 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. When HIV is newly diagnosed in the intrapartum period, infants should begin presumptive HIV therapy, and ART should be provided before postpartum hospital discharge. Special hospital programs may need to be established to support dispensing ART before discharge.

Patients taking testosterone or other medications and patients whose self-expression is less common may require additional support and linkage to care during the postpartum period .[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 HIV care provider and patient, ideally before delivery. Health care providers counseling on postpartum ART should factor in the possibility of future pregnancies (planned or unplanned) alongside the anticipated ART regimen, contraceptive choices, and any unique drug–drug interactions in the postpartum period (see Prepregnancy Counseling and Care 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 while attempting to conceive (see the Adult and Adolescent Antiretroviral Guidelines). See Recommendations for Use of Antiretroviral Drugs During Pregnancy, Table 4. HIV-Related Antepartum Screenings and Assessments During Pregnancy, Table 5. HIV-Related Laboratory Monitoring Schedule During Pregnancy, 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]

Postpartum counseling should emphasize the importance of lifelong ART. Several studies have demonstrated significant decreases in ART adherence postpartum.[15-19] During the postpartum period, medical appointment follow-up may be difficult, 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 in the context of HIV.[2,21-24] The U.S. Preventive Services Task Force recommends universal screening for postpartum depression[25] using a validated tool (e.g., the Edinburgh Postnatal Depression Scale); such screening is especially important when increased risk for postpartum depression and poor adherence is suspected. 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] Counseling should emphasize 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] If viral suppression is achieved 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). When a protease inhibitor-based ART regimen is continued but at increased 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)—with or without reliable PrEP use by the partner—eliminates the 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 cases—even before resumption of menses—increasing the likelihood 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). Contraceptive plans should not vary based on HIV status; however, because of the significantly higher prevalence of unplanned pregnancy in the context of 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, it should be inserted before postpartum hospital discharge or during the routine postpartum visit. If LARC insertion is planned for the postpartum visit and an interim contraceptive is desired, intramuscular depot medroxyprogesterone acetate is an option that can be given before postpartum hospital discharge. Counseling should advise against 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 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

In the context of HIV during pregnancy, evidence-based counseling should be provided to support shared decision-making about infant feeding options prior to and during pregnancy (see Preventing HIV Transmission During Infant Feeding. Counseling and plans for infant feeding should be reviewed again after delivery.

Lactation Inhibition

In the absence of breastfeeding, 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 in some cases.[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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Preventing HIV Transmission During Infant Feeding

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Panel's Recommendations
• When there is potential for perinatal HIV transmission, evidence-based, patient-centered counseling should be provided 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, inform 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 through breastfeeding. 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. • Replacement feeding with formula or banked pasteurized donor human milk is recommended to eliminate the risk of HIV transmission through breastfeeding when ART is not being taken and/or viral suppression has not been achieved during pregnancy (at a minimum throughout the third trimester), as well as at delivery (AI). • When ART is being taken for HIV and a sustained undetectable viral load is achieved, counseling about the options of formula feeding, use of banked donor milk, or breastfeeding should be provided. Those who choose to breastfeed should be supported in this decision (AIII). • If formula feeding is chosen, providers should support in this decision. Providers should ask about potential barriers to formula feeding and explore ways to address them (AIII). • In the case of a detectable viral load during breastfeeding, the Panel on Treatment of HIV in Pregnancy and Prevention of Perinatal Transmission and the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV recommend breastfeeding be stopped temporarily or discontinued and replacement feeding initiated while the viral load is rechecked, causes for the viremia are assessed, and, when applicable, adherence counseling is reinforced (AII) (see Situations to Consider Stopping or Modifying Breastfeeding in the text below). Most experts recommend permanent discontinuation of breastfeeding when HIV RNA is ≥200 copies/mL (CIII). o Depending on the level and persistence of viremia , next steps may include initiating or modifying infant antiretroviral prophylaxis, permanently stopping breastfeeding, and considering the need for additional infant HIV testing (see Antiretroviral Management of Infants With *In Utero*, Intrapartum, or Breastfeeding Exposure to HIV, Table 12. Antiretroviral Management of Infants With Exposure to HIV During Breastfeeding, and Table 13. Recommended Virologic Testing Schedules for Infants With Perinatal and Breastfeeding Exposure to HIV in Diagnosis of HIV Infection in Infants and Children). o If the repeat parental viral load is undetectable, a joint decision should be made by the parent and providers about whether breastfeeding may resume (AIII). • Engaging Child Protective Services or similar agencies is not an appropriate response to infant feeding choices impacted by HIV (AIII). • Clinicians are encouraged to consult the National Perinatal HIV/AIDS Hotline (1-888-448-8765) with HIV-related questions about infant feeding (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*

Counseling about infant feeding is an integral component of HIV care during pregnancy and postpartum. Ideally, this counseling should begin before pregnancy, continue during pregnancy, and be reviewed again after delivery. Patient-centered counseling should assess opinions and plans about infant feeding, engage in shared decision-making, and assist in implementing plans for infant feeding. Previously, replacement feeding with properly prepared formula or banked, pasteurized donor human milk was recommended as the only option for infant feeding 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 breastfeeding dyad 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 a sustained undetectable HIV viral load.[1-4]

The Panel on Treatment of HIV in Pregnancy and Prevention of Perinatal Transmission and the Panel on Antiretroviral Therapy and Medical Management of Children Living With HIV (the Panels) recommend that clinicians engage parents in patient-centered counseling and shared decision-making regarding infant feeding. In 2024, the American Academy of Pediatrics published an updated opinion on breastfeeding in the context of HIV, stating "pediatricians should be prepared to offer a family-centered, nonjudgmental, harm reduction approach to support people with HIV on ART with sustained viral suppression below 50 copies per mL who desire to breastfeed."[4] As part of this process, providers and parents should discuss both replacement feeding and breastfeeding and address 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 throughout the duration of breastfeeding, particularly if viral load becomes detectable (see Table 12. Antiretroviral Management of Infants With Exposure to HIV During Breastfeeding and Table 12.1. Antiretroviral Prophylaxis Dosing for Infants Who Are Breastfed in Antiretroviral Management of Infants With *In Utero*, Intrapartum, or Breastfeeding Exposure to HIV). Counseling should also address issues related to breast health (e.g., mastitis), mixed feeding, and weaning.

Panel recommendations are in line with the opinions of multiple experts and community organizations that have called for a patient-centered approach to infant feeding decision-making and providing access to the information, support, and tools parents need to make informed infant feeding decisions.[4-13] A 2016 survey of 93 clinicians in the United States who provide specialty care to women with HIV found that one-third of the providers were aware that women in their care breastfed their infants after being advised not to do so.[14] These findings underscore the importance of open communication and shared decision-making that provide an opportunity to understand patients' values and infant feeding preferences, thus allowing appropriate care and support for breastfeeding dyads.

Most of the data on HIV transmission via breast milk come from studies conducted in low- and middle-income countries. However, there is growing interest in breastfeeding by people with HIV and health care providers in the United States and other higher-income countries. Data about breastfeeding with HIV in these settings are limited but have been explored in a number of studies. A 2020 case series [15] described breastfeeding of three infants with perinatal HIV exposure in Canada. Eight observational studies published after that time have reported on groups of 7 to 72 breastfeeding infants estimated to reflect a total of 184 to 214 unique infants in Germany,[16,17] Italy,[18] Switzerland,[19] and the United States and Canada.[20-23] In these publications, participants who breastfed were on ART, generally started before or in the first trimester of pregnancy, and were documented to be virally suppressed (viral load <50 to <400 copies/mL) at the time of delivery and/or in late pregnancy. A few cases of low-level viremia were reported postpartum, with cessation of

breastfeeding in most instances. Infant ARV prophylaxis varied within and across study locations, including no ARV prophylaxis, zidovudine (ZDV) and/or nevirapine (NVP) for 4 to 6 weeks after birth, or continuing prophylaxis through one month after weaning. Some centers chose therapeutic dosing with three-drug ARV regimens for either the first 4 to 6 weeks after birth or through weaning. Although none of the studies identified cases of HIV transmission related to breastfeeding, the studies were not designed to evaluate transmission (see the subsection on Risk of Transmission below), the number of participating infants was small, and follow-up has not been completed for all participants. Some infants are still breastfeeding, and a small number were lost to follow-up. Challenges during breastfeeding—including mastitis, inadequate milk supply with need for formula supplementation, episodes of detectable viral load, and difficulty weaning—require further study to inform optimal management.

Clinicians who provide HIV care who have questions about infant feeding or are considering breastfeeding are encouraged to consult with an expert and/or the National Perinatal HIV/AIDS Hotline (1-888-448-8765).

Overview of Counseling and Management

When ART for HIV is being taken with a consistently suppressed viral load during pregnancy (at a minimum during the third trimester) and at the time of delivery, the Panel recommends counseling about the options of formula feeding, banked donor milk, or breastfeeding and supporting in infant feeding decisions.

When ART is not being taken and/or a suppressed viral load is not achieved 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 sometimes, 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.

Other countries have updated their guidelines for management of breastfeeding in the context of HIV: Switzerland in 2018,[19] Australia in 2021,[24] the United Kingdom in 2020[10] and 2022,[25] and Canada in 2023.[26] A number of institutions in the United States have developed their own protocols for counseling and providing HIV care when there is an interest in breastfeeding.[20,27-29] Although these country guidelines and institution-level protocols have some differences, they all entail common elements: standardized counseling regarding infant feeding options during HIV care, a multidisciplinary team-based approach, lactation support, adherence counseling and support, and close monitoring of the breastfeeding dyad.[25] Approaches to infant prophylaxis are quite variable (see Antiretroviral Management of Infants With *In Utero*, Intrapartum, or Breastfeeding Exposure to HIV). In a provider survey conducted in 2021, institutional protocols supporting breastfeeding with HIV were rare but were associated with higher degrees of provider comfort when patients chose to breastfeed.[30]

Special Concerns

Engaging Child Protective Services or similar agencies is not an appropriate response to infant feeding choices impacted by HIV.

There have been numerous reports that after expressing interest in or intention to breastfeed, providers threatened to make a report to Child Protective Services or actually did so. Such engagements can be extremely harmful to families; can exacerbate the stigma and discrimination associated with HIV; and are disproportionately applied to minoritized individuals, including Black, Indigenous, and other people of color.[31-33]

Other Considerations

Patients should be asked nonjudgmental questions about their self-expression, including how they want to be referred to as a parent (e.g., mother, father, another name), and how they want to describe infant feeding (e.g., breastfeeding, another name). Some patients may desire to feed their infants their own milk, although some may find it dysphoric.[34] Counseling about infant feeding options, as discussed in this section, should be provided to all pregnancies impacted by HIV. There are no evidence-based guidelines on timing of restarting testosterone after giving birth or while breastfeeding. In one published case report of restarting testosterone 13 months postpartum while still lactating, the calculated milk-to-plasma ratio was under 1.0, the calculated relative infant dose was under 1%, the infant had no observable side effects, and the infant serum testosterone concentrations remained undetectable.[35]

Approach to Counseling

Health care providers who provide HIV care during pregnancy or prepregnancy should initiate conversations about infant feeding early in pregnancy, or 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 breast milk. Less than 1 of 100 breastfed infants would be expected to acquire HIV through breast milk when ART is being taken and a sustained undetectable viral load is achieved while lactating; however, the risk is not zero. What information can I provide to help you decide?"

When breastfeeding with HIV is being considered, providers should engage 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 the breastfeeding dyad) 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.

People with HIV desire to be counseled about safe infant feeding practices and have their questions answered without judgment.[27,36] Community-based organizations have developed patient-facing materials to assist decisions around infant feeding options during pregnancy.[37] When the choice is made to breastfeed, counseling should include the importance of adherence to ART, sustained viral suppression during pregnancy and breastfeeding, and engagement in postpartum care. Points to address are listed below:

- 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.
- When ART for HIV is being taken with a sustained undetectable viral load, counsel about the options of formula feeding, use of banked donor milk, or breastfeeding. Those who choose to breastfeed should be supported in this decision.
- For those who choose to breastfeed, exclusive breastfeeding (no formula or other foods) through the first 6 months is recommended. It is important to acknowledge that there may be intermittent need to give formula (e.g., infant weight loss, milk supply not yet established, not having enough stored milk, transient increases in viral load).
- 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 HIV Management and Follow-Up).
- Access to a provider who is a breastfeeding specialist certified by the Academy of Breastfeeding Medicine (when available) or a lactation consultant with expertise in supporting breastfeeding 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 higher-resource settings and when adherent to ART with sustained viral suppression starting early in pregnancy.
- Breastfeeding provides numerous health benefits such as reduction in hypertension, type 2 diabetes, and breast and ovarian cancers and benefits for the breastfed infant such reduction in asthma, gastroenteritis and otitis media,.[38]

Some providers and/or institutions have chosen to require a signed form acknowledging the counseling provided; others have felt this practice is too stigmatizing and prefer to document the infant feeding discussion in the patient's chart without requiring a signed form.

Approach to Management

If the decision is made to breastfeed, several measures should be taken to reduce the possibility of HIV transmission. Care of the breastfeeding dyad should be coordinated prior to delivery among the maternity care provider, HIV provider, infant provider, breastfeeding specialist certified by the Academy of Breastfeeding Medicine (when available), lactation consultant, and social worker, all of whom may need education about new approaches to infant feeding with HIV.[20,26-30] Recommendations for management include the following:

- Support 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.

- Ensure continued access to ARV medications throughout the breastfeeding period, recognizing that patients may have changes to insurance status and may need support applying for assistance programs.
- Provide early active referral to a supportive lactation consultant, preferably a breastfeeding medicine provider when available, beginning prenatally or at delivery and continuing until breastfeeding is well established. The lactation consultant should be 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 after giving birth and may affect ART adherence. Postpartum depression occurs more frequently with HIV compared to without HIV[39] (see Postpartum HIV Management and Follow-Up).

- Document sustained viral suppression before delivery and throughout breastfeeding.
  - No data exist to inform the appropriate frequency of viral load testing while breastfeeding. One approach is to monitor the plasma viral load of the parent every 1 to 2 months during breastfeeding.[21,40]
  - 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 viral load becomes detectable, switching to replacement feeding is recommended (see Situations to Consider Stopping or Modifying Breastfeeding below). There are no data that clearly define a specific viral load threshold for permanent discontinuation of breastfeeding. Most experts recommend permanent discontinuation of breastfeeding when viral load is ≥200 copies/mL. Guidance about infant ARV management when viremia develops during breastfeeding is provided in Antiretroviral Prophylaxis for Infants Exposed to Detectable HIV RNA During Breastfeeding in Antiretroviral Management of Infants With *In Utero*, Intrapartum, or Breastfeeding Exposure to HIV; see Table 12. Antiretroviral Management of Infants With Exposure to HIV or Exposure During Breastfeeding and Table 12.1 Antiretroviral Prophylaxis Dosing for Infants Who Are Breastfed.

- Recommend exclusive breastfeeding in the first 6 months of life, followed by the introduction of complementary foods (e.g, solids) with continued breastfeeding, if desired.[38] Some parents may choose to stop breastfeeding and switch to formula prior to 6 months of age.
  - Provide support for exclusive breastfeeding, acknowledging that there may be scenarios where formula supplementation is needed. There is no evidence that formula supplementation increases the risk of HIV acquisition in the breastfed infant in the context of parental ART and viral suppression. 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).[41,42] The highest risk in these studies was from very early introduction of solids (before 2 months of age).[41,43] Whether this remains a risk factor when viral suppression is sustained during breastfeeding has not been studied.
  - If supplementation is needed during a hospital stay, prioritize the use of pasteurized donor human milk when feasible.

- Administer appropriate ARV prophylaxis starting at birth; see Antiretroviral Prophylaxis for Breastfeeding Infants, Table 12. Antiretroviral Management of Infants With Exposure to HIV or Exposure During Breastfeeding and Table 12.1 Antiretroviral Prophylaxis Dosing for Infants Who Are Breastfed in Antiretroviral Management of Infants With *In Utero*, Intrapartum, or Breastfeeding Exposure to HIV.
- If detectable viral load develops during breastfeeding, the Panels recommend that breastfeeding be temporarily stopped or discontinued and replacement feeding initiated. Additional infant ARV prophylaxis and infant testing are also recommended, see Situations to Consider Stopping or Modifying Breastfeeding, below, Table 12, Table 12.1, and Table 13. Recommended Virologic Testing Schedules for Infants With Perinatal and Breastfeeding Exposure to HIV
- Provide guidance on good breast care, including strategies to avoid and promptly resolve over-production of breast milk, 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,[44-46] 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.[47] 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 With Perinatal and Breastfeeding Exposure to HIV).

Situations to Consider Stopping or Modifying Breastfeeding

Situations may arise in which there is a need to temporarily stop or discontinue breastfeeding and initiate replacement feeding, such as a detectable viral load or developing mastitis or bleeding nipples during breastfeeding. If the situation is temporary, some options to consider while expressing breast milk until the condition has resolved or viral load becomes undetectable include: (1) giving previously stored expressed milk from a date when viral suppression was achieved while encouraging pumping and discarding breast milk to ensure that breastfeeding can resume; (2) pumping and flash heating breast milk before feeding it to the infant; (3) providing replacement feeding with formula or pasteurized donor human milk while encouraging pumping and discarding breast milk to ensure that breastfeeding can resume; or (4) permanently stopping breastfeeding. Flash heating, which has been documented to eliminate HIV from breast milk, 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.[48,49] Once cooled to room temperature, milk can be given to the infant 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 viral load that becomes detectable while breastfeeding, the Panels recommend temporarily stopping or discontinuing breastfeeding and initiating replacement feeding, using one of the options described above, engaging in shared decision-making, assessing the etiology of the

viremia, and repeating the viral load. Due to the risk of postnatal transmission associated with viremia during breastfeeding, the Panels advise immediate cessation of breastfeeding if viral load becomes detectable; this guidance is more directive than counseling when ART is being taken with sustained viral suppression. Most experts recommend permanent discontinuation of breastfeeding when HIV RNA is ≥200 copies/mL. The exact association between degree and duration of viremia and lactational transmission is not known. In situations where viremia is low and an addressable cause has been identified, the added risk of short-term continued breastfeeding until a repeat viral load is available is likely to be low.

Any viremia is an opportunity to review the risks and benefits of continued breastfeeding, adherence strategies, and other considerations, such as ARV prophylaxis for the breastfeeding infant (see Table 12. Antiretroviral Management of Infants With Exposure to HIV During Breastfeeding and Table 12.1. Antiretroviral Prophylaxis Dosing for Infants Who Are Breastfed in Antiretroviral Management of Infants With *In Utero*, Intrapartum, or Breastfeeding Exposure to HIV). If the repeat viral load is undetectable, a joint decision should be made by the parent and the clinician about whether breastfeeding may resume. If the repeat viral load remains detectable, support should be provided to continue replacement feeding.

The Diagnosis of HIV Infection in Infants and Children section provides guidance about HIV diagnostic testing for infants who are being breastfed. If after counseling, the choice is made to continue to breastfeeding with viremia, 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 nucleic acid test (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: Antiretroviral Treatment Regimens Recommended for Initial Therapy in Infants and Children With HIV 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 the Centers for Disease Control and Prevention 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 infants and avoiding the monetary costs of formula, benefits to breastfeeding include decreased risk of hypertension; type 2 diabetes; and breast, endometrial, and ovarian cancers.[38] An exclusive focus on the risk of perinatal HIV transmission via breastfeeding fails to acknowledge the health benefits of lactating and the health benefits that may be lost by prohibiting breastfeeding with HIV.

Access 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.[50] These outcomes 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.[51] These issues should be considered as part of counseling and support for decisions around infant feeding 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.[52]

Cultural Considerations

Environmental, social, familial, and personal pressures to consider breastfeeding may be faced during pregnancy.[5,12,50,53-58] Many factors affect a woman's decision to breastfeed her infant; these include bonding; maternal and infant health benefits; social, cultural, and religious factors; and concerns about HIV-related stigma and disclosure.[19,23,54]

Some women, especially those from a country or cultural background where breastfeeding is the norm, fear that not breastfeeding will lead to disclosure of their HIV status.[5,57,58] 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.[13]

Risk of HIV Transmission to Infants Through Breastfeeding

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.[59,60] The mechanisms of HIV transmission by breastfeeding are not fully understood.[61,62] This lack of current knowledge, and the fact that rare HIV

transmissions during breastfeeding have occurred when breast milk and/or plasma HIV viral load was undetectable, complicate decision-making.[63,64].

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.[65-69] 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. A systematic review and meta-analysis published in 2017 identified six studies with ART started at some point during pregnancy and continued for at least 6 months postpartum that provided estimates of postnatal transmission rates, excluding peripartum infections diagnosed before 6 weeks of age. The pooled postnatal transmission rate at 6 months was 1.1% (95% confidence interval, 0.32% to 1.85%), with substantial heterogeneity. Transmission rates in the included studies ranged from 0.2% to 3.1%.[70]

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. 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 daily oral 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.[71] 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.[63]

Smaller studies have also looked at HIV transmission in the context of maternal ART and viral load monitoring. 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.[72]

In a prospective follow-up of 475 breastfeeding mother–infant pairs in Zimbabwe, there were two postpartum transmissions, both from women with HIV RNA levels >1,000 copies/mL.[73] 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. When maternal plasma viral load remained <100 copies/mL during breastfeeding, there were no occurrences of infant HIV acquisition.[64]

There have been at least five additional published cases of HIV transmission when maternal viral load was <50 copies/mL close to the time of transmission. Two cases are from an observational study in Malawi. In one, ART was started 8 weeks before delivery, and maternal plasma RNA was <37 copies/mL at 1 month, 3 months, 6 months, and 12 months postpartum. The infant was breastfed until 9 months of age and tested positive for HIV at 12 months of age after testing negative at months

1, 3, and 6. HIV RNA measured in the breast milk was 293 copies/mL at 1 month postpartum and <37 copies/mL at months 3 and 6. In the second case, ART was started 14 weeks before delivery, and maternal plasma RNA was <37 copies/mL at 1 month and 3 months postpartum. The infant tested positive for HIV at 3 months of age, after testing negative at 1 month. HIV RNA measured in the breast milk was <37 copies/mL at 1 month postpartum and 90 copies/mL at 3 months.[74]

The Mma Bana study in Botswana compared triple nucleoside reverse transcriptase inhibitor (NRTI) therapy (abacavir, ZDV, and lamivudine [3TC]) to protease inhibitor (PI)–based therapy (lopinavir/ritonavir plus ZDV and 3TC). There were two lactational transmissions where maternal plasma and breast milk RNA were <50 copies/mL at 1 and 3 months postpartum, both in the NRTI arm. In one case, ART was started 4 weeks before delivery and viral load was elevated at delivery; the infant tested positive for HIV at 94 days of life after testing negative at 28 days. In the other case, ART was started 14 weeks before delivery and HIV RNA was <50 copies/mL at delivery, although issues with adherence were reported; the infant tested positive for HIV at 91 days of life after testing negative at 21 days.[75] In DOLPHIN-2 (Dolutegravir in Pregnant HIV Mothers and Their Neonates), which compared dolutegravir- versus efavirenz (EFV)-based ART started in the third trimester, out of 268 mother–infant pairs, there was one breastfeeding HIV transmission in the EFV group. HIV was diagnosed in the infant at 72 weeks of age (16 months), and maternal viral load was <50 copies/mL at 12 weeks, 24 weeks, 48 weeks, and 72 weeks postpartum.[1,2,63,71]

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 seven continued to breastfeed with ongoing counseling and frequent viral load checks. There were no cases of HIV transmission via breastfeeding.[76]

Safety of Antiretroviral Drugs During Breastfeeding

Parents are often concerned about infant exposure to ARV medications through breast milk. The non-nucleoside reverse transcriptase inhibitors (NNRTIs) NVP, EFV, and etravirine have been detected in breast milk; however, the levels of these ARV medications that have been detected in breast milk are lower than those seen in maternal plasma. Among 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.[77] 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.[77-79] Emtricitabine and 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).[77] A subanalysis 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.[80] 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.[81] For more details on the passage of ARV medications 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.[82] 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.[83] 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.[84]

The rates of serious adverse events among infants who receive ARV prophylaxis during breastfeeding are low (see Safety of Antiretroviral Drugs for Infant Prophylaxis in Antiretroviral Management of Infants With *In Utero*, Intrapartum, or Breastfeeding Exposure to HIV). 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 infant adverse events were observed between study arms.[1,66] In breastfed infants in the PROMISE study, week 26 mean lumbar spine bone mineral content was lower in infants in the maternal ART group than in the infant NVP group. This difference (about 0.23 g) was less than one-half standard deviation, considered unlikely to be clinically relevant. No infant renal safety concerns were observed.[85] An infant who acquires HIV while breastfeeding is at risk for developing ARV medication resistance due to subtherapeutic drug levels in breast milk.[71,86-88] A longitudinal retrospective study of Kenyan women with HIV from the pre-ART era showed no statistically significant difference in the composition of the bacterial microbiome of breast milk from women receiving combination antiretroviral (cART) and those receiving no ARV medications during breastfeeding.[89]

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.[66] For additional information, see Safety of Antiretroviral Drugs for Infant Prophylaxis in Antiretroviral Management of Infants With *In Utero*, Intrapartum, or Breastfeeding Exposure to HIV. 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.

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Antiretroviral Management of Infants With *In Utero*, Intrapartum, or Breastfeeding Exposure to HIV

Updated: December 19, 2024
Reviewed: December 19, 2024

Panel's Recommendations
Antiretroviral Management for Infants With Exposure to HIV During the *In Utero* and Intrapartum Periods
• All newborns with *in utero* (antepartum) or intrapartum exposure to HIV should receive one or more antiretroviral (ARV) drugs, dosed appropriately for the infant's gestational age and weight and initiated as close to the time of birth as possible, preferably within 6 hours (AII).
ARV regimen selection for infants with *in utero* or intrapartum exposure to HIV should be based on predicted risk for transmission, determined by maternal HIV RNA levels (see Table 10, Table 11, Table 11.1, and Figure 1 below) (AII).
Infants at high risk of HIV infection from *in utero* or intrapartum exposure, defined as being **perinatally exposed to viremia (HIV RNA ≥50 copies/mL) in the 4 weeks prior to delivery**, should be provided a three-drug ARV regimen, administered from birth for 2–6 weeks, that serves as presumptive HIV therapy or enhanced prophylaxis. If the duration of the three-drug regimen is shorter than 6 weeks, zidovudine (ZDV) should be continued alone to complete a total of 6 weeks of prophylaxis (AII).
• **Infants at low risk** of *in utero* and intrapartum HIV acquisition, defined as being **perinatally exposed to HIV RNA levels <50 copies/mL from 20 weeks of gestation through delivery**, should receive ZDV alone for a duration of 2 weeks (AII).
• **Infants not meeting criteria for high or low risk** should have ARV regimens and durations based on case-specific factors related to the level and timing of viremia during the pregnancy (AII) (see Table 11).
• An HIV nucleic acid test (NAT) should generally be performed at birth for all infants (AII) but is not necessary **for infants at low risk who are not being breastfed** (BIII). See Diagnosis of HIV Infection in Infants and Children and Table 13. Recommended Virologic Testing Schedules for Infants With Perinatal and Breastfeeding Exposure to HIV for guidance about infant testing.
Antiretroviral Management for Infants With Exposure to HIV During the Breastfeeding Period
• **Recommendations about extended ARV prophylaxis** are based on the current and anticipated maternal virologic status during breastfeeding (see Table 12 and Table 12.1 below). Ideally, plans should be made during the antepartum period; reassessment should take place both at delivery and regularly during the breastfeeding period (AII).
For infants at low risk of HIV acquisition during breastfeeding, some Panel members do not recommend extended ARV prophylaxis; however, other Panel members do recommend extended ARV prophylaxis with either nevirapine (NVP) or lamivudine (3TC) (CIII). 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) did not reach consensus. Infants are considered at low risk of transmission during breastfeeding when (1) maternal antiretroviral therapy is being taken while breastfeeding and sustained maternal virologic suppression (HIV RNA <50 copies/mL) was achieved for at least 3 months prior to delivery and (2) the provider and patient are confident that maternal ART adherence will be maintained during breastfeeding (AII).
• **For infants currently at low risk of HIV acquisition during breastfeeding but with concerns for future risk**, the Panels recommend extended ARV prophylaxis with either NVP or 3TC (BIII). Adherence support should always be provided during breastfeeding (Table 12) (AIII).
• **Extended ARV prophylaxis during breastfeeding, when used, should ensure continuous prophylaxis through the postnatal period.** Most experts recommend transitioning to NVP or 3TC after the completion of initial ZDV prophylaxis. However, either NVP or 3TC can be given from birth, replacing ZDV and providing both initial postnatal prophylaxis and extended prophylaxis during breastfeeding (BIII).

- Extended ARV prophylaxis during breastfeeding, when used, should continue until either 6 weeks after the last exposure to breast milk or 6 weeks after concerns about maternal virologic suppression have resolved—whichever occurs first (BIII).

Recommendations for Infant Antiretroviral Management When the Infant is Exposed to New Viremia

- Breastfeeding should be stopped temporarily or discontinued and replacement feeding initiated (see Situations to Consider Modifying or Stopping Breastfeeding in Preventing HIV Transmission During Infant Feeding) (AII). Most experts recommend permanent discontinuation of breastfeeding when HIV RNA is ≥200 copies/mL (CIII).
- An infant HIV NAT should be performed (AII) (see Diagnosis of HIV Infection in Infants and Children and Table 13. Recommended Virologic Testing Schedules for Infants With Perinatal and Breastfeeding Exposure to HIV for guidance about infant testing).
- **New viremia with HIV RNA ≥200 copies/mL**: If a maternal HIV RNA level ≥200 copies/mL (viremia) develops or there is presumed viremia (e.g., reports nonadherence to ARVs), the Panels recommend the initiation of a three-drug ARV regimen for the infant for 4–6 weeks (AII) (see Table 12 and Table 12.1).
- New viremia with HIV RNA <200 copies/mL: When maternal viremia that is quantifiable but <200 copies/mL develops, some Panel members recommend the initiation of a three-drug presumptive HIV therapy, other members recommend the initiation of single-drug ARV prophylaxis (NVP or 3TC), and others recommend infant ARV management based on repeat maternal HIV RNA testing (CII). The Panels did not reach consensus on management; consultation with an expert is suggested (see Table 12).

Infant ARV Management When Perinatal HIV Exposure is Related to a New Diagnosis of HIV During Breastfeeding

- Infants exposed to newly diagnosed maternal HIV infection during breastfeeding should be managed like infants at high risk of *in utero* or intrapartum HIV acquisition and receive a three-drug presumptive HIV therapy regimen for 2–6 weeks (see Table 12) and replacement feeding. If the duration of the three-drug regimen is shorter than 6 weeks, ZDV should be continued alone to complete a total of 6 weeks of prophylaxis (AII). See Diagnosis of HIV Infection in Infants and Children and Table 13. Recommended Virologic Testing Schedules for Infants With Perinatal and Breastfeeding Exposure to HIV for guidance about infant testing.

Providers with questions about ARV management of perinatal HIV exposure or exposure to HIV during breastfeeding 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

Risk of *In Utero* or Intrapartum HIV Transmission and Antiretroviral Management of Infants

All infants with *in utero* or intrapartum exposure to HIV should receive antiretroviral (ARV) drugs during the immediate neonatal period to reduce the risk of 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.

This section addresses ARV management of infants with exposure to HIV-1 recommended by the Panel on the Treatment of HIV During Pregnancy and Prevention of Perinatal Transmission (Perinatal Panel) and the Panel on Antiretroviral Therapy and Medical Management of Children Living With HIV (Pediatric Panel). Information about ARV management for infants perinatally exposed to HIV-2 infection is available in HIV-2 Infection and Pregnancy.

The maternal viral load (HIV RNA level) is the most important risk factor for *in utero* and intrapartum HIV transmission to the infant. Infants are at an increased risk for HIV acquisition when antiretroviral therapy (ART) is not being taken during pregnancy and when antepartum treatment does not result in antepartum viral suppression, particularly in the 4 weeks prior to delivery, but even in the second half of pregnancy. Higher viral load correlates with higher risk of transmission. A spectrum of transmission risk depends on these and other factors, including mode of delivery and health status during pregnancy and delivery. Although current assays can detect very low levels of HIV RNA, data from studies on transmission and viral load that were conducted prior to the availability of highly sensitive tests indicate that an HIV RNA level <50 copies/mL sufficiently predicts low risk of HIV transmission.[1,2]

Risk of HIV Transmission In Utero

The risk of *in utero* HIV transmission is believed to increase with gestational age, with the highest rate of *in utero* infection occurring in the third trimester. However, methodological challenges in assessing the timing of fetal infection limit the precision of risk estimates by gestational age. A definitive diagnosis of *in utero* infection during pregnancy would require invasive sampling, carrying risk that is not ethically or medically indicated. There are case reports of HIV being identified in fetal tissue as early as 8-, 15-, and 20-weeks' gestation, but whether they represented established infection remains unclear.[3-5] In a study of fetal thymuses in the second trimester, polymerase chain reaction (PCR) testing revealed that 2 of 100 samples had HIV-1.[6] For this reason, the Panels have a 20 week–gestational age as a conservative gestational age threshold below which *in utero* transmission is unlikely to occur. A modeling study using profiles of viral culture positivity and seroconversion from a cohort of 95 French infants suggests that the vast majority of *in utero* HIV infection occurs in the third trimester.[7] Another approach has been to examine how well ARVs initiated at different gestational ages prevent *in utero* transmission. Among 34 women in a U.K./Irish cohort who started ARVs during pregnancy, HIV transmission was more likely when ARVs were started later in pregnancy (median gestational age at initiation of 30.1 weeks, interquartile range [IQR] 27.4–32.6 weeks vs. 25.9 weeks, IQR 22.4–28.7 weeks, $P < 0.001$).[8] Another model made estimates of relative time of *in utero* or intrapartum transmission based on timing of ARV initiation; they estimated 3% of transmissions occurred before 14 weeks' gestation, 17% from 14 to 36 weeks, 50% from 36 weeks through onset of labor, and 30% from intrapartum exposure.[9] In summary, *in utero* HIV transmission in the context of maternal viremia is considered rare in the first trimester, uncommon but possible in the second trimester, and most common in the third trimester.

Risk of HIV Transmission Intrapartum (During Labor and Delivery)

The highest risk of vertical HIV transmission is from exposure in the intrapartum period (i.e., during labor and delivery). Risk increases with the level of maternal viremia.[2] Recommended interventions to reduce the risk of intrapartum transmission include ART for all pregnancies, intravenous zidovudine (ZDV) during labor and delivery, and scheduled cesarean delivery when there is a detectable HIV-1 viral load >1,000 copies/mL (see Intrapartum HIV Care).

Transmission Risk Assessment by HIV RNA Levels and Antenatal Time Period

Table 10 below summarizes *in utero* and intrapartum HIV transmission risk according to HIV RNA levels at three antenatal time periods for the purpose of selecting infant ARV prophylaxis. Because robust data are not available to define thresholds of risk across pregnancy, the Panels have defined time points balancing available evidence with implications for clinical management. Transmission

risk categories inform ARV choice and management of prophylaxis and presumptive HIV therapy for infants with HIV exposure.

The assessment of transmission risk is generally but not exclusively dependent on HIV RNA levels during the antepartum period. The Perinatal Panel recommends assessing maternal **HIV RNA levels at the initial antenatal visit with a review of prior levels, 2 to 4 weeks after initiating (or changing) ART, and monthly until RNA levels are undetectable. Maternal HIV RNA levels should also be assessed at least every 3 months during pregnancy and at approximately 36 weeks of gestation, or within 4 weeks of delivery** (see Initial Evaluation and Continued Monitoring of HIV During Pregnancy). However, discussion around transmission risk may not align exactly with the recommended time frames, and clinicians must continue to utilize judgment to assess risk. For example, viremia could be presumed based on reports of poor adherence for several weeks, even without a documented test. Conversely, a missed HIV RNA test in a patient with years of virologic control may not merit concern. Incident HIV infection during pregnancy and lack of receipt of ART have been previously cited as risk factors for transmission; the current guidelines incorporate the risks of those scenarios within the framework of documented or presumed viremia.

Table 10. Transmission Risk Assessment by HIV RNA Levels and Antenatal Time Period

Antenatal Time Period			Transmission Risk	
HIV RNA at <20 Weeks' Gestation	**HIV RNA ≥20** Weeks' Gestation to 4 Weeks Prior to Delivery	**HIV RNA at ≤4** Weeks Prior to Delivery	In Utero	Intrapartum
N/A[a]	N/A[a]	≥50 copies/mL[b]	High	High
N/A[a]	≥50 copies/mL[b]	<50 copies/mL	Low to moderate	Low
≥50 copies/mL[b]	<50 copies/mL	<50 copies/mL	Low	Low
<50 copies/mL	<50 copies/mL	<50 copies/mL	Low	Low

[a] HIV RNA levels in this time period do not change the transmission risk categorization because transmission risk is determined by viremia later in gestation.

[b] HIV RNA values of ≥50 copies/mL can be documented or presumed (e.g., early [acute or recent] HIV, new diagnosis of HIV, or known lapse in adherence).

Antiretroviral Management for Infants With *In Utero* or Intrapartum Exposure to HIV

Historically, the use of ARV drugs in the newborn period was referred to as ARV prophylaxis because it primarily focused on protection against newborn acquisition of HIV. More recently, clinicians have additionally sought to consider and optimize the management of newborns at elevated risk for HIV acquisition *in utero* and initiate three-drug ARV regimens as presumptive HIV therapy. In this section, the following terms will be used:

- **ARV Prophylaxis:** The administration of ARV drugs to a newborn without HIV infection to reduce the risk of HIV acquisition.
- **Presumptive HIV Therapy:** The administration of a three-drug ARV regimen to newborns at elevated risk of HIV acquisition. Presumptive HIV therapy is intended to be early treatment for a newborn who has already acquired HIV but doesn't have documentation of infection; it also

serves as enhanced ARV prophylaxis against HIV acquisition among infants at high risk but not yet infected.

- **ART:** The administration of a three-drug ARV regimen to infants and children with documented HIV infection (see Diagnosis of HIV Infection in Infants and Children and What to Start in the Pediatric Antiretroviral Guidelines).

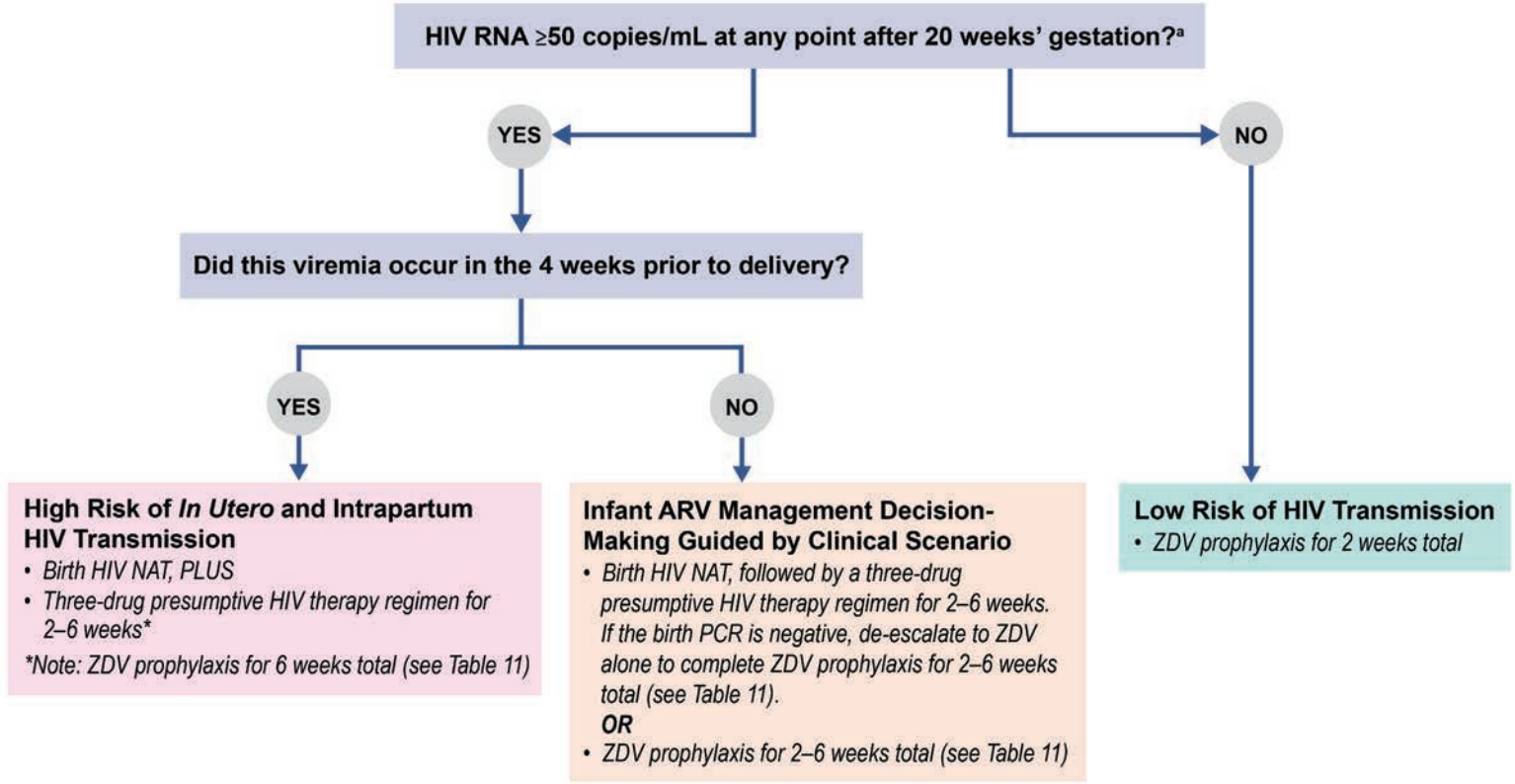
The terms ARV prophylaxis and presumptive HIV therapy describe the potential roles of ARV drugs when the HIV status of an infant is unknown, and they often overlap in neonates at high risk. For example, a presumptive HIV therapy regimen also provides drug exposure that would serve as prophylaxis for a newborn. However, it is important to note that some two-drug and three-drug ARV regimens used historically were designed and studied as prophylaxis, including some that used doses of nevirapine (NVP) that target lower exposures than the doses used for treatment of HIV infection.

The Panels recommend initiating ARV prophylaxis or presumptive HIV therapy as soon as possible after birth, preferably within 6 hours. Although the maximum interval during which newborn ARV prophylaxis can be initiated and still be beneficial is unknown, most studies support providing ARV drugs as early as possible after delivery.[10-15]

The guidance summarized in this section applies to infants perinatally exposed to HIV unless otherwise noted. The algorithm in Figure 1 and Table 11 provide an overview of neonatal ARV management recommendations according to the risk of HIV transmission from *in utero* and intrapartum exposure based on HIV RNA levels at time points during pregnancy and other factors, such as receipt of and adherence to ART. Table 11.1 summarizes the recommended ARV dosing for prophylaxis or presumptive HIV therapy in newborns with *in utero* or intrapartum HIV exposure. Additional information about dose selection for newborns, including preterm infants (<37 weeks gestational age), can be found in Appendix A: Pediatric Antiretroviral Drug Information in the Pediatric Antiretroviral Guidelines.

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 providing HIV care during pregnancy and for newborns after pregnancy, and consultants can provide referrals to local or regional pediatric HIV specialists.

Figure 1. Algorithm for Antiretroviral Management of Infants With *In Utero* or Intrapartum HIV Exposure by Risk of HIV Transmission



[a] Early (acute or recent) HIV infection in pregnancy may result in a scenario where viremia occurs early in gestation but is suppressed after 20 weeks and through the remainder of pregnancy until delivery. In these situations, decision-making guided by the clinical scenario is recommended (see Table 11).

Key: ARV = antiretroviral; NAT = nucleic acid test; PCR = polymerase chain reaction; ZDV = zidovudine

Table 11. Antiretroviral Management for Infants With *In Utero* or Intrapartum Exposure to HIV

Clinical Setting	Risk of Acquisition		Neonatal ARV Management[a,b]	Rationale
	In Utero	Intrapartum		
High Risk of Acquisition				
HIV RNA ≥50 copies/mL in the 4 weeks prior to delivery Viremia can be documented by lab or presumed by other clinical factors (e.g., new diagnosis, ART adherence problems, reports of having stopped ART prior to delivery).	High	High	Presumptive HIV therapy using a three-drug regimen of ZDV and 3TC plus either NVP (treatment dose) *or* RAL Duration is from birth for 2–6 weeks; consensus not reached by members of the Panel.[c] If the duration of a three-drug regimen is <6 weeks, and the birth NAT is negative, ZDV should be continued alone to complete a total of 6 weeks of prophylaxis. HIV NAT obtained before or immediately after starting presumptive therapy with three drugs[d,e]	Viremia in the 4 weeks immediately prior to delivery confers very high risk for *in utero* and intrapartum transmission. Plasma HIV RNA levels of 50–200 copies/mL could be expected to confer lower risk than those >200 copies/mL but could also be an indicator of poor adherence and raise concern for higher levels of viremia at other times.
Low Risk of Acquisition				
HIV RNA <50 copies/mL from 20 weeks' gestation through delivery Ideally documented by at least two consecutive tests at least four weeks apart with HIV RNA <50 copies/mL, but can be based on clinical judgment of providers.	Low	Low	ZDV for 2 weeks	Sustained virologic suppression from 20 weeks' gestation is associated with extremely low risk of transmission *in utero* or intrapartum. Although *in utero* transmission events have been documented prior to 20 weeks, the extremely low frequency of these events does not merit the presumptive HIV therapy approach.
Other Clinical Scenarios				
HIV RNA ≥50 copies/mL at >20 weeks' gestation, but HIV RNA <50 copies/mL in the 4 weeks prior to delivery	Low to Moderate	Low	HIV NAT at Birth[d,e] *Two Options for ARV Management* 1. Presumptive HIV therapy with a three-drug regimen,	Viremia in the late second and third trimester elevates risk of *in utero* transmission (increasing risk with higher HIV RNA levels and longer duration

Table 11. Antiretroviral Management for Infants With *In Utero* or Intrapartum Exposure to HIV

Clinical Setting	Risk of Acquisition		Neonatal ARV Management[a,b]	Rationale
	In Utero	Intrapartum		
			as described above for infants at high risk. If birth the HIV NAT is negative, de-escalate the prophylaxis regimen to ZDV alone to complete 2–6 weeks total.[c] 2. ZDV prophylaxis for 2–6 weeks	of viremia). *Option 1.* Some Panel members believe that the potential benefit of early treatment for an infant who acquired the infection *in utero* merits a presumptive HIV therapy approach. *Option 2.* Other Panel members believe that the marginal potential benefit and anticipated low frequency of *in utero* infection do not merit the additional complexity of and potential toxicity of presumptive HIV therapy and favor ZDV prophylaxis only. All infants should receive a minimum of 2 weeks ZDV prophylaxis, but up to 6 weeks may be used when indicated based on risk assessment.
Early (acute or recent) HIV at any point during pregnancy	Moderate to High depending on maternal HIV RNA levels and weeks' gestation	High if HIV RNA ≥50 copies/mL in the last 4 weeks of pregnancy	HIV NAT at birth[d,e] Manage infant ARVs according to the level and timing of the maternal viremia as described in the rows above (just as for an infant exposed to established infection).	Early or recent HIV diagnosed at any time during pregnancy is a unique situation because very high HIV RNA levels place infants at high risk of HIV acquisition. For infants perinatally exposed to known HIV infection, risk of transmission increases when viremia occurs later in pregnancy. Some Panel members would manage all cases with presumptive therapy, whereas others would only use it for viremia after 20 weeks' gestation.

Table 11. Antiretroviral Management for Infants With *In Utero* or Intrapartum Exposure to HIV

Clinical Setting	Risk of Acquisition		Neonatal ARV Management[a,b]	Rationale
	In Utero	Intrapartum		
Unconfirmed maternal HIV status with at least one positive HIV test at delivery or postpartum *or* Newborn has a positive HIV antibody test	High/ Uncertain	High/ Uncertain	HIV NAT at birth[d,e] Presumptive HIV therapy with a three-drug regimen as described above for newborns with a high risk of *in utero* or intrapartum HIV acquisition If supplemental testing confirms a negative maternal HIV status, discontinue infant ARV drugs immediately.	Supplemental maternal HIV testing and/or NAT testing of the infant is required to determine the level of risk and need to continue infant presumptive HIV therapy or initiate ART.[e]

[a] Infant ARVs should be initiated in the first 6 hours after delivery, especially for infants with a high risk of acquisition. See Table 11.1 for ARV dosing.

[b] See HIV-2 Infection and Pregnancy for ARV prophylaxis recommendations for infants perinatally exposed to HIV-2 mono-infection. In the event of maternal HIV-2 infection or HIV-1 and HIV-2 coinfection, 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 using ARVs that are active against HIV-2. Because HIV-2 is not susceptible to NVP, RAL should be used in presumptive HIV therapy regimens for infants at high risk of HIV acquisition with exposure to HIV-2 or to both HIV-1 and HIV-2.

[c] The optimal duration of three-drug regimen 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 for 6 weeks. The other two ARVs, (3TC and NVP) *or* (3TC and RAL), may be administered for 2 to 6 weeks; the recommended duration for treatment with three ARVs varies depending on infant HIV NAT results, maternal viral load at the time of delivery, and the 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.

[d] NAT test at birth should be obtained before or immediately after starting ARVs. See Diagnosis of HIV Infection in Infants and Children for additional information about HIV testing and NATs.

[e] When a newborn HIV NAT is positive, 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 (see When to Initiate Antiretroviral Treatment in Children with HIV Infection and What to Start in the Pediatric Antiretroviral Guidelines). However, the specimen for confirmatory HIV testing should be obtained prior to ART initiation.

Note: Providers with questions about ARV management of infants should consult an expert in pediatric HIV infection or the National Perinatal HIV Hotline (1-888-448-8765).

Key: 3TC = lamivudine; ART = antiretroviral therapy; ARV = antiretroviral; NAT = nucleic acid test; 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; RAL = raltegravir; ZDV = zidovudine

Table 11.1. Drug Dosing Recommendations for Antiretroviral Prophylaxis and Presumptive HIV Therapy in Infants With *In Utero* or Intrapartum Exposure to HIV[a]

This table provides dosing for antiretroviral (ARV) prophylaxis and presumptive HIV therapy in infants with *in utero* or intrapartum exposure to HIV. Dosing for additional ARV prophylaxis during breastfeeding is provided in Table 12.1. Antiretroviral Prophylaxis Dosing for Infants Who Are Breastfed.

For infants with HIV infection, recommendations for initial ARV therapy regimens and ARV dosing are available in the Pediatric Antiretroviral Guidelines; see What to Start and Appendix A. Pediatric Antiretroviral Drug Information.

<table>
<tr><th>ARV 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 of Gestation at Birth

Birth to Age ≤6 Weeks

• ZDV 4 mg/kg per dose orally twice daily or alternative simplified weight-band dosing (see table below)

Simplified Weight-Band Dosing for Newborns Aged ≥35 Weeks of 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 kg to <3 kg</td><td>1 mL</td></tr>
<tr><td>3 kg to <4 kg</td><td>1.5 mL</td></tr>
<tr><td>4 kg to <5 kg</td><td>2 mL</td></tr>
</table>
≥30 Weeks to <35 Weeks of Gestation at Birth

Birth to Age 2 Weeks

• ZDV 2 mg/kg per dose orally twice daily

Age 2 Weeks to ≤6 Weeks

• ZDV 3 mg/kg per dose orally twice daily

<30 Weeks of Gestation at Birth

Birth to Age 4 Weeks

• ZDV 2 mg/kg per dose orally twice daily

Age 4 Weeks to ≤6 Weeks

• ZDV 3 mg/kg per dose orally twice daily</td></tr>
<tr><td>3TC</td><td>≥32 Weeks of Gestation at Birth

Birth to Age <4 Weeks

• 3TC 2 mg/kg per dose orally twice daily</td></tr>
</table>

Table 11.1. Drug Dosing Recommendations for Antiretroviral Prophylaxis and Presumptive HIV Therapy in Infants With *In Utero* or Intrapartum Exposure to HIV[a]

<table>
<tr><th>ARV Drug</th><th>Drug Doses by Gestational Age at Birth</th></tr>
<tr><td></td><td>Age ≥4 Weeks to ≤6 weeks
• 3TC 4 mg/kg per dose orally twice daily</td></tr>
<tr><td rowspan="3">NVP[b]

Note: These are NVP treatment doses for a presumptive HIV therapy regimen. NVP dosing for extended ARV prophylaxis during breastfeeding is provided in Table 12.1.

Note: Do not use NVP if HIV-2 infection (or HIV-2 co-infection with HIV-1) is present or suspected; see HIV-2- Infection and Pregnancy.</td><td>≥37 Weeks of Gestation at Birth
Birth to Age ≤6 Weeks
• NVP 6 mg/kg per dose orally twice daily</td></tr>
<tr><td>≥34 Weeks to <37 Weeks of Gestation at Birth
Birth to Age <1 Week
• NVP 4 mg/kg per dose orally twice daily
Age ≥1 Week to ≤6 Weeks
• NVP 6 mg/kg per dose orally twice daily</td></tr>
<tr><td>≥32 Weeks to <34 Weeks of Gestation at Birth
Birth to Age <2 Weeks
• NVP 2 mg/kg per dose orally twice daily
Age ≥2 Weeks to <4 Weeks
• NVP 4 mg/kg per dose orally twice daily
Age ≥4 Weeks to ≤6 Weeks
• NVP 6 mg/kg per dose orally twice daily</td></tr>
<tr><td>RAL</td><td>≥37 Weeks of Gestation at Birth and Weighing ≥2 kg[c]
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 kg to <3 kg</td><td>0.4 mL (4 mg) once daily</td></tr>
<tr><td>3 kg to <4 kg</td><td>0.5 mL (5 mg) once daily</td></tr>
<tr><td>4 kg 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 kg to <3 kg</td><td>0.8 mL (8 mg) twice daily</td></tr>
<tr><td>3 kg to <4 kg</td><td>1 mL (10 mg) twice daily</td></tr>
</table></td></tr>
</table>

Table 11.1. Drug Dosing Recommendations for Antiretroviral Prophylaxis and Presumptive HIV Therapy in Infants With *In Utero* or Intrapartum Exposure to HIV[a]

ARV Drug	Drug Doses by Gestational Age at Birth
	4 kg to <5 kg: 1.5 mL (15 mg) twice daily **4 to 6 Weeks: Twice-Daily Dosing — Approximately 6 mg/kg per dose** 3 kg to <4 kg: 2.5 mL (25 mg) twice daily 4 kg to <6 kg: 3 mL (30 mg) twice daily 6 kg to <8 kg: 4 mL (40 mg) twice daily
ABC[d] Note: The Panels do not recommend ABC as part of three-drug regimen for newborns with HIV exposure. However, in situations where ZDV is not available or the infant has ZDV-associated toxicity, ABC could be considered an alternative to ZDV.	≥37 Weeks' Gestation at Birth *Birth to ≤1 Month* • ABC 2 mg/kg per dose orally twice daily *Age ≥1 Month to ≤6 Weeks* • ABC 4 mg/kg per dose orally twice daily

[a] The optimal duration of three-drug regimens for newborns at high risk of HIV acquisition is unknown; all infants should receive the ZDV component of the three-drug regimen for 6 weeks. The other two ARVs, (3TC and NVP) *or* (3TC and 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] 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.

[c] 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. 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.

[d] 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-B*5701 allele should be confirmed prior to the administration of ABC.

Key: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; 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 Infant Antiretroviral Drugs in Specific Clinical Situations

In this section, Table 11. Antiretroviral Management for Infants With *In Utero* or Intrapartum Exposure to HIV, and Figure 1. Antiretroviral Management Algorithm for Infants With *In Utero* or Intrapartum HIV Exposure by Risk of Transmission, the Panels present available data and recommendations for ARV management of newborns born with *in utero* and intrapartum exposure to HIV.

Infants at High Risk of HIV Acquisition From In Utero *or Intrapartum Exposure*

The Panels recommend that all newborns at high risk for HIV acquisition from *in utero* and intrapartum exposure **have an HIV nucleic acid test (NAT) at birth to determine *in utero* HIV infection status and receive presumptive HIV therapy** (see Table 11 and Figure 1).[14,16-21] HIV infection newly diagnosed during pregnancy is generally associated with high HIV RNA levels that would confer an elevated high risk of transmission to the infant, especially in the case of recent (early or acute) infection (see Table 11 and 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.[22-31] Because of these potential benefits of early ART the Panels recommend a three-drug presumptive HIV therapy regimen consisting of two nucleoside reverse transcriptase inhibitors (ZDV plus lamivudine [3TC]) plus either a non-nucleoside reverse transcriptase inhibitor (NNRTI) (NVP at treatment dose, see Table 11.1) or an integrase strand transfer inhibitor (INSTI) (raltegravir [RAL]) for newborns at high risk of acquisition of HIV:

- ZDV plus 3TC plus NVP (at treatment dose, see Table 11.1) *or*
- ZDV plus 3TC plus RAL

In the event of maternal HIV-2 infection or concomitant HIV-1 and HIV-2 infection, the RAL-containing regimen should be used for presumptive therapy because HIV-2 is not susceptible to NVP.

Although no clinical trials have compared the safety and efficacy of presumptive HIV therapy with single-drug or two-drug regimens, existing data suggest that presumptive HIV therapy in neonates has not been associated with serious adverse events (see Antiretroviral Drug Safety of Infant Prophylaxis below).

The pharmacokinetic (PK) and safety data of the three-drug regimens used for presumptive HIV therapy have provided reassuring evidence for its use in the neonatal period. Although the use of NVP to prevent 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 tenfold lower than targeted therapeutic levels. However, studies of treatment doses of NVP and RAL have established safe doses that achieve targeted PK parameters.[21,32-37]

At this time, the Panels do not recommend abacavir (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 an increased risk of ZDV toxicity may exist, such as in infants with anemia or neutropenia. Negative testing for HLA-B*5701 allele should be confirmed prior to the administration of ABC. New dosing recommendations for ABC in neonates based on the IMPAACT P1106 trial and two observational European and African cohorts are now available from the World Health Organization (WHO).[38] ABC is not approved by the U.S. Food and Drug Administration for use in neonates and infants aged <3 months. However, 2 mg/kg per dose twice daily 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).[39]

The optimal duration of a three-drug regimen in newborns at high risk of HIV acquisition is unknown. Consulting an expert in pediatric HIV is recommended when selecting a therapy duration based on case-specific risk factors and interim HIV NAT results. HIV NAT diagnostic testing at birth (prior to or immediately after starting ARVs) is recommended for infants at high risk for HIV acquisition. A positive birth NAT test indicates *in utero* HIV infection. Panel members varied in their recommendations for the duration of presumptive HIV therapy. Some Panel members would opt to discontinue additional medications and complete 6 weeks ZDV prophylaxis alone if infant birth NAT results are negative, whereas other Panel members would continue presumptive HIV therapy for 2 to 6 weeks, depending on the risk of HIV transmission. Panel members agreed that ZDV should be continued for 6 weeks in all scenarios, regardless of the duration of the other two drugs. If the birth NAT is positive, the infant should receive an ART regimen recommended for the treatment of HIV infection (see What to Start: Antiretroviral Treatment Regimens Recommended for Initial Therapy in Infants and Children With HIV and Appendix A: Pediatric Antiretroviral Drug Information in the Pediatric Antiretroviral Guidelines).

Newborns at Low Risk of HIV Acquisition from In Utero *or Intrapartum Exposure*

An infant perinatally exposed to HIV RNA levels <50 copies/mL and no HIV RNA levels ≥50 copies/mL after 20 weeks' gestation is considered to have low risk of HIV acquisition and should receive prophylaxis with ZDV alone for 2 weeks.

When ART is taken during pregnancy and labor and viral load is undetectable near or at the time of delivery, the risk of HIV acquisition in newborns is <1%.[2] In the Pediatric AIDS Clinical Trials Group (PACTG) 076 study, ZDV alone reduced the incidence of HIV transmission by 66%, and ZDV is recommended as prophylaxis for neonates when maternal ART resulted in consistent viral suppression during pregnancy.[40] Other studies have also compared NVP to ZDV infant prophylaxis.[41,42] The ANRS French Perinatal Cohort observed that NVP infant prophylaxis was associated with less anemia than ZDV infant prophylaxis. 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.[43] However, evidence supporting a reduced duration of ZDV prophylaxis in infants born to mothers who were suppressed virologically during pregnancy and at the time of delivery is mounting.[44-46]

No studies directly compare the efficacy of a 2-week versus 4-week duration of infant ZDV prophylaxis. However, high-income countries have some experience with a 2-week duration of infant prophylaxis. The United States, as well as the United Kingdom and other European countries, recommends a 2-week neonatal ZDV prophylaxis regimen when the risk of HIV acquisition from exposure is low and/or very low, with varying criteria across countries.[47,48] Compared with the

6-week ZDV regimen, a 2 to 4 week ZDV regimen has been reported to allow earlier recovery from anemia in otherwise healthy newborns.[49,50] In a cohort of 87 Swiss infants born to women with HIV RNA levels <50 copies/mL in the last trimester who did not receive ARV prophylaxis, in accordance with Swiss ARV guidance at that time, none acquired HIV infection.[51]

Other Clinical Scenarios

An infant perinatally exposed to **HIV RNA levels ≥50 copies/mL after 20 weeks of gestation but HIV RNA levels <50 copies/mL for the 4 weeks prior to delivery** is considered to have low-to-moderate risk for *in utero* and low risk for intrapartum acquisition of HIV (see Table 10). This assessment takes into consideration that low-level viremia could reflect intermittent adherence between laboratory tests. Low-level viremia (e.g., ≥50 copies/mL to 200 copies/mL) is not expected to confer a high risk of *in utero* transmission of HIV but has been associated with elevated risk of subsequent virologic failure.[52,53] The Panels did not reach consensus on infant ARV management (see Table 11) for this clinical scenario and consider factors such as the magnitude and duration of elevated HIV RNA levels,[2] maternal adherence to ART, and parental input in decision-making.

Some Panel members recommend that these infants receive presumptive HIV therapy until the results of birth HIV NAT are available. If the birth HIV NAT is negative, excluding *in utero* HIV acquisition, the Panels recommend de-escalation of presumptive HIV therapy to ZDV prophylaxis to complete ZDV for a total of 6 weeks. This provides a balanced risk/benefit approach to quickly identifying *in utero* HIV acquisition, limiting exposure to presumptive HIV therapy in the event HIV transmission has not occurred *in utero*, and promptly administering very early presumptive therapy in the event of *in utero* infection. Very early ART has been shown to provide durable virologic suppression and reduce early viral reservoirs enabling HIV remission in some children with *in utero* HIV acquisition.[31,54] See When to Initiate Antiretroviral Therapy in Children With HIV Infection. However, other Panel members argue that the data supporting the potential benefit of early ART has not been demonstrated for this specific scenario, would likely apply to a small number of infants, and carries risk of avoidable toxicity to infants without *in utero* infection; for these reasons, they recommend 2 to 6 weeks of ZDV prophylaxis. Providers must decide which rationale aligns with their own assessment and should consider involving parents in the decision.

When **early (acute or recent) HIV is diagnosed during pregnancy,** infant ARVs should be managed according to the gestational timing of maternal viremia (see Table 11). Because HIV RNA levels are generally very high in these situations, some Panel members would manage all infants with a three-drug ARV regimen even with undetectable maternal viral load after 20 weeks. Other Panel members would base decisions about infant ARVs on the timing of viremia.

When there is a **positive maternal HIV test at delivery or postpartum or infants have a positive HIV antibody test after birth,** infants should receive a three-drug regimen as described above for infants at high risk of HIV acquisition. If supplemental testing confirms a negative maternal HIV status, infant ARV drugs should be discontinued immediately.

Newborns Exposed to Antiretroviral Drug-Resistant Virus

The optimal approach to selecting an ARV regimen for newborns exposed to ARV drug-resistant virus is unknown. Some studies have suggested that ARV drug-resistant virus may have decreased replicative capacity (reduced viral fitness) and transmissibility.[55] The transmission of drug-resistant virus to infants does occur.[56-62] Whether resistant virus increases the risk of vertical HIV acquisition

by the infant remains unclear. A secondary analysis of data from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development–HIV Prevention Trials Network (HPTN) 040/PACTG 1043 did not find that the presence of drug-resistance mutations in mothers who had not received ARV drugs before the start of the study increased the risk of *in utero* or peripartum transmission (adjusted odds ratio 0.8; 95% confidence interval [CI], 0.4–1.5).[61] However, a case-control study found that resistance to NNRTIs in the breastfeeding mother was an independent risk factor for the vertical transmission of HIV during breastfeeding in the PROMISE trial.[63]

Although no trials have compared the efficacy of neonatal prophylaxis regimens customized to address maternal drug resistance, the Panels recommend considering maternal drug resistance when selecting the three-drug regimen for presumptive HIV therapy. For example, an infant at high risk of infection perinatally exposed to HIV with NNRTI resistance could potentially benefit from a three-drug regimen based on RAL rather than NVP. However, other factors must also be considered, such as gestational age (limits the number of agents with available dosing) and feasibility for the caregiver to administer the regimen (e.g., the preparation of RAL is more difficult than NVP).

Maraviroc (MVC) has been approved recently for infants ≥2 kg and may provide an additional ARV option for newborns perinatally exposed to multidrug-resistant HIV-1 that remains CCR5-tropic.[64] 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.

For assistance in selecting a three-drug ARV regimen for newborns perinatally exposed to known or suspected drug resistance, consultation with a pediatric HIV specialist or the National Perinatal HIV hotline (1-888-448-8765) is recommended.

Antiretroviral Prophylaxis for Breastfeeding Infants

HIV care should include counseling about infant feeding options (e.g., formula feeding, banked donor human milk, breastfeeding) throughout pregnancy. The conversation should include decision-making about the risk and potential benefits of ARV prophylaxis. Recommendations and dosing for infant ARV prophylaxis during breastfeeding are summarized in Table 12 and Table 12.1. In general, infant ARV prophylaxis during breastfeeding should begin after initial ZDV prophylaxis is completed. However, some experts recommend initiating ARV prophylaxis with NVP or 3TC in place of ZDV from birth for simplicity. The duration of extended infant ARV prophylaxis can also vary based on provider and parent preference. The most conservative course is to continue prophylaxis until 6 weeks after the last exposure to breast milk. However, long-standing maternal virologic suppression may be exhibited during breastfeeding, and with provider's guidance, the decision may be made to stop prophylaxis while continuing to breastfeed. The Panels recommend patient-centered, evidence-based counseling to support shared decision-making about infant feeding. See Preventing HIV Transmission During Infant Feeding for more information on counseling, management, and monitoring.

Antiretroviral Prophylaxis for Breastfeeding Infants in the Setting of Sustained Virologic Suppression (HIV RNA <50 Copies/mL)

The Panels could not reach consensus on recommendations regarding the use of extended infant ARV prophylaxis during breastfeeding. For infants considered to be at low risk, Panel members agreed on the provision of 2 weeks of ZDV to infants for standard prophylaxis for HIV exposure, but some Panel members prefer to extend the duration of ZDV prophylaxis to 4 to 6 weeks when the

infant is being breastfed. For the period after initial postnatal prophylaxis, some Panel members recommend no additional prophylaxis when virologic suppression is maintained throughout breastfeeding, but other Panel members recommend extended ARV prophylaxis with NVP or 3TC during breastfeeding. Both NVP and 3TC have been used effectively for extended prophylaxis during breastfeeding.[65,66] 3TC has been studied through 12 months of age and requires twice-daily administration.[66] NVP has been studied through 18 months of age and is given once daily.[65] Concerns related to the use of NVP include impaired efficacy in the context of maternal NNRTI and the development of NNRTI resistance if an infant acquires HIV while receiving NVP during breastfeeding (see Newborns Exposed to Antiretroviral Drug-Resistant Virus above).

When extended prophylaxis is used, most experts recommend transitioning to NVP or lamivudine 3TC after completion of the initial ZDV prophylaxis. However, NVP can be given from birth, replacing ZDV and providing both initial postnatal prophylaxis and extended prophylaxis during breastfeeding. ZDV should not be used for a period of more than 6 weeks.

Given the lack of consensus by the Panels for a recommendation about extended ARV prophylaxis during breastfeeding, **the Panels advise providers to involve the parent(s) in open discussion and shared decision-making,** weighing values about risk tolerance (for transmission and toxicity) and other issues related to infant prophylaxis (e.g., prematurity). For additional information, see Safety of Antiretroviral Drugs Used for Infant Prophylaxis below.

Most data to guide decisions about infant ARV prophylaxis during breastfeeding are from studies in sub-Saharan Africa, where breastfeeding is recommended for all pregnancies impacted by HIV infection and standard practice for prophylaxis also differs. The WHO recommends six weeks of NVP for all infants who are breastfed when maternal ART is being received in resource-limited countries.[67] In the PROMISE study, among 1,219 infants of mothers on ART, there were seven HIV transmissions reported. Among these, five mothers had documented detectable viral loads immediately prior to the first report of the infant's positive HIV NAT; the remaining two mothers had elevated viral loads in subsequent testing.[68] 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 infants with HIV and 232 infants who were uninfected and their mothers[69] 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.[70] This meta-analysis was limited by the heterogeneity in studies but reported an overall postnatal HIV transmission rate of 1.08% (95% CI, 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 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.[71]

See ARV Prophylaxis for Infants When There Is a Concern About Risk of Future Viremia During Breastfeeding, below, for additional data supporting the efficacy of NVP and 3TC as prophylaxis during breastfeeding.

Taken together, existing data support the efficacy of maternal ART during breastfeeding with documented sustained viral suppression to prevent postnatal transmission of HIV, suggesting

that the recommended management of 2 weeks of ZDV prophylaxis for infants at low risk of *in utero* or intrapartum exposure is appropriate for breastfed infants when sustained maternal HIV RNA levels of <50 copies/mL have been achieved. This approach is currently recommended by the British HIV Association (BHIVA).[47]

Table 12. Antiretroviral Management of Infants With Exposure to HIV During Breastfeeding

Maternal HIV RNA levels should be monitored periodically during breastfeeding because the status of viral suppression can change over time (see Preventing HIV Transmission During Infant Feeding). Decisions about infant antiretroviral (ARV) management during breastfeeding should be based on clinical assessment and incorporate shared decision-making when indicated.

Providers with questions about ARV management of infants should consult an expert in pediatric HIV infection or the National Perinatal HIV Hotline (1-888-448-8765).

Level of Transmission Risk During Breastfeeding by Maternal HIV RNA Levels	Description	Infant ARV Management During Breastfeeding[a]
Sustained Viral Suppression (HIV RNA <50 copies/mL)	When sustained maternal virologic suppression during pregnancy (at a minimum during the third trimester has been achieved, documented by at least two HIV RNA measurements below the limits of detection at least 1 month apart) and breastfeeding and there are no concerns about adherence	• After completion of 2-week ZDV prophylaxis in infants at low risk of *in utero* or intrapartum transmission, some Panel members recommend no additional ARV prophylaxis, but others recommend extended prophylaxis with NVP or 3TC during breastfeeding. The Panels did not reach consensus about the use of extended ARV prophylaxis during breastfeeding (see Table 12.1). • Most Panel members recommend that, if used, extended ARV prophylaxis should be continued until 6 weeks after last exposure to breast milk. However, it may be reasonable to discontinue prophylaxis earlier when concern for maternal viremia is low.
Current HIV RNA Levels <50 copies/mL But Concerns About Future Risk	When maternal virologic suppression has been achieved during pregnancy but there is concern about future risk (e.g., ART adherence or loss of virologic suppression for other reasons) during breastfeeding	• Consider extended ARV prophylaxis with NVP or 3TC (see Table 12.1). • Recommended duration is until 6 weeks after last exposure to breast milk. Providers and parents may consider cessation earlier if concerns about future risk for viremia have resolved. • Provide added adherence support as indicated.

Table 12. Antiretroviral Management of Infants With Exposure to HIV During Breastfeeding

Level of Transmission Risk During Breastfeeding by Maternal HIV RNA Levels	Description	Infant ARV Management During Breastfeeding[a]
New Viremia During Breastfeeding (HIV RNA **≥200 copies/mL**)	When maternal viremia with HIV RNA ≥200 copies/mL develops or presumed viremia (e.g., nonadherence, interrupted access to ARVs)	• Breastfeeding should be stopped temporarily or discontinued and replacement feeding initiated (see Situations to Consider Modifying or Stopping Breastfeeding in Preventing HIV Transmission During Infant Feeding). Most experts recommend permanent discontinuation of breastfeeding if HIV RNA ≥200 copies/mL, but some support resuming breastfeeding once re-suppressed. • Perform infant HIV NAT.[a] • Initiate presumptive HIV therapy using three-drug regimen of ZDV, 3TC, and DTG.[b] For infants aged <4 weeks, ZDV and 3TC plus NVP (treatment dose) or RAL should be used. See Table 12.1 for dosing information. • Duration of 2–6 weeks; consensus was not reached by Panel members. • If the duration of the three-drug regimen is <6 weeks, and the NAT is negative, continue ZDV alone to complete a total of 6 weeks of prophylaxis.
New Viremia During Breastfeeding (HIV RNA <200 copies/mL)	The Panels did not reach consensus about neonatal management when maternal viremia develops that is quantifiable but <200 copies/mL.	• Breastfeeding should be stopped temporarily or discontinued and replacement feeding initiated (see Situations to Consider Modifying or Stopping Breastfeeding in Preventing HIV Transmission During Infant Feeding). • Perform infant HIV NAT.[a] • Some Panel members recommend initiation of presumptive ARV therapy (as described for new viremia ≥200 copies/mL, above); other Panel members recommend initiation of single-drug ARV prophylaxis (see Table 12.1). • Some Panel members recommend management based on repeat HIV RNA testing. • Consultation with an expert is suggested.

Table 12. Antiretroviral Management of Infants With Exposure to HIV During Breastfeeding

Level of Transmission Risk During Breastfeeding by Maternal HIV RNA Levels	Description	Infant ARV Management During Breastfeeding[a]
New Diagnosis of HIV When Breastfeeding	Newly diagnosed maternal HIV while breastfeeding infant	• Stop breastfeeding and initiate replacement feeding. • Perform infant HIV NAT.[a] • Initiate presumptive HIV therapy using three-drug regimen of ZDV, 3TC, and DTG.[b] For infants aged <4 weeks, ZDV and 3TC plus NVP (treatment dose) or RAL should be used. See Table 12.1 for dosing information. • Duration of 2 to 6 weeks; consensus was not reached by Panel members. • If the duration of three-drug regimen is <6 weeks and the NAT is negative, continue ZDV alone to complete a total of 6 weeks of prophylaxis.

[a] An HIV NAT at birth is recommended for all breastfeeding infants. A NAT should be obtained before or immediately after starting ARVs. See Diagnosis of HIV Infection in Infants and Children for additional information about infant NATs during breastfeeding and follow-up testing after maternal viremia.

[b] DTG, a second-generation integrase strand transfer inhibitor with a higher barrier to resistance than RAL, can be used in infants aged ≥4 weeks and weighing ≥3 kg.

Note: Given limited data, decisions about infant ARV prophylaxis during breastfeeding should be based on shared decision-making with the infant's parents.

Key: 3TC = lamivudine; ART = antiretroviral therapy; ARV = antiretroviral; DTG = dolutegravir; NAT = nucleic acid test; NVP = nevirapine; the Panels = 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 12.1. Antiretroviral Prophylaxis Dosing for Infants Who Are Breastfed

ARV Prophylaxis for Infants When Maternal Sustained Viral Suppression is Achieved	
Recommended Regimen	Recommended Duration and Dosing
ZDV	ZDV administered for 2 weeks after birth (see Table 11.1 for dosing)
Options for Extended Postnatal Prophylaxis[a]	
Recommended Regimen	Recommended Duration and Dosing
ZDV	ZDV administration continued for 4–6 weeks after birth (See Table 11.1 for dosing; note that ZDV is not recommended for prophylaxis beyond this initial postnatal period.)

Table 12.1. Antiretroviral Prophylaxis Dosing for Infants Who Are Breastfed

<table>
<tr><td>NVP[b,c]</td><td>NVP administered starting at birth or after completion of initial prophylaxis ZDV, through 6 weeks after cessation of breastfeeding

Simplified Age-Based NVP Dosing for Newborns ≥32 Weeks' Gestation Receiving Extended NVP Prophylaxis During Breastfeeding[b,c]

<table>
<tr><th>Age</th><th>Dose and Volume of NVP 10 mg/mL Oral Syrup Administered Once Daily</th></tr>
<tr><td>Birth to 6 weeks</td><td>2.0 to < 3.0 kg: 10 mg (1.0 mL)
≥ 3.0 kg: 15 mg (1.5 mL)</td></tr>
<tr><td>6 weeks to 6 months</td><td>20 mg (2.0 mL)</td></tr>
<tr><td>6 months to 9 months</td><td>30 mg (3.0 mL)</td></tr>
<tr><td>9 months to 18 months</td><td>40 mg 4.0 mL</td></tr>
</table>
</td></tr>
<tr><td>3TC</td><td>3TC administered starting after completion of initial prophylaxis ZDV, through 6 weeks after cessation of breastfeeding

Age 2 Weeks to <4 Weeks

• 3TC 2 mg/kg per dose orally twice daily

Age ≥4 Weeks to 12 months

• Use simplified weight-band dosing outlined in the table below.

Simplified Weight-Band Dosing for 3TC (10 mg/ml Solution) When Used as Prophylaxis During Breastfeeding[d]

<table>
<tr><th>Weight Band</th><th>Dose and Volume of 3TC 10 mg/mL Oral Solution Administered Twice Daily</th></tr>
<tr><td>2 to < 3 kg</td><td>10 mg (1 mL)</td></tr>
<tr><td>3 kg to <4 kg</td><td>15 mg (1.5 mL)</td></tr>
<tr><td>4 kg to <8 kg</td><td>25 mg (2.5 mL)</td></tr>
<tr><td>≥8 kg</td><td>50 mg (5 mL)</td></tr>
</table>
</td></tr>
<tr><th colspan="2">Recommended Infant ARV Management When Maternal Viremia Develops or HIV is Diagnosed During Breastfeeding[a]</th></tr>
<tr><th>Presumptive HIV Therapy Regimens</th><th>Recommended Duration and Dosing</th></tr>
<tr><td>ZDV plus 3TC plus DTG[e]</td><td>Three-drug presumptive HIV therapy regimen. ZDV and 3TC plus NVP or RAL should be used in place of DTG for infants aged <4 weeks and/or weighing <3 kg.[e,f] See Table 11.1 for dosing of ZDV and 3TC in infants aged <6 weeks. Refer to drug sections in Appendix A: Pediatric Antiretroviral Drug Information for appropriate age-based dosing of DTG and for dosing of ZDV, 3TC, NVP, or RAL in infants aged >6 weeks.</td></tr>
</table>

Table 12.1. Antiretroviral Prophylaxis Dosing for Infants Who Are Breastfed

	Presumptive HIV therapy is recommended for a duration of 2–6 weeks (see Table 12).

[a] Consultation and referrals to local or regional Pediatric HIV specialists are available through the National Perinatal HIV Hotline (1-888-448-8765).

[b] NVP dosing is adapted from the Consolidated Guidelines on HIV Prevention, Testing, Treatment, Service Delivery and Monitoring: Recommendations for a Public Health Approach. For infants at low risk of transmission, these doses can be given from birth. (Simplified Age-Based Dosing for Newborns ≥32 Weeks' Gestation Receiving Extended NVP Prophylaxis During Breastfeeding in the World Health Organization's Consolidated Guidelines on HIV Prevention, Testing, Treatment, Service Delivery and Monitoring: Recommendations for a Public Health Approach, July 2021)

[c] 3TC should be used as extended ARV prophylaxis during breastfeeding when there is evidence or concern for maternal NVP resistant virus (including HIV-2 infection or HIV-1/HIV-2 co-infection) or when an infant cannot tolerate NVP. Dosing recommendations for 3TC are included in the table.

[d] Dosing for extended 3TC prophylaxis during breastfeeding, based on established 3TC dosing for treatment and weight-band dosing used in PROMISE-EPI Source: Mennecier A, Kankasa C, et al. Optimised prevention of postnatal HIV transmission in Zambia and Burkina Faso (PROMISE-EPI): a phase 3, open-label, randomised controlled trial. *Lancet*. 2024;403(10434):1362-1371. https://pubmed.ncbi.nlm.nih.gov/38484756.

[e] DTG, a second-generation integrase strand transfer inhibitor with a higher barrier to resistance than RAL, is preferred in infants aged ≥4 weeks and weighing ≥3 kg.

[f] When maternal HIV infection is diagnosed while breastfeeding, a three-drug presumptive HIV therapy regimen is recommended for the infant, with a duration of 2–6 weeks (see Table 12.1). The same regimen is recommended for infants at high risk of HIV acquisition after *in utero* or intrapartum exposure (see Table 11 and Table 11.1). No trials have evaluated the use of multidrug regimens to prevent transmission after cessation of breastfeeding with early (acute or recent) HIV infection. Some Panel members recommend 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.

Key: 3TC = lamivudine; ARV = antiretroviral; NVP = nevirapine; RAL = raltegravir; ZDV = zidovudine

Antiretroviral Prophylaxis for Infants When There Is Concern About the Risk of Future Viremia During Breastfeeding

When there is an interest in breastfeeding and the criteria for the lowest anticipated risk of breast milk transmission is met, with current and recent HIV RNA levels of <50 copies/mL, there may be concern about future adherence in the postpartum period or factors that may impact virologic suppression (e.g., postpartum depression, interrupted access to ARVs).[72] Lapses in adherence in the postpartum period are common, with increased risk among women of younger age and more recent ART initiation.[73] Providers may consider additional adherence history and postpartum adherence challenges following prior pregnancies when making recommendations about infant prophylaxis during breastfeeding. There may be anticipated changes in social structure, such as moving to a new home, in the postpartum period that may generate new challenges to adherence. It is also important for providers to elicit parents' concerns, regardless of the provider's assessment. If there are concerns about ARV adherence during breastfeeding, the Panels recommend extended infant ARV prophylaxis during breastfeeding with either NVP or 3TC and the addition of maternal adherence support (see Table 12 and Table 12.1).

Data suggest that infant prophylaxis can be very effective in preventing breast milk transmission in the context of maternal viremia. In the PROMISE trial, only 7 of the 1,211 (0.58%) analyzed infants in the infant NVP prophylaxis arm acquired HIV infection.[68] A randomized controlled trial in Burkina Faso and Zambia found that initiation of same day infant 3TC prophylaxis in women with a

viral load of >1,000 copies/mL during breastfeeding resulted in a reduction in postnatal HIV transmission compared to local standard of care.[66] Although findings did not reach statistical significance because the study was underpowered, the findings suggest that early infant diagnosis, in conjunction with on-demand HIV RNA testing in the breastfeeding mother and extended infant prophylaxis, could be a valuable approach in eliminating postnatal HIV transmission risk. A pooled analysis of these trials reported that mothers with a viral load of 40 to 1,000 copies/mL in the initial 6 to 8 weeks postpartum were at high risk for having a viral load >1,000 copies/mL at 6 or 12 months postpartum.[74] Given the efficacy demonstrated in the trials, the Panels believe that extended ARV prophylaxis should be considered for breastfeeding infants when there is concern about future risk of HIV exposure during episodes of maternal viremia.

Antiretroviral Prophylaxis for Infants Exposed to Detectable HIV RNA During Breastfeeding

Parents should receive counseling and be involved in decision-making about infant ARV prophylaxis and management of infant feeding. In situations where there is increased risk of postnatal transmission due to the development/occurrence of viremia during breastfeeding, the Panels advise initiation of additional infant ARV prophylaxis to prevent breastfeeding-associated HIV transmission. When detectable maternal HIV RNA levels develop during breastfeeding, the infant should be tested for HIV infection (using a NAT) prior to or immediately after initiating ARVs, as well as at specified time points after cessation of breastfeeding and completion of presumptive HIV therapy (see Diagnosis of HIV Infection in Infants and Children and Table 13. Recommended Virologic Testing Schedule for Infants With Perinatal and Breastfeeding Exposure to HIV). If infant HIV testing returns a positive HIV NAT result, see Infants with HIV Infection below and What to Start in the Pediatric Antiretroviral Guidelines).

When new maternal viremia develops, the Panels recommend that breastfeeding be stopped temporarily or discontinued and replacement feeding initiated (see Situations to Consider Modifying or Stopping Breastfeeding in Preventing HIV Transmission During Infant Feeding). Most experts recommend permanent discontinuation of breastfeeding when HIV RNA is ≥200 copies/mL. This guidance is more directive than counseling when suppressive ART is being taken. In situations where viremia is lower and an addressable cause has been identified, the added risk of short term continued breastfeeding would be less.

Management of New Maternal Viremia With HIV RNA ≥200 Copies/mL While Breastfeeding

In cases where new maternal viremia with an HIV RNA level ≥200 copies/mL occurs while breastfeeding, the Panels recommend immediate initiation of infant presumptive HIV therapy using a three-drug regimen of ZDV plus 3TC plus DTG (NVP or RAL in place of DTG, if infant age < 4 weeks) (see Table 12 and Table 12.1 above). The drugs should be administered together for 2 to 6 weeks, with duration based on timing of results of infant NAT. As for management of high risk around the time of birth, if 3TC plus (DTG or NVP or RAL) are discontinued, ZDV should be continued alone to complete a total of 6 weeks prophylaxis.

As noted above, in cases where new maternal viremia with an HIV RNA level ≥200 copies/mL develops while breastfeeding, the Panels recommend permanent cessation of breastfeeding. However, the decision may be made to continue to breastfeed in which case longer durations of

ARVs for infants may be indicated. Discussion with parents and consultation with the National Perinatal HIV Hotline (1-888-448-8765) or consultation with another expert is suggested.

Management of New Maternal Viremia With HIV RNA <200 Copies/mL While Breastfeeding

In cases where new maternal viremia that is quantifiable but with HIV RNA <200 copies/mL occurs while breastfeeding, some Panel members recommend initiation of presumptive HIV therapy for the infant, other Panel members recommend initiation of single-drug ARV prophylaxis (with NVP or 3TC), and other Panel members recommend infant ARV management based on repeat maternal HIV RNA testing. The rationale for the cutoff of 200 copies/mL is that low-level viremia <200 copies/mL has been shown to predict future virologic failure with HIV RNA >200 copies/mL.[75] The Panels did not reach consensus about infant ARV prophylaxis or presumptive HIV therapy in this situation (see Table 12). Discussion with parents and consultation with the National Perinatal HIV Hotline (1-888-448-8765) or consultation with another expert is suggested.

Special Situations in Breastfeeding Infants

Initiation or Continuation of Breastfeeding With Viremia

The Panels strongly advise against initiating or continuing breastfeeding infants at high risk of HIV acquisition from *in utero,* intrapartum, and/or postnatal exposure. 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 Preventing HIV Transmission During Infant Feeding). Discussion with parents and consultation with the National Perinatal HIV Hotline (1-888-448-8765) or consultation with another expert is recommended.

Infants Exposed to Newly Diagnosed Maternal HIV While Breastfeeding

When maternal HIV is suspected (e.g., a positive initial screening test), breastfeeding should be discontinued immediately, until HIV is ruled out. Pumping and temporarily discarding or freezing breast milk can be recommended when maternal HIV while breastfeeding is suspected but HIV serostatus is not yet confirmed and continuation of breastfeeding is desired. 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 maternal HIV infection is confirmed while breastfeeding.[76] See New HIV Diagnosis While Breastfeeding in Diagnosis of HIV Infection in Infants and Children for guidance about infant testing.

Breastfed infants exposed to newly diagnosed maternal HIV diagnosis during breastfeeding are considered to be at high risk of HIV acquisition and treated accordingly with a three-drug presumptive HIV therapy regimen for 2 to 6 weeks (see Table 12 and Table 12.1). No trials have evaluated the use of multidrug regimens to prevent transmission after cessation of breastfeeding by a parent with early (acute or recent) HIV infection. Given the higher risk of postnatal transmission from early (acute or recent) HIV infection while 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. The National Perinatal HIV Hotline (1-888-448-8765) can provide

referrals to local or regional pediatric HIV specialists.

Safety of Antiretroviral Drugs Used for Infant Prophylaxis

This section is intended to provide the information needed for clinical management and counseling parents on decision-making around infant prophylaxis. When used alone for prophylaxis in low-risk scenarios during the neonatal period and breastfeeding, ARVs appear highly safe. The most prominent toxicity in the neonatal period is anemia from ZDV given alone or in combination regimens; anemia occurs after 2–4 weeks but recovers with the cessation of treatment to levels similar to controls (see Initial Postnatal Management of the Neonate Exposed to HIV). During the breastfeeding period, 3TC has been shown to be safe through at least 41 weeks. NVP has been shown to be safe for infants from birth through 18 months of life; one trial identified cases with concerns of a hypersensitivity reaction, but larger subsequent trials did not report hypersensitivity reactions. Three-drug combinations appear safe within the durations currently recommended (i.e., 2–6 weeks).

Based on existing safety data, longitudinal laboratory monitoring for adverse events is not needed in otherwise healthy infants receiving currently recommended ARVs used for prophylaxis in the first 6 weeks of life. The American Academy of Pediatrics recommends periodic monitoring of hematologic and liver toxicity in breastfeeding infants receiving ARV prophylaxis beyond this period and for extended durations.[77]

Zidovudine

ZDV was the first agent studied for prophylaxis against HIV transmission to infants and remains the standard of care for prophylaxis in low-risk situations. The major side effect from short-term (6 weeks or less) use of ZDV appears to be transient anemia.

- In the landmark PACTG 076 trial, 415 infants were randomized and received ZDV or placebo; hemoglobin levels in the ZDV arm were lower at the end of the 6-week treatment course but recovered and were equivalent between arms by 12 weeks.[43] No other toxicities were significantly different between arms, and no new toxicities were identified through 18 months of follow up.[78]
- Subsequent trials of 6-week regimens of ZDV alone did not identify other significant toxicities.[20]
- 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.[49] Severe cases of anemia can be treated with erythropoietin[79]; substitution of ZDV with 3TC and/or NVP[41] can also be considered.

Lamivudine

3TC has been extensively studied in combination with ZDV, but data primarily from two trials support the safety of 3TC used alone as prophylaxis during breastfeeding through at least 41 weeks of life.

- The Mitra Study was an open-label single-arm prospective cohort trial in which 398 infants were treated with ZDV + 3TC from birth to 1 week of age, and then with 3TC alone for the duration of breastfeeding (maximum of 6 months) plus 2 weeks after stopping breastfeeding.[80] No serious adverse events were attributed to the study drug.

- In ANRS 12174, 1,273 infants were randomized at 7 days to receive either lopinavir/ritonavir (LPV/r) or 3TC through the completion of breastfeeding (median duration 41 weeks)[81]; there were no differences in adverse events rates between the arms.
- In ANRS 12397 PROMISE-EPI, in infants breastfed by mothers with HIV who were viremic during pregnancy, 3TC was initiated as prophylaxis at 6 weeks and 6 months, and continued through 12 months of age; the initial report noted no safety concerns, but the full results have not yet been published.[82,83]

Nevirapine

Several trials support the safety of once-daily NVP in the first 6 weeks of life and through breastfeeding. Although reactions concerning hypersensitivity were reported in the Breastfeeding, Antiretrovirals, and Nutrition (BAN) trial, no cases have been identified in subsequent large trials or from clinical programs. Strong data also support the safety of twice-daily NVP used in a three-drug presumptive HIV therapy regimen.

- In the SWEN trial, infants were randomized to either single dose (n = 1,047) or 6-week courses (n = 977) of once-daily NVP; adverse events were common overall (~40%) but without significant differences by arm.[81]
- In the BAN trial, 2,369 mother-infant dyads were randomized to infant prophylaxis with once-daily NVP, maternal ARV treatment, or enhanced control until the cessation of breastfeeding but no longer than 28 weeks.[84] A hypersensitivity reaction (rash, with eosinophilia in 10 infants, with or without fever) developed in 16 (1.9%) infants within 4 weeks after the initiation of NVP therapy; reactions resolved after NVP was replaced with 3TC. Hypersensitivity was the only adverse event significantly different between arms.
- In HPTN 046, 1,519 breastfeeding infants were randomized to 6 months of once-daily NVP or placebo (after 6 weeks of NVP from birth); no differences in adverse event rates were noted by arm through 12 months of follow up.[81]
- In the PEPI-Malawi trial, 3,016 infants were randomized to receive NVP with 1 week of ZDV (control), once daily NVP extended through 14 weeks, or NVP + ZDV extended through 14 weeks.[85] Among the three arms, no significant differences were seen in serious adverse event rates overall, nor among adverse events deemed probably associated with study drugs. However, the extended NVP + ZDV arm had significantly more serious adverse events deemed possibly related to NVP or ZDV, the most common of which was neutropenia.
- In IMPAACT 1077BF, the breastfeeding component of the PROMISE trial, 2,431 mother-infant dyads were randomized to either maternal ART or infant NVP prophylaxis (once daily) continued until 18 months after delivery or breastfeeding cessation[65]; the median duration of breastfeeding was 16 months in both arms. No differences were seen between study arms in Grade 3 or 4 adverse event rates or liver or skin toxicity. Of the 1,204 infants in the NVP arm who started on the study-recommended regimen, only 20 (2%) stopped the recommended regimen because of concerns of toxicity, and no cases of hypersensitivity were reported.
- The French Perinatal Cohort observed less frequent Grade 2 or higher anemia in 830 infants receiving once-daily NVP versus ZDV prophylaxis in a high-resource setting.[41]
- In IMPAACT P1115, infants at high risk of HIV acquisition were given NVP twice daily as part of a three-drug presumptive HIV therapy approach; NVP was dosed as 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 thereafter for preterm neonates (34 to <37 weeks gestational age).[21] Among 438 neonates enrolled, 389 (89%) were born at term; 36 were subsequently found to have *in utero* HIV infection. Division of AIDS (DAIDS) Grade 3 or 4 adverse events that were classified as at least possibly related to ARVs were reported in 30 infants (7%; 95% CI, 5–10) but did not lead to cessation of NVP in any cases; neutropenia (25 neonates [6%]) and anemia (six neonates [1%]) were the most commonly reported toxicities.

Abacavir

Data on the use of ABC in HIV-exposed neonates are limited, but suggest it is well tolerated. In a metanalysis and population PK model that included data from three separate PK trials with a total of 45 infants aged <3 months and born to women with HIV, no adverse events of Grade 3 or greater were attributed to ABC.[86] At this time, the Panels suggest using ABC in neonates as an alternative to ZDV in rare situations and only after negative HLA-B*5701 allele testing.

Raltegravir

The primary toxicity of concern with the use of RAL in the neonatal period has been the potential increase in bilirubin levels, but at recommended dosing, RAL appears safe. 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, RAL binds to albumin, raising concern that the displacement of bilirubin could lead to hyperbilirubinemia. However, *in vitro* studies suggested RAL would be safe at the drug exposures achieved for treatment.[87] IMPAACT P1110, the single-arm regulatory Phase 1/2 trial that established dosing for RAL, evaluated safety in 52 infants of 34 weeks gestational age and older; no adverse events were attributed to RAL, and no bilirubin levels exceeded 16 mg/dL.[88]

Combination ARV Regimens

Combination ARV regimens are associated with elevated risk of toxicity compared to single agents, but the three-drug regimens currently recommended for presumptive HIV therapy in neonates (e.g., NVP/ZDV/3TC or RAL/ZDV/3TC) appear very safe when used for 6 or fewer weeks. Early studies of two and three-drug regimens used as prophylaxis suggested that hematologic and mitochondrial toxicity is more common than with exposure to a single NRTI.[89-93] However, more recent studies provide data about the safety of the ARV regimen that is currently recommended for presumptive HIV therapy, suggesting it is generally well tolerated, but does confer an increased risk of anemia.

- In IMPAACT P1115, 438 infants of at least 34 weeks gestational age at high risk of HIV acquisition initiated NVP plus 2 NRTIs (ZDV + 3TC in 96%) within 48 hours of life and continued until *in utero* infection was excluded by HIV DNA testing at birth (a median of 13 days).[21] Grade 3 or 4 adverse events at least possibly related to ARVs occurred in 30 (7%) of 438 infants, with neutropenia (25 [6%]) and anemia (6 [1%]) being the most common. Toxicity led to the permanent discontinuation of ZDV in nine (2%) of 438 participants (four found to have *in utero* HIV, and five without) with neutropenia and anemia being the primary reasons for discontinuation; no other ARVs were permanently discontinued because of toxicity.

- A prospective cohort study in Thailand reported a greater proportion of infants receiving ZDV/3TC/NVP for 6 weeks experienced Grade 2 anemia (38%) at 1 month compared to infants receiving ZDV alone (21%, $P = 0.007$).[94] However, the risk of Grade 3 anemia was lower and similar between arms at 9.2% versus 10.2%, respectively ($P = 0.81$). Hemoglobin levels recovered by 2 months, at which time there was no difference between the arms. No differences in neutropenia or hepatotoxicity between the groups were observed.
- A retrospective study described outcomes of 148 Canadian infants at high risk of HIV transmission treated with three drugs for 6 weeks including ARV based on NVP (40%), nelfinavir (50%), and LPV/r (5%); all together, infants receiving combination regimens had lower hemoglobin levels than infants who received ZDV alone over 6 months, but no difference was seen between the subgroup receiving NVP-based treatment compared to ZDV alone.[32]

Generalizability of Available Safety Data

A number of considerations affect the generalizability of the safety data reviewed here to current patient populations.

- The majority of trials included were completed at a time when mothers of infants receiving prophylaxis were not receiving ART. It is possible that ARVs passed through breast milk could add to toxicity in infants also receiving prophylaxis during breastfeeding. Current data suggest that only clinically insignificant, small amounts of approved ARVs enter the breast milk, but this hypothetical possibility must be considered for new agents. See Safety of Antiretroviral Drugs During Breastfeeding in Preventing HIV Transmission During Infant Feeding for more details.
- This section focused on the risk of severe (Grade 3 or 4) adverse events; most trials did not report the frequencies of lower-grade toxicities. Please see the DAIDS reference tables for more information.[95]
- The overall rate of adverse events was high in many of the trials. For example, in IMPAACT 1077BF, approximately 35% of infants in both arms experienced Grade 3 adverse events or death, a rate much higher than experienced in settings with more health care resources.[65] The high rate of events unrelated to study drugs overall may reflect the limited health care resources in the settings in sub-Saharan Africa. However, some data suggest that the normal value ranges developed in the United States may not be applicable in other settings or countries.[96,97] As a result, it is difficult to extrapolate the individual risk of events for an infant in settings that differ from the trials. However, the possibility of an added risk of adverse events from agents can still be evaluated by comparing arms in randomized trials.
- This section focuses on agents and approaches that are currently recommended. Safety data about approaches that are no longer recommended (e.g., NVP plus ZDV) can be found in archived guidelines.
- Additional information about ARV toxicity can be found in the Pediatric Antiretroviral Guidelines (see Appendix A: Pediatric Antiretroviral Drug Information); however, data summarized there are generally from clinical trials and other studies of children with HIV, in whom the coadministration of other ARVs and comorbidities may also have contributed to toxicity.

Infants With HIV Infection

When infant HIV testing returns a positive HIV NAT result, the Pediatric Antiretroviral Guidelines recommend rapid initiation of ART (defined as initiating ART immediately or within days of HIV diagnosis) without waiting for a confirmatory test, given the low likelihood of a false-positive HIV NAT (see When to Initiate Antiretroviral Treatment in Children with HIV Infection and Diagnosis of HIV Infection in Infants and Children). ART should be discontinued if subsequent negative NAT testing excludes the presence of HIV infection. What to Start in the Pediatric Antiretroviral Guidelines provides recommendations about initial ART for infants and children with HIV, including those who are receiving presumptive HIV therapy or other ARV prophylaxis at the time of diagnosis.

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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 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).
- An assay that detects HIV non–B subtype viruses or Group O infections (e.g., an HIV RNA NAT or a total DNA/RNA test) is recommended for use in infants and children perinatally exposed to known or suspected non–B subtype virus or Group O infections (AII).
- Virologic diagnostic testing using an HIV NAT (see Table 13 below) is recommended for all infants with perinatal HIV exposure at the following ages:
  - Birth (AII)
    - The test at birth generally should be performed in all infants with perinatal HIV exposure but is not necessary for infants at low risk of HIV acquisition (HIV RNA levels <50 copies/mL from 20 weeks of gestation through delivery put infants at low risk of HIV acquisition). Birth testing should be performed in infants at low risk of HIV acquisition if there are plans to breastfeed or there are concerns about loss to follow-up (BIII).
  - 14 to 21 days (AII)
  - 1 to 2 months (AII)
  - 4 to 6 months (AII)
- For infants who receive presumptive HIV therapy, additional virologic diagnostic testing is recommended 2 to 6 weeks after antiretroviral (ARV) drugs are discontinued (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 (and no positive virologic tests), with one negative test obtained at age ≥1 month (and at least 2–6 weeks after discontinuation of infant ARVs) 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 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 (AII).
- 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 if the gap between the tests at ages 1 to 2 months and 4 to 6 months is greater than 3 months. See Preventing HIV Transmission During Infant Feeding.
  - Virologic diagnostic testing should be performed at least 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 and 4 to 6 months after cessation (BII).

Infants with potential HIV exposure after birth (e.g., diagnosis of HIV during breastfeeding, premasticated feeding, sexual abuse, contaminated blood products, percutaneous exposure) require additional testing using HIV antigen/antibody and/or HIV NAT assays, based on age at time of exposure and the maternal HIV status at delivery (AII).

- Age-appropriate HIV testing is also recommended for infants and children with signs and/or symptoms of HIV, even in the absence of documented or suspected HIV exposure (AII).
- For children aged ≥18 months, HIV antibody (or HIV antigen/antibody) tests are recommended for diagnostic testing (AII).
  - When early (acute or recent) HIV infection is suspected, additional testing with an HIV NAT may be necessary to diagnose HIV infection (AII).

Note: The National Perinatal HIV Hotline 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 all by age 4 to 6 months. Antibody tests, including antigen/antibody combination immunoassays, do not establish the presence of HIV in infants because HIV antibodies that have been transferred transplacentally may be detected (i.e., false positive); 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 antiretroviral therapy (ART) through transplacental transfer of antiretroviral (ARV) drugs to the fetus during pregnancy 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] A 2019 systematic review provides additional information on the global and regional molecular epidemiology of Group M subtype infections and recombinants among subtypes.[4] Newer HIV RNA PCR assays are usually "dual-target" assays, which target two separate highly conserved regions on the HIV genome. Dual-target HIV assays are better than older RNA assays at detecting non–subtype B HIV infection and Group O strains[5-10] (See Clinical and Laboratory Monitoring of Pediatric HIV Infection).

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 with known perinatal HIV exposure. 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 aged <18 months.[11-13] Children with perinatal HIV exposure who are aged ≥18 months occasionally have residual HIV antibodies from the antepartum period; definitive confirmation of HIV infection in children in this age group who remain HIV antibody–positive should be based on a NAT (see Special

Situations below). Diagnosis in children aged ≥18 months relies primarily on HIV antibody and antigen/antibody tests (see Diagnostic Testing in Children with Postnatal HIV Exposure below).[1]

An infant who has a positive HIV antibody test but the maternal HIV status is unknown (see Pregnancy and Postpartum HIV Testing and Identification of Perinatal and Postnatal 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,[3] and receive presumptive HIV therapy as soon as possible (see Antiretroviral Management of Infants with *In Utero*, Intrapartum, or Breastfeeding Exposure to HIV).

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 <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 ART is being taken and viral suppression is achieved and sustained during pregnancy and postpartum.

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), one negative virologic test at age ≥8 weeks at least 2 weeks after discontinuing multidrug ARV prophylaxis/presumptive therapy, or one negative HIV antibody test at age ≥6 months.[1, 3]

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 infant ARVs) 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.[14] 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

Virologic testing at birth provides insights about the timing of HIV transmission and supports early HIV diagnosis for rapid initiation of ART when indicated (see When to Initiate Antiretroviral Treatment in Children With HIV Infection in the Pediatric Antiretroviral Guidelines). Infants who have a positive virologic test result at or before age 48 hours are considered to have early (*in utero*)

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.[15-17]

In addition to early HIV diagnosis, results of birth testing are used in clinical decisions about infant ARV management. Negative HIV virologic testing at birth would rule out *in utero* infection and allow de-escalation of a three-drug presumptive HIV therapy regimen for some infants. See Table 11 and associated content in Antiretroviral Management of Infants With *In Utero*, Intrapartum, or Breastfeeding Exposure to HIV.

Virologic testing at birth should generally be performed for all infants with perinatal HIV exposure but is not necessary for infants who are at low risk of infection (HIV RNA levels <50 copies/mL from 20 weeks gestation through delivery put infants at low risk of HIV acquisition) unless there are plans to breastfeed. When breastfeeding is planned for an infant at low risk of HIV acquisition, a birth test provides baseline information, should the infant subsequently have a positive test. Virologic testing at birth should also be considered whenever there are concerns that the newborn may be lost to follow-up without testing.

Specimens for HIV testing at birth should be obtained before or immediately after initiating an ARV drug regimen; however, presumptive HIV therapy or ARV prophylaxis 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 Age 14 to 21 Days

Some children with perinatal HIV exposure can have a positive NAT between 14 and 21 days of age.[3] Early identification of infection permits transition from presumptive HIV therapy to treatment doses of ART (see When to Initiate Antiretroviral Treatment in Children With HIV Infection 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 infants with perinatal HIV exposure. 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.[18] 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 suggest performing an additional virologic test 2 to 6 weeks after ARV drugs are discontinued (i.e., at age 8–12 weeks when the infant receives 6 weeks of prophylaxis), 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.[18, 19] 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.

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.

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.[20, 21]

Antibody Testing at Age ≥18 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.

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

Some may choose to breastfeed with HIV (see Preventing HIV Transmission During Infant Feeding). A descriptive study of 72 people with HIV who breastfed their infants in North America reported high variability in policies, infant ARV prophylaxis, and infant and parental testing practices among institutions and noted the need to identify best care practices.[22] Table 13 summarizes the recommended diagnostic testing schedule for infants who are being breastfed. 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 to provide baseline information should the infant subsequently have a positive test. 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 at least every 3 months during breastfeeding. At cessation of breastfeeding, virologic diagnostic testing should be performed at 4 to 6 weeks and 4 to 6 months after breastfeeding has ended, regardless of the age of the child when breastfeeding is discontinued. If the infant is receiving extended ARV prophylaxis during breastfeeding, an additional test should be done at least 2 weeks after cessation of ARV prophylaxis. If an infant's virologic test result is positive, a repeat test should be performed as soon as possible and ART should be initiated.

No data exist to inform the appropriate frequency of maternal viral load testing during breastfeeding. One approach is to monitor plasma viral load every 1 to 2 months during breastfeeding. Additional infant virologic testing using an HIV NAT is indicated if the maternal viral load becomes detectable during breastfeeding (for infant ARV prophylaxis considerations, see Table 12 and Table 12.1 in Antiretroviral Management for Infants With *In Utero*, Intrapartum, or Breastfeeding Exposure to HIV). If maternal viral load is detectable and breastfeeding continues, 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, irrespective of when breastfeeding ends,

virologic testing should be performed at 4 to 6 weeks and 4 to 6 months after cessation of breastfeeding. If the breastfed infant is receiving presumptive HIV therapy or ARV prophylaxis, this virologic testing should be performed at least 2 weeks after discontinuation of infant ARV administration. Consultation with an expert and/or the National Perinatal HIV Hotline (8884488765) 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 Preventing HIV Transmission During Infant Feeding.

Table 13. Recommended Virologic Testing Schedules for Infants With Perinatal and Breastfeeding Exposure to HIV

Infants With Perinatal HIV Exposure[a]	
Risk Category	**Age at HIV NAT[b,c] Testing**
Infants at *High* Risk of HIV Acquisition Infants with perinatal HIV exposure to— • Viremia (HIV RNA ≥50 copies/mL) in the 4 weeks prior to delivery • Early (acute or recent) HIV during pregnancy or HIV diagnosed in labor or postpartum Note: Viremia can be documented by a laboratory or presumed by other clinical factors (e.g., new diagnosis, ART adherence challenges, stopping ART prior to delivery).	Birth 14–21 days 1–2 months 2–3 months (see note below) 4–6 months All infants at high risk of perinatal HIV transmission should have specimens obtained for HIV testing at birth before or immediately after initiating an ARV drug regimen; however, presumptive HIV therapy should not be delayed. Note: Additional virologic testing is recommended 2 to 6 weeks after infant ARV drugs are discontinued (i.e., at age 2 to 3 months if the infant receives 6 weeks of ARV drugs). 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 of HIV Acquisition Who Are Not Being Breastfed Infants with perinatal HIV exposure to— • Sustained viral suppression (<50 copies/mL) from 20 weeks of gestation through delivery Note: Ideally, sustained viral suppression is documented by HIV RNA testing, including at least two consecutive tests obtained at least 4 weeks apart with HIV RNA <50 copies/mL, but can be based on the clinical judgment of providers.	Birth (see note below) 14–21 days 1–2 months (see note below) 4–6 months Note: A birth test generally should be performed but is not necessary for infants at low risk of HIV acquisition unless there are concerns that the newborn could be lost to follow-up without further testing. Note: For infants at low risk of HIV acquisition, testing may be timed to occur at least 2 weeks after cessation of ZDV prophylaxis.
Infants Not Meeting Criteria for High or Low Risk of HIV Acquisition • In these clinical scenarios, some infants may receive presumptive HIV therapy and others may receive only ZDV prophylaxis.	For all infants in this group, a NAT should be obtained at birth and the NAT testing schedule for infants at high risk of HIV acquisition (shown above) should be followed.

	The timing of virologic testing 2 to 6 weeks after ARV drugs are discontinued will vary based on the duration of infant ARV drugs.
See Table 11 and Table 11.1 in Antiretroviral Management of Infants With *In Utero*, Intrapartum, or Breastfeeding Exposure to HIV for information about presumptive HIV therapy and ZDV prophylaxis, including duration of ARV drugs.	
Infants With Perinatal HIV Exposure at Low Risk of HIV Acquisition Who Are Being Breastfed	
Guidance for Virologic Testing During Breastfeeding	**Age at HIV NAT[b,c] Testing**
From Birth to Age 6 Months A NAT test at birth is recommended for infants with perinatal HIV exposure who are at low risk of HIV acquisition and are being breastfed.	Birth 14–21 days 1–2 months (see note below) 4–6 months Note: NAT testing of the infant should be performed at least every 3 months during breastfeeding. An additional virologic test should be performed if the gap between the tests at ages 1 to 2 months and 4 to 6 months is greater than 3 months. In addition to the standard time points after birth, NAT testing also should be performed at 4 to 6 weeks and 4 to 6 months after cessation of breastfeeding, regardless of the age when breastfeeding ends.
If Breastfeeding Continues Beyond 6 Months of Age	NAT testing of the infant should be performed at least every 3 months during breastfeeding and at 4 to 6 weeks and 4 to 6 months after cessation of breastfeeding, regardless of the age when breastfeeding ends.
If Viremia Develops While Breastfeeding (a detectable viral load)	Prompt NAT testing of the infant Additional testing time points are based on the clinical scenario and use of infant ARV prophylaxis or presumptive HIV therapy; see Table 12 in Antiretroviral Management of Infants With *In Utero*, Intrapartum, or Breastfeeding Exposure to HIV. If there is a detectable maternal viral load and breastfeeding continues, some Panel members would recommend monthly virologic testing of the infant as an approach to early detection of HIV infection during ongoing exposure. Consultation with an expert is recommended to determine the need for infant ARV prophylaxis or presumptive HIV therapy and additional testing time points.
Consultation with an expert and/or the National Perinatal HIV Hotline (888-448-8765) is recommended for questions about HIV diagnostic testing for infants with perinatal HIV exposure who are being breastfed. See Table 12 in Antiretroviral Management of Infants With *In Utero*, Intrapartum, or Breastfeeding Exposure to HIV for information about extended ARV prophylaxis and presumptive HIV therapy during breastfeeding. See Preventing HIV Transmission During Infant Feeding for additional guidance about breastfeeding.	

[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] If maternal HIV-2 infection is suspected or confirmed, infant testing for HIV-2 can follow the same schedule (see Virologic Assays to Diagnose HIV-2 Infections below).

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

Diagnostic Testing in Children With Postnatal HIV Exposure

Infants and children with potential HIV exposure after birth (e.g., HIV diagnosed during breastfeeding, premasticated feeding, sexual abuse, contaminated blood products, percutaneous exposure) require age-appropriate testing. Infants with perinatal HIV exposure who have these additional exposures after birth require HIV NAT testing for diagnosis. Infants aged <18 months who were not exposed to HIV at delivery and infants aged ≥18 months who have these potential exposures require HIV antigen/antibody testing, unless the time between potential exposure and testing indicates that the patient is in the window for seroconversion, when an HIV NAT is more sensitive. Repeat testing may still be required (see Pregnancy and Postpartum HIV Testing and Identification of Perinatal and Postnatal HIV Exposure for additional information).

New HIV Diagnosis While Breastfeeding

Infants may be exposed to HIV through breastfeeding if acute or primary maternal HIV infection occurs or when pre-existing HIV infection was not diagnosed during pregnancy or postpartum.[23] Diagnosis of HIV during breastfeeding should prompt health care professionals to counsel to discontinue breastfeeding immediately to reduce the risk of postnatal transmission to the infant. In these situations, infant virologic diagnostic testing using an HIV NAT is recommended immediately and 14 to 21 days, 4 to 6 weeks, and 4 to 6 months after the infant's last exposure to breast milk (i.e., cessation of breastfeeding). A virologic test also should be performed at least 2 weeks after cessation of presumptive HIV therapy if provided (see ARV Management of Infants With *In Utero*, Intrapartum, or Breastfeeding Exposure to HIV). Duplicate tests are not needed if some of these time points overlap with standard post-natal testing. For additional information, consult the National Perinatal HIV Hotline (1-888-448-8765).

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.[24-30] If this occurs in children with perinatal HIV exposure aged <18 months with prior negative virologic tests, it will be necessary for such children to undergo virologic diagnostic testing because they may have residual HIV antibodies from the antepartum period (see Special Situations below).

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 present a potential risk of HIV transmission, no reported cases of HIV transmission from these activities have been documented.[31]

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 ≥18 months relies primarily on HIV antibody and antigen/antibody tests.[1, 32] 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.[33] 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.[34]
- 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.

For information on diagnosis of HIV-2 infection, see Virologic Assays to Diagnose HIV-2 Infections below.

Special Situations

Late Seroreversion (Aged ≥18 Months)

Non-breastfed children with perinatal HIV exposure, no other HIV transmission risk factor, and no clinical or virologic laboratory evidence of HIV infection may have residual HIV antibodies from the antepartum period up to age 24 months. These children are called late seroreverters.[35-38] In one study, 14% of children with HIV exposure who did not have HIV infection seroreverted after age 18 months.[38] 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.[39] 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. 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.

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.[40-42] 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.

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 age 1 month, 3 months, and 6 months and is comparable to the specificity of HIV DNA PCR.[19] 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]

The sensitivity of HIV RNA assays is affected by maternal antenatal ART or ARV drugs administered to the infant as prophylaxis or presumptive therapy.[43] 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.[19] Between 2010 and 2016, a significant decline in baseline viremia was noted in South Africa's Early Infant Diagnosis program, with loss of detectability documented among some infants with HIV. This decline may have reflected the administration of various prophylactic ARV regimens during those years.[44] Further studies are necessary to evaluate the sensitivity of HIV RNA assays during receipt of multidrug ARV prophylaxis or presumptive HIV therapy in infants when maternal antenatal ART was received.

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.

An HIV qualitative RNA assay is an alternative diagnostic test that can be used for infant testing.[16, 45-49]

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 age 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 age 3 months and 6 months.[3, 16]

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.[18] 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 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.[50] 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.[51] 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.[52]

The AMPLICOR® HIV-1 DNA test has been used widely for diagnosis of HIV in infants perinatally exposed to 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. 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.[53] Data from the CDC National HIV Surveillance System (NHSS) showed that the number of non–U.S. born children with HIV living in the United States 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.[54] 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.[55] 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.[56] 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.[57] 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.[58] Non–subtype B and Group O strains may be seen in countries with links to these geographical regions.[59-63] The geographical distribution of HIV groups is available at the HIV Sequence Database.

Current HIV RNA PCR assays and the qualitative diagnostic RNA assays are better at detecting non–subtype B HIV infection and the less-common Group O strains than older RNA assays[5-10, 49] (see Clinical and Laboratory Monitoring of Pediatric HIV Infection). The increased sensitivity is due to amplification of more than one highly conserved region of the HIV genome. HIV DNA assays, though generally less sensitive, may be more sensitive in detecting HIV infection when the infant is receiving ART because identification is based on detection of cell-associated DNA in whole blood or dried blood spots and does not rely on active viral replication.[16, 64]

A qualitative RNA assay, a quantitative RNA assay, or a total DNA/RNA (total nucleic acid) test should be used for infant testing in addition to a DNA PCR assay when evaluating an infant exposed to HIV infection linked to an area that is endemic for non–subtype B HIV or Group O strains, such as Africa or Southeast Asia. These additional tests are also indicated 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.[65-69]

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.[70-72] HIV-2 infection also is well documented in France and Portugal, which have large numbers of immigrants from these regions.[73, 74] 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.[75-77] (See HIV-2 Infection and Pregnancy.)

HIV-2 should be suspected if HIV infection is linked to an area that is endemic for HIV-2 infection or if HIV test results are suggestive of HIV-2 infection (i.e., 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).[78]

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 exposed to 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.[79, 80] Clinicians should consult with an expert in pediatric HIV infection when caring for infants with suspected or known exposure to HIV-2.[70, 81]

The diagnosis of HIV-2 in children with only non-perinatal exposure or in children with perinatal exposure aged ≥18 months should also follow the Centers for Disease Control and Prevention and Association of Public Health Laboratories 2014 laboratory testing guidelines, which recommend using an HIV-1/HIV-2 antibody differentiation immunoassay that distinguishes between HIV-1 and HIV-2 antibodies for supplemental testing. 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.[79, 80]

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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 birth (see Antiretroviral Management of Infants With *In Utero*, Intrapartum, or Breastfeeding Exposure to HIV) (AI). • Longitudinal laboratory monitoring for adverse events is not needed in otherwise healthy infants receiving currently recommended ARV drugs for prophylaxis in the first 6 weeks of life (see Safety of Antiretroviral Drugs Used for Infant Prophylaxis in Antiretroviral Management of Infants with *In Utero*, Intrapartum, or Breastfeeding Exposure to HIV) (AII). • Nucleic acid tests (e.g., DNA and RNA polymerase chain reaction [PCR] assays) are required for diagnosing 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 perinatally exposed to 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[a] desires, as well as the use of premasticated food (prechewed or prewarmed in the mouth). Counseling against premastication and discussion of safe infant feeding options should be provided (see Preventing HIV Transmission During Infant Feeding) (AIII). • Screening for congenital cytomegalovirus (cCMV) is recommended in the first 21 days of life using a PCR assay in urine and/or saliva (see Cytomegalovirus in the Pediatric Opportunistic Infection Guidelines) (CIII). In certain states, universal newborn screening for cCMV using dried blood spots is recommended. This test currently serves as an adjunct to urinary and salivary testing for cCMV pending further validation. • Infants perinatally exposed to hepatitis B surface antigen (HBsAg) positive should be tested for HBsAg and should receive hepatitis B (HBV) 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. Post-vaccination serologic testing for HBV should be performed between 9 and 12 months of age (see Hepatitis B Virus/HIV Coinfection) (AI). • Infants with perinatal exposure to hepatitis C virus (HCV) should receive an HCV RNA PCR assay at age 2 to 6 months (see Hepatitis C Virus/HIV Coinfection) (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 maternal health history should be obtained. With pregnancies impacted by HIV, there may be 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, and tuberculosis. Infants perinatally exposed to 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 perinatally exposed to 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).

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.

Antiretroviral Prophylaxis and Presumptive HIV Therapy in Infants

All newborns exposed to HIV should receive appropriate antiretroviral (ARV) drugs as soon as possible, preferably within 6 hours after birth (see Antiretroviral Management of Infants With *In Utero*, Intrapartum, or Breastfeeding Exposure to HIV). Providers should instruct caregivers on how to measure and administer ARV drugs correctly, provide access to medications after discharge, explain the importance of adherence, and suggest strategies for avoiding missed doses (see Adherence to Antiretroviral Therapy in Children and Adolescents With HIV).

Based on existing safety data, longitudinal laboratory monitoring for adverse events is not needed in otherwise healthy infants receiving currently recommended ARV drugs used for prophylaxis unless administration occurs beyond 6 weeks of life. The American Academy of Pediatrics recommends periodic monitoring of hematologic and liver toxicity in breastfeeding infants receiving ARV prophylaxis with nevirapine (NVP) beyond this period and for extended durations.[2] See Safety of Antiretroviral Drugs Used for Infant Prophylaxis in Antiretroviral Management of Infants With *In Utero*, Intrapartum, or Breastfeeding Exposure to HIV.

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).[3] Combination ARV regimens are associated with an elevated risk of toxicity compared with single agents, but the three-drug regimens currently recommended for presumptive treatment (e.g., NVP/ZDV/lamivudine [3TC] or raltegravir [RAL]/ZDV/3TC) appear very safe when used for 6 or fewer weeks. For more information, see Combination ARV Regimens in Antiretroviral Management of Infants With *In Utero*, Intrapartum, or Breastfeeding Exposure to HIV.

Infants who are found to have hematologic abnormalities may need to discontinue ARV drugs. Clinicians should base the decision to discontinue ARV drugs on the individual needs of the patient. Considerations include the extent of the abnormality, whether related symptoms are present, the duration of ARV drugs received by the infant, and the risk of HIV infection (as assessed by maternal history of ARV drugs, viral load near birth, and mode of birth). A 2-week ZDV neonatal regimen **is recommended** in situations where there is a low risk of perinatal HIV transmission (see specific criteria in Table 11. Antiretroviral Management for Infants With *In Utero* or Intrapartum Exposure to HIV in Antiretroviral Management of Infants With *In Utero*, Intrapartum, or Breastfeeding Exposure to HIV).[4] The shorter ZDV regimen may mitigate the risk of anemia in infants who are HEU.

Hyperbilirubinemia

The primary toxicity of concern with the use of RAL in the neonatal period has been the potential displacement of unconjugated bilirubin from albumin binding sites. However, at recommended dosing, RAL appears safe. 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, RAL binds albumin, raising a theoretical concern that displacement of bilirubin could lead to hyperbilirubinemia. However, *in vitro* studies suggest RAL is safe at the drug exposures achieved for treatment.[5] IMPAACT P1110, the single-arm regulatory Phase 1/2 trial that established dosing for RAL, evaluated safety in 52 infants of 34 weeks gestational age and older; no adverse events were attributed to RAL, and no bilirubin levels exceeded 16 mg/dL.[6]

Prophylaxis Against *Pneumocystis jirovecii* Pneumonia

To prevent *Pneumocystis jirovecii* pneumonia, all high-risk infants perinatally exposed to 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).[7] 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.[8-13] Screening for cCMV is recommended in the first 21 days of life. Early diagnosis allows for 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 assay, and a routine newborn audiologic evaluation. For infants diagnosed with cCMV, longitudinal audiologic follow-up and neurodevelopmental assessments are recommended (see Cytomegalovirus).[14] 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 allduring each pregnancy.[15,16] The Centers for Disease Control and Prevention (CDC) recommends HCV testing for all infants and children perinatally exposed to current or probable HCV infection. Infants with perinatal exposure to HCV should receive a nucleic acid test (NAT) for HCV RNA at age 2 to 6 months to identify children in whom chronic HCV infection might develop.[17] 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) occur for all during each pregnancy, preferably in the first trimester, regardless of vaccination status or history of testing (see Hepatitis B Virus/HIV Coinfection).[19] The CDC recommends that infants perinatally exposed to HBsAg be tested for HBsAg. In the context of a positive maternal HBsAg screening, all infants 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. Post-vaccination serologic testing for HBV should be performed between 9 and 12 months of age (see Evaluating and Managing Infants Who Were Exposed to HIV in Hepatitis B Virus/HIV Coinfection). 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 diagnostic testing using NATs (e.g., 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 With Perinatal and Breastfeeding Exposure to HIV in Diagnosis of HIV Infection in Infants and Children.

Infant Feeding Practices and Risk of HIV Transmission

Evidence-based, patient-centered counseling should be provided to support shared decision-making about infant feeding prior to conception or as early as possible in pregnancy with HIV. Plans for infant feeding should be reviewed throughout pregnancy and again after birth. 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 Preventing HIV Transmission During Infant Feeding). For information on ARV prophylaxis duration and HIV screening frequency for breastfeeding infants, see Antiretroviral Management of Infants With *In Utero*, Intrapartum, or Breastfeeding Exposure to HIV, 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) in the context of pregnancy 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 pregnancies 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 increased 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 during pregnancy with 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: June 12, 2025
Reviewed: June 12, 2025

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
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 during pregnancy and among 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 pregnancy. 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 mother 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 pregnancy. 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 pregnancy. 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 with potential *in utero* or intrapartum exposure to dolutegravir, 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 Pregnancy: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy

Updated: June 12, 2025
Reviewed: June 12, 2025

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. The 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.	June 12, 2025

Table 14. Antiretroviral Drug Use in Pregnancy: 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) (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)	FTC (Emtriva) *Capsule*[c] • 200 mg *Oral Solution* • 10 mg/mL FTC/EFV/TDF[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)	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*	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.	June 12, 2025

Table 14. Antiretroviral Drug Use in Pregnancy: 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
Truvada Note: Generic products are available for some formulations.	• 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	• 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		
Lamivudine (3TC) *Epivir* (3TC/TDF)	3TC (Epivir)[c] *Tablets* • 150 mg	Pregnancy *PK in Pregnancy* • PK not significantly altered in pregnancy	High placental transfer to fetus[b]	June 12, 2025

Table 14. Antiretroviral Drug Use in Pregnancy: 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
Cimduo (3TC/ZDV) (3TC/DOR/TDF) *Delstrigo* (3TC/DTG) *Dovato* (3TC/ABC) (3TC/EFV/TDF) *Symfi* (3TC/EFV/TDF) *Symfi Lo* (3TC/ABC/DTG) *Triumeq* (3TC/ABC/DTG) *Triumeq PD* (3TC/ABC/ZDV) Note: Generic products are available for some formulations.	• 300 mg *Oral Solution* • 10 mg/mL 3TC/TDF (Cimduo) • 3TC 300-mg/TDF 300-mg tablet 3TC/ZDV[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[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	*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* • 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* • 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	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.	

Table 14. Antiretroviral Drug Use in Pregnancy: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations[a]	Use in Pregnancy	Last Reviewed
	3TC/ABC/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[c] • 3TC 150-mg/ABC 300-mg/ ZDV 300-mg tablet	*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* • 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/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	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. 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)*	*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.	June 12, 2025

Table 14. Antiretroviral Drug Use in Pregnancy: 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/DRV/c/FTC (Symtuza) • TAF 10-mg/DRV 800-mg/ COBI 150-mg/FTC 200-mg tablet	• 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*[d] (TDF/3TC) *Cimduo* (TDF/FTC/RPV) *Complera* (TDF/DOR/3TC) *Delstrigo* (TDF/EVG/c/FTC)	TDF (Viread) *Tablet*[c] • 300 mg *Powder* • 40-mg/1-g oral powder TDF/EFV/FTC (Atripla)[c,d] • TDF 300-mg/EFV 600-mg/ FTC 200-mg tablet TDF/3TC (Cimduo) • TDF 300-mg/3TC 300-mg tablet TDF/FTC/RPV (Complera)	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	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.	June 12, 2025

Table 14. Antiretroviral Drug Use in Pregnancy: 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
Stribild (TDF/EFV/3TC) *Symfi* (TDF/EFV/3TC) *Symfi Lo* (TDF/FTC) *Truvada* Note: Generic products are available for some formulations.	• 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/FTC (Truvada)[c] • TDF 300-mg/FTC 200-mg tablet	○ TDF 300 mg once daily without regard to food • Powder ○ TDF 8 mg/kg daily (up to a maximum of TDF 300 mg). Take with food. *TDF/EFV/FTC (Atripla)[d]* • One tablet once daily at or before bedtime. Take on an empty stomach to reduce side effects. *TDF/3TC (Cimduo)* • One tablet once daily without regard to food *TDF/FTC/RPV (Complera)* • One tablet once daily with food *TDF/DOR/3TC (Delstrigo)* • One tablet once daily without regard to food *TDF/EVG/c/FTC (Stribild)* • One tablet once daily with food *TDF/EFV/3TC (Symfi or Symfi Lo)* • One tablet once daily on an empty stomach and preferably at bedtime *TDF/FTC (Truvada)* • One tablet once daily without regard to food		
Zidovudine (ZDV) *Retrovir*	ZDV (Retrovir) *Capsule*	Pregnancy *PK in Pregnancy*	High placental transfer to fetus[b]	June 12, 2025

Table 14. Antiretroviral Drug Use in Pregnancy: 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/3TC) (ZDV/ABC/3TC) Note: Generic products are available for all formulations.	• 100 mg *Tablet* • 300 mg *Oral Solution* • 10 mg/mL *IV Solution* • 10 mg/mL ZDV/3TC • ZDV 300-mg/3TC 150-mg tablet ZDV/ABC/3TC • ZDV 300-mg/ABC 300-mg/3TC 150-mg tablet	• 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 birth. 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	No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects)	
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)	Pregnancy *PK in Pregnancy* • No PK studies in human pregnancy *Dosing in Pregnancy*	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	June 12, 2025

Table 14. Antiretroviral Drug Use in Pregnancy: 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
	• DOR 100-mg/ 3TC 300-mg/ TDF 300-mg tablet	• 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	evidence exists of teratogenicity in rats or rabbits.	
Efavirenz (EFV) (EFV/FTC/TDF) (EFV/3TC/TDF) *Symfi* (EFV/3TC/TDF) *Symfi Lo* Note: Generic products are available for some formulations.	EFV *Capsules* • 50 mg • 200 mg *Tablet* • 600 mg EFV/FTC/TDF • EFV 600-mg/FTC 200-mg/TDF 300mg tablet EFV/3TC/TDF (Symfi) • EFV 600-mg/3TC 300-mg/TDF 300mg tablet EFV/3TC/TDF (Symfi Lo) • EFV 400-mg/3TC 300-mg/TDF 300mg 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* • One tablet once daily at or before 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 during pregnancy or when planning to become pregnant. This is consistent with both the British HIV Association and WHO guidelines for use of ARV drugs in pregnancy.	June 12, 2025

Table 14. Antiretroviral Drug Use in Pregnancy: 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
		• 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	EFV should be continued in pregnancy when a virally suppressive, EFV-based regimen is being received, because ARV drug changes during pregnancy may be associated with loss of viral control and an increased risk of perinatal transmission (see Antiretroviral Therapy Use During Prepregnancy and Early 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 *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	June 12, 2025
Nevirapine (NVP)	NVP *Tablet* • 200 mg[c] *Oral Suspension* • 50 mg/5 mL[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	High placental transfer to fetus[b] No evidence of human teratogenicity 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 pregnancy when CD4 counts ≥250 cells/mm^3 only if the benefit clearly outweighs the risk. A	June 12, 2025

Table 14. Antiretroviral Drug Use in Pregnancy: 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
		• NVP 200 mg once daily (using immediate release tablet) for a 14-day lead-in period; thereafter, NVP 200 mg twice 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.	potential increased risk of life-threatening hepatotoxicity exists in pregnancy when CD4 counts are high. 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.	
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. When standard dosing of RPV is received during pregnancy, viral loads should be monitored more frequently. For guidance about the use of combination products in pregnancy, please see the specific sections on other components (i.e., CAB, DTG, FTC, TAF, TDF). Standard Adult Doses	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.	June 12, 2025

Table 14. Antiretroviral Drug Use in Pregnancy: 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 (Edurant) • RPV 25 mg once daily with food *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[c] (generic product only) • 150 mg[c] (generic product only) • 200 mg[c] • 300 mg[c] *Oral Powder* • 50-mg packet	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)	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.	June 12, 2025

Table 14. Antiretroviral Drug Use in Pregnancy: 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
	ATV/c (Evotaz) • ATV 300-mg/COBI 150-mg tablet	o Use of ATV/c **is not recommended** during pregnancy because ATV C_{trough} 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. 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 during the second and third trimesters when either TDF or an H2-receptor antagonist is also being received. • 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	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. **Note:** Please see FDA label for full list of drugs with potential interactions, including several anticonvulsants and other drugs for which administration with ATV/r is contraindicated.	

Table 14. Antiretroviral Drug Use in Pregnancy: 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 Without RTV Boosting • ATV 400 mg once daily with food; ATV without RTV boosting **is not recommended** when used with TDF, H2-receptor antagonists, PPIs, or during pregnancy. *In ARV-Naive Patients With RTV Boosting* • ATV/r 300 mg/100 mg once daily with food • When combined with EFV in ARV-naive patients: ATV/r 400 mg/100 mg once daily with food *In ARV-Experienced Patients* • ATV 300 mg plus RTV 100 mg once daily with food • **Do not use** with PPIs or EFV. *In ARV-Experienced Patients Who Are Receiving an H2-Receptor Antagonist* • ATV/r 300/100 mg once daily with food *In ARV-Experienced Patients Who Are Receiving an H2-Receptor Antagonist and TDF* • ATV/r 400 mg/100 mg once daily with food *Powder Formulation* • Oral powder is taken with RTV once daily with food at the same recommended adult dose as the capsules. *ATV/c (Evotaz)* • One tablet once daily with food		

Table 14. Antiretroviral Drug Use in Pregnancy: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations[a]	Use in Pregnancy	Last Reviewed
Darunavir (DRV) *Prezista* Note: Must be combined with low-dose RTV or COBI boosting. (DRV/c) *Prezcobix* (DRV/c/FTC/TAF) *Symtuza*	DRV (Prezista) *Tablets* • 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 during all pregnancies. • 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 *Patients Who Are ARV-Naive* • 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	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.	June 12, 2025

Table 14. Antiretroviral Drug Use in Pregnancy: 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
		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		
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.	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.	June 12, 2025

Table 14. Antiretroviral Drug Use in Pregnancy: 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
		• 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/200 mg once daily *Tablet* • 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.	June 12, 2025

Table 14. Antiretroviral Drug Use in Pregnancy: 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 *IV infusion (diluted infusion with 250 mL 0.9% sodium chloride)* • IBA 2,000-mg loading dose over 30 minutes, followed by IBA 800-mg maintenance doses over 15 minutes administered every 2 weeks *IV push (undiluted)* • IBA 2,000-mg loading dose over 90 seconds, followed by IBA 800-mg maintenance doses over 30 seconds 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 exposed to IBA during pregnancy. The FDA requires collection of prospective data on IBA exposure 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.	June 12, 2025
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. *Dosing in Pregnancy*	Moderate placental transfer to fetus[b] No evidence of teratogenicity in rats or rabbits; insufficient data to assess teratogenicity in humans	June 12, 2025

Table 14. Antiretroviral Drug Use in Pregnancy: 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
		• 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 Standard Adult Doses *Initiation Option 1*	No human data are available regarding placental or breast milk passage. Data are insufficient to assess for teratogenicity in humans. No evidence of teratogenicity in rats or rabbits.	June 12, 2025

Table 14. Antiretroviral Drug Use in Pregnancy: 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
		• 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)	June 12, 2025

Table 14. Antiretroviral Drug Use in Pregnancy: 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 published 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	No human data are available regarding placental passage. Insufficient data to assess for teratogenicity in humans. No evidence of teratogenicity in rats or rabbits.	June 12, 2025

Table 14. Antiretroviral Drug Use in Pregnancy: 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
		(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 ▪ Patients should be monitored for approximately 10 minutes for postinjection reactions. A 23-gauge, 1.5-inch IM needle is recommended for the injection and is provided in the packaging. Longer, 2-inch needles		

Table 14. Antiretroviral Drug Use in Pregnancy: 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
		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 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	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 ARVs. DTG is a *Preferred* ARV drug for use during pregnancy, irrespective of trimester, and when 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.	June 12, 2025

Table 14. Antiretroviral Drug Use in Pregnancy: 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/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		

Table 14. Antiretroviral Drug Use in Pregnancy: 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. If EVG/c is being taken when pregnancy occurs, consider frequent viral load monitoring or switching to a more effective recommended regimen. If a regimen that contains EVG/c is continued during pregnancy, 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.	June 12, 2025
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. • Once-daily dosing (i.e., two RAL 600-mg film-coated tablets) should not be used during pregnancy until more information is available.	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.	June 12, 2025

Table 14. Antiretroviral Drug Use in Pregnancy: 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	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 patients who are ARV-naïve 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* (DRV/c) *Prezcobix* (EVG/c/FTC/TDF)	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	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*	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.	June 12, 2025

Table 14. Antiretroviral Drug Use in Pregnancy: 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
Stribild (DRV/c/FTC/TAF) *Symtuza*	DRV/c (Prezcobix) • DRV 800-mg/ COBI 150mg 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	• 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 *DRV/c/FTC/TAF (Symtuza)* • One tablet once daily with food		
Ritonavir (RTV)	RTV (Norvir) *Capsule*	Pregnancy *PK in Pregnancy*	Low placental transfer to fetus[b]	June 12, 2025

Table 14. Antiretroviral Drug Use in Pregnancy: 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
Norvir (LPV/r) *Kaletra*	• RTV 100 mg *Tablet* • RTV 100 mg *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.	• 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) *Tablet* • Take with food.	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. 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.	

Table 14. Antiretroviral Drug Use in Pregnancy: 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
		Capsule or Powder • 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).

[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

[d] As of June 2023, Atripla brand products are no longer 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;

Table 14. Antiretroviral Drug Use in Pregnancy: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy

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: June 12, 2025
Reviewed: June 12, 2025

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 PK during pregnancy are equivalent to the PK 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 PK.[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 birth 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 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 (APR) releases the latest birth defect data for ABC and other antiretroviral (ARV) drugs twice a year through an updated interim report released in June and December. The APR 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. Figure 1. Summary of Birth Defects Among First Trimester Exposures in the APR interim report provides a summary of the number and prevalence of birth defects per live births among cases of first-trimester exposure to ABC and other ARV drugs reported to the APR where there are sufficient data to determine 95% confidence intervals. The data in Figure 1 can be compared with the prevalence of birth defects in the U.S. population (2.72 birth defects per 100 live births) based on the Centers for Disease Control and Prevention's surveillance system (The Metropolitan Atlanta Congenital Defects Program or MACDP) and with the Texas Birth Defects Registry ([TBDR] 4.17 per 100 live births).

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),[7] in the French Perinatal Cohort (aOR 1.01, 0.73–1.41),[8] or in a series of 897 births to women with HIV in Spain between 2000 and 2009 (aOR 0.99, 0.34–2.87).[9]

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.[10]

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 births 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.[11]

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.[12,13]

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.[14]

Animal Studies

Carcinogenicity

Preputial and clitoral gland tumors and malignant hepatic tumors were seen in rodents at ABC exposures that were 6 to 32 times those observed in humans who received the recommended dose.[15]

Reproduction/Fertility

No effect on reproduction or fertility in rodents was seen at ABC doses that were about eight times the exposures seen in humans who received the recommended dose.[15]

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

ABC dose evaluated, resulting in exposures approximately nine times the human exposure at the recommended dose.[15]

Placental and Breast Milk Passage

ABC crosses the placenta and is excreted into the breast milk of lactating rats.[15]

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 *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)* • 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. The 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).

[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 birth in the Pediatric AIDS Clinical Trials Group (PACTG) 394 study[2] and in a European study.[3, 4] Similarly, when FTC was used in combination with tenofovir disoproxil fumarate (TDF) for pre-exposure prophylaxis (PrEP) in women without HIV infection, steady-state trough concentrations were below the estimated protective trough concentrations of FTC in 45.2% of pregnant participants.[5] 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 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[2] was 0.85 (range, 0.46–1.07).

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[6] in three infants (19%). 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.[7] In a study of 50 women without HIV who received daily oral FTC 200 mg and TDF 300 mg as 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.[8]

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.[9] 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 a trial in South Africa in which participants without HIV infection who were in weeks 14 through 24 of pregnancy were randomized to start or defer (until after birth) FTC in combination with TDF as PrEP, use of FTC-containing PrEP in pregnancy was reassuringly not associated with preterm birth or small for gestational age infants.[10]

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.[11] In a large French cohort, FTC exposure in the first trimester was associated with lower risk of birth defects.[12]

The Antiretroviral Pregnancy Registry (APR) provides updated birth defect data for FTC and other antiretroviral (ARV) drugs twice a year through an interim report released in June and December. The APR 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. Figure 1. Summary of Birth Defects Among First Trimester Exposures in the APR interim report provides a summary of the number and prevalence of birth defects per live births among cases of first-trimester exposure to FTC and other ARV drugs reported to the APR where there are sufficient data to determine 95% confidence intervals. The data in Figure 1 can be compared with the prevalence of birth defects in the U.S. population (2.72 birth defects per 100 live births) based on the Centers for Disease Control and Prevention surveillance system (The Metropolitan Atlanta Congenital Defects Program [MACDP]) and with the Texas Birth Defects Registry (TBDR; 4.17 per 100 live births).

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.[13]

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.[14]

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.[14]

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.[14]

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.[15]

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) (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[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* • 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).

[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)

Updated: June 12, 2025
Reviewed: June 12, 2025

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% 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 (APR), 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.

In a large French cohort with data collected between 1994 and 2010, first-trimester 3TC exposure 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.[6] In the United States, the APR provides updated birth defect data for 3TC and other antiretroviral (ARV) drugs twice a year through an interim report released in June and December. The APR 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. Figure 1. Summary of Birth Defects Among First Trimester Exposures in the APR interim report provides a summary of the number and prevalence of birth defects per live birth among cases of first-trimester exposure to 3TC and other ARV drugs reported to the APR where there are sufficient data to determine 95% confidence intervals. The data in Figure 1 can be compared with the total prevalence of birth defects in the U.S. population (2.72 birth defects per 100 live births) based on the Centers for Disease Control and Prevention surveillance system (The Metropolitan Atlanta Congenital Defects Program [MACDP]) and with the Texas Birth Defects Registry ([TBDR] 4.17 per 100 live births).

An analysis of APR data demonstrated a lower risk of spontaneous abortions, induced abortions, and preterm births with use of 3TC-containing regimens than with use of ARV regimens that do not include 3TC.[7]

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.[8]

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.[9]

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.[9]

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.[9]

Placental and Breast Milk Passage

In studies of pregnant rats, 3TC was transferred to the fetus through the placenta.[9]

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) (3TC/DOR/TDF) *Delstrigo* (3TC/DTG) *Dovato* (3TC/ABC) (3TC/EFV/TDF) *Symfi* (3TC/EFV/TDF) *Symfi Lo* (3TC/ABC/DTG) *Triumeq* (3TC/ABC/DTG) *Triumeq PD* (3TC/ABC/ZDV) 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[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[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/ABC/DTG (Triumeq) • 3TC 300-mg/ABC 600-mg/ DTG 50-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* • 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 PD) • Pediatric dispersible tablet: 3TC 30-mg/ABC 60-mg/ DTG 5-mg 3TC/ABC/ZDV[c] • 3TC 150-mg/ABC 300-mg/ ZDV 300-mg tablet	*3TC/ABC* • 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/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* • One tablet twice daily without regard to food	

[a] Individual ARV drug doses may need to be adjusted in people with renal or hepatic insufficiency (for details, see the Adult and Adolescent Antiretroviral Guidelines, Appendix B).

[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 antiretroviral (ARV) drugs administered. However, TAF exposures appear to be adequate in the second and third trimesters based on comparisons with historical data in nonpregnant adults.

TAF PK 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 pregNAnt women with HIV (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. A separate study in pregnant women receiving TAF 25 mg with bictegravir and emtricitabine (FTC) showed that the total TAF AUC was approximately 22% to 43% lower during pregnancy than postpartum, but the unbound AUC was approximately 6% to 17% lower.[4] Trough concentrations of the active tenofovir-diphosphate form in peripheral blood mononuclear cells were comparable but variable between pregnancy and postpartum.

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[5] 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.[6] 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.[7] 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 with 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 (APR) provides updated birth defect data for TAF and other ARV drugs twice a year through an interim report released in June and December. The APR has monitored sufficient numbers of first-trimester TAF exposures 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 TAF. In the APR interim report, Figure 1. Summary of Birth Defects Among First Trimester Exposures provides a summary of the number and prevalence of birth defects per live births among cases of first-trimester exposure to TAF and other ARV drugs reported to the APR where there are sufficient data to determine 95% confidence intervals. The data in Figure 1 can be compared with the prevalence of birth defects in the U.S. population (2.72 birth defects per 100 live births) based on the Centers for Disease Control and Prevention birth defects surveillance system (Metropolitan Atlanta Congenital Defects Program [MACDP]) and with the Texas Birth Defects Registry (TBDR; 4.17 birth defects per 100 live births).

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 antiretroviral therapy regimens in pregnancy, which found lower composite adverse outcomes in the group receiving DTG and 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 lower neonatal mortality than the arm receiving EFV+FTC/TDF (3.7% vs. 1.9%).[8] A posthoc 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]

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,[11] and they also showed that lower antepartum weight gain was associated with a higher risk of adverse pregnancy outcomes.[12] However, the potential implications of excessive weight gain and other adverse safety outcomes when TAF-containing regimens are prescribed during pregnancy have also been evaluated[13-15] in U.S.-based cohorts with variable findings. A systematic analysis[12,16] of these collective studies identified a higher risk of excessive maternal weight gain and hypertensive disorders among pregnant women on TAF/integrase strand transfer inhibitor (INSTI) ART regimens in comparison to those not on a TAF/INSTI ART regimen but did not identify any differences in the risk of gestational diabetes mellitus. However, because TAF was administered with an INSTI across these studies, the effect of TAF alone could not be examined.

Renal safety has also 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]

Infant Safety Outcomes

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.[17] 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.

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.[18]

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.[18]

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.[18]

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 *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. 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 people with renal or hepatic insufficiency (for details, see the Adult and Adolescent Antiretroviral Guidelines, Appendix B).

[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 concentration (C_{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 C_{trough} 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 (ARV) regimens during the third trimester, but no differences were identified among these groups in the postpartum period.

HIV Pre-Exposure Prophylaxis

An *in silico* simulation of plasma TFV exposures in 1,000 pregnancies when the standard daily dose of TDF 300 mg/FTC 200 mg is prescribed demonstrated that plasma C_{trough} fell below the protective

threshold of 35.5 ng/mL among 34.0%, 43.8%, and 65.1% of pregnancies in the first, second, and third trimesters, respectively.[7] Simulations were also performed with double dosing (i.e., TDF 600 mg/FTC 400 mg), which suggested that lower proportions would fall below protective thresholds during pregnancy.

In a study of women who did not have HIV and were using TDF as part of pre-exposure prophylaxis (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.[8] A separate study in pregnant and postpartum adolescents and young women receiving TDF/FTC under directly observed therapy identified a similar magnitude of difference in DBS concentrations between pregnancy and postpartum.[9] 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%. Further studies are needed to better understand associations between the PK in plasma and cells, as well as the efficacy and safety in these populations.

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.[1,2,10] 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.[11]

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.[12] 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.[13]

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.[14]

Reproduction/Fertility

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.[15] In contrast, a trial involving Kenyan and Ugandan women without HIV but whose sexual partners had HIV (serodifferent 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.[16]

Teratogenicity

No associations have been identified between TDF use and the risk of overall birth defects. The Antiretroviral Pregnancy Registry (APR) provides updated birth defect data for TDF and other ARV drugs twice a year through an interim report released in June and December. The APR 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. In the APR interim report, Figure 1. Summary of Birth Defects Among First Trimester Exposures provides a summary of the number and prevalence of birth defects per live births among cases of first-trimester exposure to TDF and other ARV drugs reported to the APR where there are sufficient data to determine 95% confidence intervals (CIs). The data in Figure 1 can be compared with a total prevalence of birth defects in the U.S. population (2.72 birth defects per 100 live births), based on the Centers for Disease Control and Prevention surveillance system (The Metropolitan Atlanta Congenital Defects Program [MACDP]) and with the Texas Birth Defects Registry ([TBDR] 4.17 birth defects per 100 live births).

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)[17,18]; and Pediatric HIV/AIDS Cohort Study (PHACS) (n = 2,580, with 431 first-trimester TDF exposures).[19] 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).[20]

Adverse Pregnancy Outcomes

Available evidence is mixed regarding the relationship between TDF and adverse pregnancy outcomes, such as fetal growth effects and preterm birth. Although 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 compared with women who received regimens containing nevirapine (NVP), LPV/r, or zidovudine (ZDV)/3TC. 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 ARV regimens.[21] However, 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]

Maternal TDF use was linked to an increased risk of low birth weight (LBW) (<2,500 g) in a Dutch study of 74 HIV-exposed infants (including 9 with *in-utero* TDF exposure).[22] SGA at birth was more frequent in the dolutegravir (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 Virologic Efficacy and Safety of ART Combinations with TAF/TDF, EFV, and DTG (VESTED) trial, but this difference was not

statistically significant.[23] 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[24-26] or very LBW, SGA,[24,25,27] and newborn length-for-age and head circumference–for-age z-scores[24] or body size parameters at birth.[28] Duration of maternal TDF use also has not been associated with long-bone (femur and humerus) growth in infants[29] or infant length at birth.[30]

In the Promoting Maternal–Infant Survival Everywhere (PROMISE) trial, no significant differences were observed between the TDF- and 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.[26] Subsequent analyses demonstrated persistence of this association even after adjustment for multiple well-established clinical, demographic, and obstetrical risk factors.[31] 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, no relationship between maternal TFV-DP concentrations in DBS and very preterm delivery/early neonatal death was identified.[32] 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.[33] Other studies have shown either no difference[23,25] or a lower risk[34] of these outcomes with TDF-containing therapy.

See the TAF section for a discussion of the findings of the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT 2010)/VESTED trial, which suggests that TDF, compared with TAF, may be associated with a higher rate of adverse pregnancy outcomes when DTG regimens are started in pregnancy.[23,35]

HIV PrEP

A systematic analysis of 13 studies among 8,712 pregnant women in Africa either did not identify or showed a reduced risk of preterm birth among women on oral PrEP in comparison to no oral PrEP.[36] There were also no associations identified with LBW and very LBW, SGA, or neonatal death.

Other Safety Data

Maternal Safety Outcomes

TDF has not been associated with an increased risk of renal side effects in pregnancy. In contrast, TDF use has been associated with variable effects on maternal bone mineral density, with more notable declines in women with HIV.[37-39]

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,[40] nor when comparing TDF- to TAF-containing ART regarding renal function changes, toxicity, or treatment discontinuations due to renal toxicity.[41] 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

compared with ZDV alone or ZDV in combination with other ARVs. However, these differences were not deemed to be clinically relevant, and no significant differences were seen in these measures among infants.[42]

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[43] or in infant mortality.[44]

Evidence is inconsistent regarding the association between maternal TDF use during pregnancy and transient, small growth delays during the first year of life. Some studies have shown that TDF exposure negatively impacts infant growth measures despite no differences being identified at birth,[22,24,28,45] whereas others have not identified an effect of TDF on infant growth rates.[30,44] In cases where infantile growth delays were identified, differences are of uncertain clinical significance.[46]

The impact of maternal TDF use on infant bone mineral status also remains uncertain and requires further longitudinal evaluation. Some studies have shown lower mean whole-body bone mineral content (BMC), whole-body-less-head BMC,[47] and lumbar spine BMC[48] among those exposed to TDF either *in utero* or through breastmilk, whereas others have not identified any effects on these measures or other bone metabolism markers.[49-51]

The impact of TDF exposure on renal function has also been examined in multiple studies. One study among mothers who 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.[52] However, a separate study identified no differences in creatinine clearance between those exposed to maternal TDF compared with those on NVP prophylaxis.[53]

See Long-Term Follow-Up of Infants Exposed to Antiretroviral Drugs for additional information.

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.[54]

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.[54]

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.[54]

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.[55]

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*[d] (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/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)[c,d] • 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/FTC (Truvada)[c] • TDF 300-mg/FTC 200-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)*[d] • 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/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/FTC (Truvada)* • One tablet once daily without regard to food	

[a] Individual ARV drug doses may need to be adjusted in people with renal or hepatic insufficiency (for details, see the Adult and Adolescent Antiretroviral Guidelines, Appendix B).

[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.

[d] As of June 2023, Atripla brand products are no longer 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 (PK) 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 when viral loads are unknown or elevated. 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 via only 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]

The Antiretroviral Pregnancy Registry (APR) provides updated birth defect data for ZDV and other ARV drugs twice a year through an interim report released in June and December. The APR has monitored sufficient numbers of first-trimester exposures to ZDV in humans to be able to detect at least a 1.5-fold increase in the risk of overall birth defects and a twofold increase in the 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. Figure 1. Summary of Birth Defects Among First Trimester Exposures in the APR interim report provides a summary of the number and prevalence of birth defects per live births among cases of first-trimester exposure to ZDV and other ARV drugs reported to the APR where there are sufficient data to determine 95% confidence intervals (CIs). The data in Figure 1 can be compared with the prevalence of birth defects in the U.S. population (2.72 birth defects per 100 live births) based on the Centers for Disease Control and Prevention surveillance system (The Metropolitan Atlanta Congenital Defects Program [MACDP]) and with the Texas Birth Defects Registry ([TBDR] 4.17 per 100 live births). Similarly, a series of 897 infants exposed to HIV born in Spain between 2000 and 2009 reported[15] 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). 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.[16]

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[17] of cardiac defects among all prenatal infants exposed to ZDV 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, $P = 0.08$).

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.[18] 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.[19] 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.[20] A small follow-up study by the same authors identified hypertension among infants with *in utero* exposure to ZDV.[21]

Cancer has not been observed more frequently among infants exposed to ZDV compared with other infants exposed to HIV or unexposed to HIV in a long-term follow-up study for the original PACTG 076 study,[22] in prospective cohort studies,[23] and in matches between HIV surveillance and cancer registries.[24,25]

Other Safety Information

Mitochondrial dysfunction in mothers and infants exposed to nucleoside reverse transcriptase inhibitors during pregnancy has been reported in case reports and case series, and in some, but not all, 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 who met 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).[26,27]

Animal Studies

Carcinogenicity

Late-appearing, non-metastasizing vaginal squamous cell carcinomas were seen in mice and rats, predominantly among those given the highest doses (approximately 3–24 times the estimated human exposure with a dose of 100 mg every 4 hours).[28]

With transplacental exposure followed by postnatal exposure in mice (approximately three times the exposure of humans receiving the recommended dose), vaginal tumors were noted.[28]

One group of authors attributed the vaginal tumors in ZDV-treated mice to vaginal exposure from high urine ZDV concentrations.[29]

Reproduction/Fertility

ZDV has been shown to have no effect on reproduction or fertility in rodents.[28]

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).[28]

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.[28]

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) (ZDV/ABC/3TC) 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 • ZDV 300-mg/3TC 150-mg tablet ZDV/ABC/3TC • ZDV 300-mg/ABC 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 birth. 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).

[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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Summary

- Pharmacokinetic (PK) 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.
- Severe skin reactions, including Stevens-Johnson syndrome/toxic epidermal necrolysis, have been reported during postmarketing experience with regimens containing DOR in nonpregnant adults.

Human Studies in Pregnancy

Pharmacokinetics

No clinical PK studies of DOR in pregnancy 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 (APR) provides updated birth defect data for DOR and other antiretroviral drugs twice a year through an interim report released in June and December. For the most recent data about DOR, refer to Table 5. Number of Birth Defects by Trimester of Earliest Exposure to Each Drug in the current APR interim report. Available data are limited and insufficient for drawing conclusions about the risk of birth defects among infants who were exposed to DOR.

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.[3]

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.[3]

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.[3]

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.[3]

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 *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.

[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).

Key: 3TC = lamivudine; ARV = antiretroviral; DOR = doravirine; PK = pharmacokinetic; TDF = tenofovir disoproxil fumarate

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Efavirenz (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 birth 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 birth 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 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 birth.[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 the 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 birth 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

The Antiretroviral Pregnancy Registry (APR) provides updated birth defect data for EFV and other antiretroviral (ARV) drugs twice a year through an interim report released in June and December. The APR has monitored sufficient numbers of first-trimester exposures to EFV 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 EFV. Figure 1. Summary of Birth Defects Among First Trimester Exposures in the APR interim report provides a summary of the number and prevalence of birth defects per live births among cases of first-trimester exposure to EFV and other ARV drugs reported to the APR where there are sufficient data to determine 95% CIs. The data in Figure 1 can be compared with the prevalence in the U.S. population (2.72 birth defects per 100 live births) based on the Centers for Disease Control and Prevention surveillance system (The Metropolitan Atlanta Congenital Defects Program [MACDP]) and with the Texas Birth Defects Registry ([TBDR] 4.17 per 100 live births).

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%).[13] 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 0.78; 95% CI, 0.56–1.08). Across all births, one neural tube defect (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%.[14]

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.[15] 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 APR) 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.[16]

More recently, Zash et al. reported on the outcomes of a large birth surveillance study in Botswana. Among 7,959 births 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%).[17] 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.[18]

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 when planning to conceive; this is consistent with the British HIV Association guidelines and WHO guidelines for use of ARV drugs in pregnancy, both of which note that EFV can be used throughout pregnancy.[19-21] EFV should be continued in pregnancy when a virologically suppressive, EFV-based regimen is being received because ARV drug changes during pregnancy may be associated with loss of viral control and an increased risk of perinatal HIV transmission.[22]

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. Only 4.7% of children had been exposed to EFV *in utero*.[23] 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.[23]

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.[24] 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 risk 1.53; 95% CI, 0.94–2.51). This association was stronger when comparing EFV exposure at conception to no exposure during pregnancy (adjusted relative risk 1.92; 95% CI, 1.09–3.36) and considering follow-up and case diagnosis only through age 2 (adjusted relative risk 2.14; 95% CI, 1.11–4.12).[25]

Safety

The Promoting Maternal and Infant Survival Everywhere (PROMISE) trial randomized ART-naive antepartum and postpartum women with HIV, CD4 >350 cells/μL, and median alanine aminotransferase <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.[26]

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.[27-31] (see Prepregnancy Counseling and Care 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.[32] 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.[33]

Reproduction/Fertility

EFV has had no observable effects on reproduction or fertility in rodents.[33]

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.[34] The malformations included anencephaly and unilateral anophthalmia in one fetus, microphthalmia in another fetus, and cleft palate in a third fetus.[33]

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.[33] 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.[35]

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.[33]

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.[33]

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) (EFV/FTC/TDF) (EFV/3TC/TDF) *Symfi* (EFV/3TC/TDF) *Symfi Lo* Note: Generic products are available for some formulations.	EFV *Capsules* • 50 mg • 200 mg *Tablet* • 600 mg EFV/FTC/TDF • 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* • 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 during pregnancy or when 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 pregnancy when a virally suppressive, EFV-based regimen is being received because ARV drug changes during pregnancy may be associated with loss of viral control and an increased risk of perinatal transmission (see Antiretroviral Therapy Use During Prepregnancy and Early 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).

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

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)

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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 (PK) in pregnant women have been reported in two studies. Ramgopal et al. found approximately 1.1-fold to 1.4-fold increases in total ETR area under the curve (AUC), minimum plasma concentration (C_{min}), and maximum plasma concentration (C_{max}) during the second (n = 13) and third (n = 10) trimesters 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 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 birth 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 birth 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] The Antiretroviral Pregnancy Registry (APR) provides updated birth defect data for ETR and other ARV drugs twice a year through an interim report released in June and December. For the most recent data about ETR, refer to Table 5. Number of Birth Defects by Trimester of Earliest Exposure to Each Drug in the current APR interim report. The most recent data are insufficient to draw conclusions about the risk of birth defects among infants who were exposed to ETR.

Animal Studies

Carcinogenicity

ETR was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests.[7] 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.[7]

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.[7]

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.[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
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 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 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).

[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 (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 an 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 conducted in pregnant women who received NVP as part of antiretroviral therapy (ART) 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 (APR) provides updated birth defect data for NVP and other antiretroviral (ARV) drugs twice a year through an interim report released in June and December. The APR has monitored sufficient numbers of first-trimester exposures to NVP 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 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. Figure 1. Summary of Birth Defects Among First Trimester Exposures in the APR interim report provides a summary of the number and prevalence of birth defects per live births among cases of first-trimester exposure to NVP and other ARV drugs reported to the APR where there are sufficient data to determine 95% confidence intervals. The data in Figure 1 can be compared with a total prevalence of birth defects in the U.S. population (2.72 birth defects per 100 live births) based on the Centers for Disease Control and Prevention surveillance system (The Metropolitan Atlanta Congenital Defects Program [MACDP]) and with the Texas Birth Defects Registry ([TBDR] 4.17 per 100 live births). 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.[9] 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.[10]

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%.[11, 12] 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 T lymphocyte (CD4) cell 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.[12] Higher CD4 counts also have been associated with an increased risk of severe, NVP-associated skin rash.[13]

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, or 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.[14-17] Published literature reports rash and hyperbilirubinemia in infants exposed to NVP through breast milk.[11]

Data are conflicting regarding the increased risk of hepatotoxicity in pregnant women receiving NVP.[18] 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%).[19] 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.[20, 21] 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.[22]

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).[19] Another systematic review[23] reported a significant association between increased toxicity risk and the initiation of NVP-based ART 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).[24] NVP (as a component of a combination regimen) should be initiated during pregnancy when CD4 counts ≥250 cells/mm^3 only if the benefit clearly outweighs the risk. When CD4 counts <250 cells/mm^3 during pregnancy, patients 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 patients who are receiving NVP during pregnancy 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.[25] 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%).[26]

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.[11]

Reproduction/Fertility

Female rats showed impaired fertility at systemic NVP exposures comparable to human therapeutic exposures.[11]

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.[11]

Excerpt from Table 14

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations[a]	Use in Pregnancy
Nevirapine (NVP)	NVP *Tablet* • 200 mg[c] *Oral Suspension* • 50 mg/5 mL[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 immediate release tablet) for a 14-day lead-in period; thereafter, NVP 200 mg twice 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 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 pregnancy when CD4 counts ≥250 cells/mm^3 only if the benefit clearly outweighs the risk. A potential increased risk of life-threatening hepatotoxicity exists in pregnancy when CD4 counts are high. 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).

[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. When standard oral dosing of RPV is received during pregnancy, viral loads should be monitored more frequently.
- 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 an increased risk of congenital anomalies.

Human Studies in Pregnancy

Pharmacokinetics

RPV exposure after oral dosing is decreased by 20% to 50% during pregnancy. The International Maternal Pediatric Adolescent AIDS Clinical Trials P1026s (IMPAACT P1026) study evaluated 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 approximately 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 for RPV. PK parameters between participants were highly variable in this study.[1] A subsequent study among 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] Based on these findings, the authors recommended therapeutic drug monitoring during the third trimester and oral RPV dosing with meals. A third study among 15 women during pregnancy reported that total RPV exposure after oral dosing decreased by approximately 30%, and unbound RPV levels decreased by 22% to 25% compared to their postpartum concentrations.[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%, $P = 0.046$). Birth outcomes were similar between these groups.[5] For considerations regarding switching antiretroviral (ARV) drugs during

pregnancy, see Antiretroviral Therapy Use During Prepregnancy and Early Pregnancy. When the standard oral dose of RPV is received during pregnancy, viral loads should be monitored more frequently (see Initial Evaluation and Continued Monitoring of HIV During Pregnancy).

No studies have been conducted on the PKs of ongoing intramuscular injections of long-acting cabotegravir (CAB) and RPV (LA CAB/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 ARV regimens throughout the remainder of their pregnancies. From the Phase 2b/3/3b clinical trials of LA CAB/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 LA CAB/RPV.[6] A physiologically-based pharmacokinetics (PBPK) model of LA CAB/RPV initiation during pregnancy early in the second trimester predicted a reduction in RPV plasma concentrations of 23.0 at the first trough (C_{trough}) after the first injection. After the sixth injection in the second and third trimesters, plasma RPV concentrations were 29.2% lower. These reductions are attributable to the predicted induction of uridine diphosphate glucuronosyltransferase 1A1 and cytochrome P450 3A4 during the second and third trimesters.[7] An additional PBPK model predicted that the RPV C_{trough} at Week 12 for monthly and bimonthly long-acting RPV would be below 50 ng/mL in at least 40% and more than 90% of the pregnant population.[8] A single case report of bimonthly LA CAB/RPV found that RPV concentrations were 70% to 75% lower[9] than historical nonpregnant levels; viral suppression was maintained.

See Cabotegravir for data about CAB.

Placental and Breast Milk Passage

RPV has moderate-to-high placental transfer compared to other ARV drugs. IMPAACT P1026 included data on RPV concentration at birth 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.[2,10] No data exist on whether RPV is excreted in breast milk in humans.

Teratogenicity/Adverse Pregnancy Outcomes

The Antiretroviral Pregnancy Registry (APR) provides updated birth defect data for ATV and other ARV drugs twice a year through an interim report released in June and December. The APR has 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. Figure 1. Summary of Birth Defects Among First Trimester Exposures in the APR interim report provides a summary of the number and prevalence of birth defects per live births among cases of first-trimester exposure to ATV and other ARV drugs reported to the APR where there are sufficient data to determine 95% confidence intervals. The data in Figure 1 can be compared with the prevalence of birth defects in the U.S. population (2.72 birth defects per 100 live births) according to the Centers for Disease Control and Prevention's surveillance system (The Metropolitan Atlanta Congenital Defects Program or MACDP) and with the Texas Birth Defects Registry ([TBDR] 4.17 per 100 live births).

In the Phase 2b/3/3b trials of LA CAB/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 birth 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 *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. When standard dosing of RPV is received during pregnancy, viral loads should be monitored more frequently. For guidance about the use of combination products in pregnancy, please see the specific sections on other components (i.e., CAB, DTG, FTC, TAF, TDF). Standard Adult Doses *RPV (Edurant)* • RPV 25 mg once daily with food *RPV/FTC/TDF (Complera)*	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
		• 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).

[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)

Updated: June 12, 2025
Reviewed: June 12, 2025

Summary

- Atazanavir (ATV) concentrations are reduced during pregnancy.
  - Only ritonavir-boosted ATV (ATV/r) should be used in pregnancy, as ATV 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 birth.

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 birth 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 (ARV) 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 patients who are ARV-naive) 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 ARV-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.

Coadministration of tenofovir alafenamide (TAF) and ATV/r in nonpregnant adults has no effect on ATV levels but results in 89% and 162% higher mean TAF and TFV AUCs, respectively.[11] The U.S. Food and Drug Administration advises that no clinically significant drug interactions are expected between TAF and ATV/r and therefore, does not recommend dose adjustment or drug substitution.[12]

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, than paired postpartum C_{trough} (P = 0.0625 and P = 0.0313, respectively).[13] Concomitant use of ATV and COBI **is not recommended** during pregnancy because of these substantial reductions in drug exposures (see Cobicistat).[14]

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 birth.[1,4,15]

In a study of three women, the median ratio of breast milk ATV concentration to plasma ATV concentration[16] 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).[17] On the other hand, there was no association between first-trimester ATV

exposure and birth defects in a French cohort, although this study[18] had <50% power to detect an aOR of 1.5.

The Antiretroviral Pregnancy Registry (APR) provides updated birth defect data for ATV and other ARV drugs twice a year through an interim report released in June and December. The APR 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. Figure 1. Summary of Birth Defects Among First Trimester Exposures in the APR interim report provides a summary of the number and prevalence of birth defects per live births among cases of first-trimester exposure to ATV and other ARV drugs reported to the APR where there are sufficient data to determine 95% confidence intervals (CIs). The data in Figure 1 can be compared with the prevalence of birth defects in the U.S. population (2.72 birth defects per 100 live births) based on the Centers for Disease Control and Prevention surveillance system (The Metropolitan Atlanta Congenital Defects Program [MACDP]) and with the Texas Birth Defects Registry ([TBDR] 4.17 per 100 live births).

See Antiretroviral Drug Regimens and Pregnancy Outcomes for a discussion of the potential association between the use of boosted PIs and preterm birth.

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.[20] 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.[1,3,4,15,21-23] Maternal bilirubin levels do not correlate well with neonatal bilirubin levels.[24] 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.[21,22] Elevated neonatal bilirubin in neonates exposed to ATV is not associated with UGT-1 genotypes that have been linked to decreased UGT function.[23]

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.[25,26] 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.[27]

Hypoglycemia (glucose <40 mg/dL) that could not be attributed to maternal glucose intolerance, difficult birth, 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.[15] This report of infant hypoglycemia is similar to a prior report in which 2 of 14 infants who were exposed to PIs (i.e., nelfinavir, saquinavir, or indinavir) developed hypoglycemia during the first day of life; both infants with hypoglycemia had been exposed to nelfinavir.[28]

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.[15]

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.[15]

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.[15] 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.[29, 30] Maternal administration of ATV (with TDF/FTC or abacavir/lamivudine) was associated with delayed postnatal (infant) growth and with effects on brain development and cognitive and motor outcomes in mice.[31,32]

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.[33]

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.[15]

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[c] (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 C_{trough} 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 during the second and third trimesters when either TDF or an H2-receptor antagonist is also being received. • 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.	Note: Please see FDA label for full list of drugs with potential interactions, including several anticonvulsants and other drugs for which administration with ATV/r is contraindicated.

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).

[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; C_{trough} = trough concentration; COBI = cobicistat; EFV = efavirenz; FDA = U.S. Food and Drug Administration; 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 600 mg/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 (ARV)-experienced patients.[2,6] The U.S. Food and Drug Administration recommends the use of once-daily DRV/r 800-mg/100-mg dosing during pregnancy only when viral suppression was achieved on a stable, once-daily DRV/r regimen before pregnancy and when 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, 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 AUC reductions during the second and third trimesters of 63% and 49% and C_{trough} reductions of 83% and 83% during the second and third trimesters, 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 participants 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 (APR) provides updated birth defect data for DRV and other ARV drugs twice a year through an interim report released in June and December. The APR 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. Figure 1. Summary of Birth Defects Among First Trimester Exposures in the APR interim report provides a summary of the number and prevalence of birth defects per live births among cases of first-trimester exposure to DRV and other ARV drugs reported to the APR where there are sufficient data to determine 95% confidence intervals. The data in Figure 1 can compared with the prevalence of birth defects in the U.S. population (2.72 birth defects per 100 live births) according to the Centers for Disease Control and Prevention surveillance system (The Metropolitan Atlanta Congenital Defects Program [MACDP]) and with the Texas Birth Defects Registry ([TBDR] 4.17 per 100 live births).

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) *Tablets* • 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 during all pregnancies. • 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 *Patients Who Are ARV-Naive* • 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	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
		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).

[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 mg/150 mg twice daily or LPV/r 500 mg/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 birth.
- 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 participants who are antiretroviral (ARV)-naive. However, higher C_{trough} are recommended for participants who are PI-experienced, 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 pregnancies 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. 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.

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 birth 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 birth 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 hair–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 (APR) provides updated birth defect data for LPV/r and other ARV drugs twice a year through an interim report

released in June and December. The APR 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. Figure 1. Summary of Birth Defects Among First Trimester Exposures in the APR interim report provides a summary of the number and prevalence of birth defects per live births among cases of first-trimester exposure to LPV, RTV, and other ARV drugs reported to the APR where there are sufficient data to determine 95% confidence intervals (CIs). The data in Figure 1 can be compared with the prevalence of birth defects in the U.S. population (2.72 birth defects per 100 live births) based on the Centers for Disease Control and Prevention surveillance system (The Metropolitan Atlanta Congenital Defects Program [MACDP]) and with the Texas Birth Defects Registry ([TBDR] 4.17 per 100 live births).

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).[25] Compared with ZDV alone, ZDV plus 3TC plus LPV/r was associated with increased rates of preterm birth (<37 weeks). The Surveillance Monitoring for Antiretroviral Therapy 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.[26] 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.[27] 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 birth than the use of NNRTI-based regimens.[28] For a more detailed discussion of ARV drug regimens and adverse pregnancy outcomes, please refer to Antiretroviral Drug Regimens and Pregnancy 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.[29,30]

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.[31]

Reproduction/Fertility

No effects on fertility were observed in male and female rats.[31]

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.[32]

Placental and Breast Milk Passage

No information is available on placental transfer of LPV in animals.[31]

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 *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. Standard Adult Doses • LPV/r 400 mg/100 mg twice daily, *or* • LPV/r 800 mg/200 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
		Tablet • 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).

[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

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Fostemsavir (Rukobia, FTR)

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Fostemsavir (FTR) is a prodrug of the active drug temsavir, a gp120-directed attachment inhibitor.

Summary

- Pharmacokinetic (PK) 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 PK studies of FTR have been reported in pregnancy.

Placental and Breast Milk Passage

No data are available on placental or breast milk passage of FTR in humans.

Teratogenicity/Adverse Pregnancy Outcomes

The Antiretroviral Pregnancy Registry (APR) provides updated birth defect data for FTR and other antiretroviral drugs twice a year through an interim report released in June and December. For the most recent data about FTR, refer to Table 5. Number of Birth Defects by Trimester of Earliest Exposure to Each Drug in the current APR interim report. Available data are limited and insufficient for drawing conclusions about the risk of birth defects among infants who were exposed to FTR.

Animal Studies

Carcinogenicity

Temsavir was not genotoxic or mutagenic *in vitro.*[1]

Reproduction/Fertility

FTR did not adversely affect the fertility of male or female rats at temsavir exposures approximately 10 times (males) and 186 times (females) higher than those achieved in humans at the recommended dose.[1]

Teratogenicity/Adverse Pregnancy Outcomes

No adverse embryo-fetal effects were observed in rats and rabbits at temsavir exposures of approximately 180 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.[1]

Placental and Breast Milk Passage

When FTR was administered to pregnant rats, FTR-related drug materials (e.g., temsavir or metabolites) crossed the placenta and were detectable in fetal tissue. Temsavir is excreted in rat milk and was present at concentrations similar to those measured in maternal plasma on Day 11 postpartum.[1]

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).

Key: ARV = antiretroviral; FTR = fostemsavir; PK = pharmacokinetic

References

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Ibalizumab-uiyk (Trogarzo, IBA)

Updated: June 12, 2025
Reviewed: June 12, 2025

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 pregnancy 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, IBA has the potential to be transmitted to the developing fetus during pregnancy. 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 exposed to IBA during pregnancy.

The U.S. Food and Drug Administration requires collection of prospective data on exposure of 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 infants with IBA exposure based on the degree of immunosuppression observed. The safety of administering live or live-attenuated vaccines in infants with IBA exposure 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 *IV infusion (diluted infusion with 250 mL 0.9% sodium chloride)* • IBA 2,000-mg loading dose over 30 minutes, followed by IBA 800-mg maintenance doses over 15 minutes administered every 2 weeks *IV push (undiluted)* • IBA 2,000-mg loading dose over 90 seconds, followed by IBA 800-mg maintenance doses over 30 seconds 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 exposed to IBA during pregnancy. The FDA requires collection of prospective data on IBA exposure 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).

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)

Updated: June 12, 2025
Reviewed: June 12, 2025

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

The Antiretroviral Pregnancy Registry (APR) provides updated birth defect data for MVC and other ARV drugs twice a year through an interim report released in June and December. For the most recent data about MVC, refer to Table 5. Number of Birth Defects by Trimester of Earliest Exposure

to Each Drug in the current APR interim report. Available data are limited and insufficient for drawing conclusions about the risk of birth defects among 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.[5] 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 (range 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.[6]

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.[7]

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.[8] Studies in lactating rats indicate that MVC is secreted extensively into rat milk.[7]

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 *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. *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).

[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)

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Summary

- Pharmacokinetic (PK) 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.
- LEN is U.S. Food and Drug Administration (FDA) approved for heavily treatment-experienced adults with multidrug-resistant HIV-1 infection whose current antiretroviral (ARV) regimen is failing due to resistance, intolerance, or safety considerations.
- LEN is under evaluation for HIV pre-exposure prophylaxis (PrEP); LEN is not FDA approved for HIV prevention.

Human Studies in Pregnancy

Pharmacokinetics

No data are available on the PK of LEN with continuing subcutaneous (SQ) 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 (APR) provides updated birth defect data for LEN and other ARV drugs twice a year through an interim report released in June and December. The APR has not monitored sufficient numbers of first-trimester exposures to LEN to report on the risk of overall birth defects.

In the PURPOSE 1 study[2], a Phase 3, double-blind, randomized controlled trial of adolescent girls and young women in South Africa and Uganda, participants were assigned to receive twice-yearly SQ LEN versus daily oral emtricitabine (FTC) plus tenofovir alafenamide (TAF) or daily oral FTC plus tenofovir disoproxil fumarate (TDF; active control) for HIV PrEP. At the time of the interim analysis, there were 510 pregnancies among 487 participants—193 in the LEN group, 219 in the FTC/TAF group, and 98 in the FTC/TDF group—with 277 delivery outcomes and 233 ongoing pregnancies. Pregnancy outcomes were similar to those expected for the general population. No documented incident HIV was reported among participants receiving LEN (see PrEP to Prevent HIV During Periconception, Antepartum, and Postpartum Periods).

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.[3]

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.[3]

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.[3]

Placental and Breast Milk Passage

LEN was detected at low levels in the plasma of nursing rat pups.[3]

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 or breast milk passage. 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).

Key: ARV = antiretroviral; LEN = lenacapavir; PK = pharmacokinetic; SQ = subcutaneous

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Bictegravir (BIC)

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Reviewed: June 12, 2025

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,[1,2] a case series,[3,4] and one case report.[5]

IMPAACT 2026[6] evaluated the PK of BIC among 27 pregnant women, which showed that total BIC area under the curve (AUC) was decreased by 46% to 52%; the concentrations at 24 hours postdose (C_{24h}) were 62% to 68% lower during pregnancy compared to postpartum.[1] Seven of 12 (58%) participants during the second trimester and 13 of 21 (62%) during the third trimester fell below the 10th percentile AUC for nonpregnant adults, but none of these women had a detectable viral load. 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 approximately sevenfold and 5.9-fold above the EC_{95}.[1] Because BIC is highly protein bound and pregnancy can be associated with decreased plasma protein binding, unbound drug concentrations were also assessed. Compared with postpartum, the percent unbound was 45% and 42% higher in the second and third trimesters, respectively. However, median unbound BIC concentrations remained lower during pregnancy (3.83 ng/mL and 3.01 ng/mL for the second and third trimesters, respectively, compared to 5.83 ng/mL during postpartum). Virologic suppression (<40 copies/mL) was maintained in 88% to 92% of participants across pregnancy, birth, and postpartum, and no confirmed infant HIV infections occurred among the 26 for whom data are available.

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 70% to 74% 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. 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 birth, and no infant HIV infections occurred.

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, and thus no dose adjustment is recommended. Separate large cohort studies have also demonstrated rates of virologic suppression (<50 copies/mL) of approximately 82% to 91% through birth with BIC/tenofovir alafenamide/emtricitabine.[7]

Placental and Breast Milk Passage

Placental transfer of BIC is high, with a mean/median umbilical cord blood–to–maternal plasma ratio of approximately 1.4 at birth.[1,2] The estimated median half-life in neonates based on washout data is prolonged in comparison to adults, with one study estimating 43 hours (interquartile range 38–58; n = 10)[2] and another estimating 33 hours (interquartile range 26–46; n = 25).[1] These umbilical cord blood–to–maternal plasma ratios are comparable to a previous case series in which 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 birth, 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 woman, which revealed a ratio of 0.01 and subsequent estimated infant daily dose of 0.01 mg/kg.[8] Additional data are needed to refine our understanding of the breast milk passage of BIC.

Teratogenicity/Adverse Pregnancy Outcomes

The Antiretroviral Pregnancy Registry (APR) provides updated birth defect data for BIC and other antiretroviral (ARV) drugs twice a year through an interim report released in June and December. The APR 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. Figure 1. Summary of Birth Defects Among First Trimester Exposures in the APR interim report provides a summary of the number and prevalence of birth defects per live births among cases of first-trimester exposure to BIC and other ARV drugs reported to the APR where there are sufficient data to determine 95% confidence intervals. The data in Figure 1 can be compared with the prevalence of birth defects in the U.S. population (2.72 birth defects per 100 live births) based on the Centers for Disease Control and Prevention surveillance system (The Metropolitan Atlanta Congenital Defects Program [MACDP]) and with the Texas Birth Defects Registry ([TBDR] 4.17 per 100 live births).

Separate, smaller retrospective studies with sample sizes of approximately 50 to 150 participants have also reported pregnancy outcomes with BIC and have not identified higher rates of congenital anomalies with exposure occurring during the first trimester[7,9] or at any time during pregnancy.[10]

Animal Studies

Carcinogenicity

BIC has not been shown to be genotoxic or mutagenic *in vitro*.[11]

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.[11]

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).[11]

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.[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
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).

[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; C_{trough} = trough concentration; FDC = fixed-dose combination; FTC = emtricitabine; PK = pharmacokinetics; TAF = tenofovir alafenamide

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Cabotegravir (CAB)

Updated: June 12, 2025
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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.
- Long-acting CAB and rilpivirine (RPV) (LA CAB/RPV) is FDA approved for HIV treatment.
- CAB-LA is FDA approved for HIV pre-exposure prophylaxis (PrEP).

Human Studies in Pregnancy

Pharmacokinetics

Prospective CAB PK data during pregnancy and postpartum are limited to preliminary data from the HIV Prevention Trials Network (HPTN) 084 protocol open-label extension (OLE)[1] in which, upon diagnosis of pregnancy, HIV-negative participants were given the choice of continuing the current regimen (either CAB-LA or TDF/FTC) or switching to a self-selected regimen (CAB-LA or TDF/FTC) for HIV PrEP. Monthly PK sampling was performed among a subset of 75 participants; preliminary PK data from the first 50 participants, all of whom were continuing on CAB from before pregnancy (median number of CAB-LA intramuscular injections before conception was 6, range 4–7), found that concentrations decreased in pregnancy but were largely maintained above the protocol-defined exposure target of four times the protein-adjusted 90% inhibitory concentration (PA-IC_{90}) of 0.664 µg/mL. No PK data are reported on CAB-LA initiation in pregnancy.

A case report of a single pregnancy on bi-monthly LA CAB/RPV reported that CAB concentrations were comparable to those in nonpregnant individuals.[2] No other prospective PK data on LA CAB/RPV for HIV treatment during pregnancy and postpartum exists. Earlier clinical trial PK data are limited to pregnant women who stopped receiving CAB injections for the treatment of HIV once pregnancy was recognized and began an alternative oral antiretroviral (ARV) regimen throughout the remainder of their pregnancies.[3]

Placental and Breast Milk Passage

Median (interquartile range [IQR] 25–75) CAB maternal-to-fetal concentration ratio assessed using an *ex vivo* dually perfused human cotyledon model was 10% (IQR 5–16), suggesting low placental transfer.[4] No data are available describing breast milk passage of CAB in humans.[5] See Rilpivirine for data about RPV.

Teratogenicity/Adverse Pregnancy Outcomes

The Antiretroviral Pregnancy Registry (APR) provides updated birth defect data for CAB and other ARV drugs twice a year through an interim report released in June and December. The APR has not monitored sufficient numbers of first-trimester exposures to CAB to report on the risk of overall birth defects.

In HPTN 084 OLE,[6] there were 351 confirmed pregnancies. Pregnancy-related maternal adverse event incidence was 43.7 (95% confidence interval [CI], 30.9–60.0), 52.9 (95% CI, 24.2–100.5), and 40.0 (95% CI, 14.7–87.1) per 100 person-years among those using CAB-LA during pregnancy, using CAB-LA starting before pregnancy, or no CAB-LA use, respectively. Adverse pregnancy outcome rates were similar across groups; negative outcomes were reported in 28% (55/194), 35% (24/69), and 26% (11/43) of pregnancies with CAB-LA use during pregnancy, CAB-LA use starting before pregnancy, or no CAB-LA use, respectively. One major congenital anomaly was observed in the CAB-LA during pregnancy group and was not considered related to CAB-LA exposure.[7]

In earlier 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 LA injectable), resulting in 8 elective abortions, 6 spontaneous abortions (5 in the first trimester), 1 ectopic pregnancy, and 10 live births (1 oral, 9 LA 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 birth occurred due to induction of labor.[1] 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.[7]

CAB was not genotoxic in the bacterial reverse mutation assay, mouse lymphoma assay, or *in vivo* rodent micronucleus assay.[8] 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.[7]

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.[9] 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.[10] 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 published 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

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations[a]	Use in Pregnancy
		• 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 postinjection 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).

[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: June 12, 2025
Reviewed: June 12, 2025

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, total 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] A subsequent analysis revealed that DTG protein binding in these women was decreased during pregnancy so that unbound DTG concentrations during late pregnancy were comparable to postpartum concentrations, despite the decrease in total (bound plus unbound) concentrations.[8] 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 loads below 50 copies/mL during the third trimester.[7]

In contrast, PK sampling during pregnancy and the early postpartum period of 17 African women 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.[9] 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 (APR) provides updated birth defect data for DTG and other antiretroviral (ARV) drugs twice a year through an interim report released in June and December. The APR has monitored sufficient numbers of first-trimester exposures to DTG 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 DTG. Figure 1. Summary of Birth Defects Among First Trimester Exposures in the APR interim report provides a summary of the number and prevalence of birth defects per live births among cases of first-trimester exposure to DTG and other ARV drugs reported to the APR where there are sufficient data to determine 95% confidence intervals. The data in Figure 1 can be compared with the prevalence in the U.S. population (2.72 birth defects per 100 live births) based on the Centers for Disease Control and Prevention surveillance system (The Metropolitan Atlanta Congenital Defects Program [MACDP] and with the Texas Birth Defects Registry ([TBDR] 4.17 per 100 live births).

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 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.[18]

INSTI regimens, including those with DTG, are associated with weight gain and other metabolic effects, such as hyperglycemia and changes in folate metabolism, both during pregnancy and among nonpregnant adults with HIV.[19,20] The impact of these metabolic effects on pregnancy outcomes is unknown.[20] 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 associated with high maternal weight, such as gestational hypertension, gestational diabetes mellitus, and macrosomia.[21] 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.[22] In a study randomizing pregnant women from nine countries (88% from sub-Saharan Africa) to DTG- or efavirenz-based ARV regimens, women receiving DTG had greater antepartum weight gain, which was associated with fewer adverse pregnancy outcomes.[23] 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.[24]

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.[24]

Teratogenicity/Adverse Pregnancy Outcomes

Studies of DTG in rats and rabbits have shown no evidence of developmental toxicity, teratogenicity, or effects on reproductive function.[24]

Placental and Breast Milk Passage

Studies in rats have demonstrated that DTG crosses the placenta and is excreted into breast milk.[24]

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 ARVs. DTG is a *Preferred* ARV drug for use during pregnancy, irrespective of trimester, and when 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. [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 (C_{trough}) are reduced during pregnancy by approximately 85% with use of EVG in fixed-dose combination (FDC) 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 an FDC 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 concentration at 24 hours postdose (C_{24h}) was 81% lower during the second trimester and 89% lower during the third trimester than during the postpartum period. COBI AUC was 44% and 59% lower and C_{24h} was 60% and 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 53% of women during the second trimester and 62% of women during the third trimester, while 28% of women failed to reach the exposure target during the postpartum period. Plasma HIV RNA at birth 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 C_{trough} was reduced by 77% during the third trimester compared with the postpartum period. EVG C_{trough} 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 FDC tablets that contain EVG and COBI, the prescribing information for these products has been changed to indicate that these formulations **are not recommended** for use in pregnancy and should not be initiated in pregnancy; frequent viral load monitoring or use of an alternative regimen **is recommended** if these formulations are being taken when pregnancy occurs.[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 (APR) provides updated birth defect data for EVG and other antiretroviral (ARV) drugs twice a year through an interim report released in June and December. The APR 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] Figure 1. Summary of Birth Defects Among First Trimester Exposures in the APR interim report provides a summary of the number and prevalence of birth defects per live births among cases of first-trimester exposure to EVG and other ARV drugs reported to the APR where there are sufficient data to determine 95% confidence intervals. The data in Figure 1 can be compared with the prevalence in the U.S. population (2.72 birth defects per 100 live births) based on the Centers for Disease Control and Prevention surveillance system (The Metropolitan Atlanta Congenital Defects Program [MACDP]) and with the Texas Birth Defects Registry ([TBDR] 4.17 per 100 live births).

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. If EVG/c is being taken when pregnancy occurs, consider frequent viral load monitoring or switching to a more effective recommended regimen. If a regimen that contains EVG/c is continued during pregnancy, 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).

[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 (PK) 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

Three PK studies found third-trimester RAL exposure was commensurate with postpartum levels. 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, evaluated the PK of RAL 400 mg twice daily in 42 pregnant women. RAL PK 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 birth. 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 on RAL 400 mg twice daily 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 for HIV during pregnancy, 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 woman 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] Most recently, a Brazilian PK study of RAL elimination among pregnant and postpartum women on RAL 400 mg twice daily (third trimester [n = 15], birth [n = 15], and postpartum data [n = 8]) also found similar RAL plasma exposure in the third trimester and postpartum.[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.[8] Other case reports have shown cord blood–to–maternal blood drug level ratios of 1.00 to 1.06.[9-11] In three cases of preterm birth at 29 to 33 weeks gestation (in two of these cases, RAL was added to the maternal ARV regimen shortly before anticipated preterm birth), cord blood–to–maternal plasma ratios ranged from 0.44 to 1.88.[12]

Limited data indicate that maternal doses of up to 1,200 mg daily of RAL are transferred at low levels in breast milk and are not expected to cause any adverse effects in breastfed infants.[13] 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.[14] A single case study demonstrated low RAL transfer into breast milk and little accumulation.[15]

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 the groups were observed.[16] 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.[17]

The Antiretroviral Pregnancy Registry (APR) provides updated birth defect data for RAL and other ARV drugs twice a year through an interim report released in June and December. The APR 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. Figure 1. Summary of Birth Defects Among First Trimester Exposures in the APR interim report provides a summary of the number and prevalence of birth defects per live births among cases of first-trimester exposure to RAL and other ARV drugs reported to the APR where there are sufficient data to determine 95% CI. The data in Figure 1 can be compared with the prevalence of birth defects in the U.S. population (2.72 birth defects per 100 live births) based on the Centers for Disease Control and Prevention's surveillance system (The Metropolitan Atlanta Congenital Defects Program [MACDP]) and with the Texas Birth Defects Registry ([TBDR] 4.17 per 100 live births).

The IMPAACT P1081 study randomized 408 women in Africa, South America, Thailand, and the United States who had never used ART and 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 birth.[18] 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.[19-25]

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.[1,2,18] 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.[26] 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.[27] 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.[28]

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.[29] 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).[29] 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.[30]

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.[31]

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.[31]

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.[31]

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.[31]

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 Tablet* • 400 mg *Chewable Tablets* • 25 mg • 100 mg RAL (Isentress HD) *Film-Coated Tablet* • 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** during pregnancy 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 patients who are ARV-naïve 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).

[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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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 EVG/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** when starting or changing regimens during pregnancy.OBJ

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 ritonavir 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 seven of their births with a median cord blood–to–maternal plasma ratio[5] of 0.09. In 27 neonates born to mothers who were receiving EVG/c, COBI was below the assay quantitation limit of 10 ng/mL in all washout PK samples taken between 2 hours and 9 days post birth.[5] No data are available on breast milk passage of COBI in humans.

Teratogenicity/Adverse Pregnancy Outcomes

The Antiretroviral Pregnancy Registry (APR) provides updated birth defect data for COBI and other antiretroviral (ARV) drugs twice a year through an interim report released in June and December. The APR 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. Figure 1. Summary of Birth Defects Among First Trimester Exposures in the APR interim report provides a summary of the number and prevalence of birth defects per live births among cases of first-trimester exposure to COBI and other ARV drugs reported to the APR where there are sufficient data to determine 95% confidence intervals. The data in Figure 1 can be compared with the prevalence of birth defects in the U.S. population (2.72 birth defects per 100 live births) according to the Centers for Disease Control and Prevention surveillance system (The Metropolitan Atlanta Congenital Defects Program [MACDP]) and with the Texas Birth Defects Registry ([TBDR] 4.17 per 100 live births).

Animal Studies

Carcinogenicity

No increases in tumor incidence relevant to humans were seen in rodent studies.[12]

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.[12]

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.[12]

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).

[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)

Updated: June 12, 2025
Reviewed: June 12, 2025

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 (APR) provides updated birth defect data for RTV and other antiretroviral drugs twice a year through an interim report released in June and December. The APR 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. Figure 1. Summary of Birth Defects Among First Trimester Exposures in the APR interim report provides a summary of the number and prevalence of birth defects per live births among cases of first-trimester exposure to RTV and other ARV drugs reported to the APR where there are sufficient data to determine 95% confidence intervals. The data in Figure 1 can be compared with the prevalence of birth defects

in the U.S. population (2.72 birth defects per 100 live births) based on the Centers for Disease Control and Prevention surveillance system (The Metropolitan Atlanta Congenital Defects Program [MACDP]) and with the Texas Birth Defects Registry ([TBDR] 4.17 per 100 live births).

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.[9]

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.[9]

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).[9]

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 *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. 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 Powder* • 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).

[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

Delavirdine

Didanosine

Enfuvirtide

Fosamprenavir

Indinavir

Nelfinavir

Saquinavir

Stavudine

Tipranavir

Zalcitabine

Amprenavir (Agenerase)

Last Updated: November 7, 2007; Last Reviewed: November 7, 2007

Amprenavir is classified as FDA pregnancy category C and is no longer available in the United States.

Animal Studies

Carcinogenicity

In vitro screening tests for carcinogenicity have been negative. An increase in benign hepatocellular adenomas and hepatocellular carcinomas was observed in male mice and rats at the highest doses evaluated, which produced systemic exposures in mice 2-fold and in rats 4-fold higher than systemic exposure in humans receiving therapeutic doses of amprenavir. Female mice and rats were not affected.

Reproduction/Fertility

No effect has been seen on reproductive performance, fertility, or embryo survival in rats at exposures about twice those of human therapeutic exposure.

Teratogenicity/Adverse Pregnancy Outcomes

In pregnant rabbits, administration of amprenavir resulting in systemic exposures about one-twentieth of that observed with human therapeutic exposure was associated with abortions and an increased incidence of minor skeletal variations resulting from deficient ossification of the femur, humerus trochlea, and humerus. In rat fetuses, thymic elongation and incomplete ossification of bones were also attributed to amprenavir at systemic exposures about one-half that associated with the recommended human dose. Reduced body weights of approximately 10% – 20% were observed in offspring of rodents administered amprenavir from Day 7 of gestation to Day 22 of lactation (exposures approximately twice that observed with the human therapeutic dose). However, the subsequent development of the offspring, including fertility and reproductive performance, was not affected by maternal administration of amprenavir.

Placental and Breast Milk Passage

Whether amprenavir crosses the placenta is unknown. Amprenavir is excreted in the milk of lactating rats; it is not known if it is excreted in human milk.

Human Studies in Pregnancy

There have been limited studies of amprenavir in pregnant women and no studies in neonates. Amprenavir oral solution contains high levels of excipient propylene glycol in the oral solution vehicle; this is not true for the capsular formulation. Propylene glycol is metabolized by the alcohol and aldehyde dehydrogenase enzyme pathway. Some patients, including infants and children below the age of 4 years, pregnant women, patients with hepatic or renal failure, and patients treated with disulfiram or metronidazole, are not able to adequately metabolize and eliminate propylene glycol, thereby leading to its accumulation and potential adverse events. Thus, while the capsule formulation of amprenavir may be used in pregnancy, amprenavir oral solution is contraindicated in pregnant women and infants and in children under the age of 4 years.

Delavirdine (Rescriptor)

Last Updated: November 7, 2007; Last Reviewed: November 7, 2007

Delavirdine is classified as FDA pregnancy category C and is no longer available in the United States.

Animal Studies

Carcinogenicity

In vitro screening tests for carcinogenicity have been negative. In rats, delavirdine was noncarcinogenic at all doses studied. In mice, delavirdine was associated with an increase in hepatocellular adenoma and carcinoma in both males and females and urinary bladder tumors in males at systemic exposures 0.5- to 3-fold higher than human exposure at therapeutic doses for female mice and at exposures 0.2- to 4-fold higher in male mice.

Reproduction/Fertility

Delavirdine does not impair fertility in rodents.

Teratogenicity/Adverse Pregnancy Outcomes

Delavirdine is teratogenic in rats; doses of 50 to 200 mg/kg/day during organogenesis caused ventricular septal defects.

Exposure of rats to doses approximately 5 times human therapeutic exposure resulted in marked maternal toxicity, embryotoxicity, fetal developmental delay, and reduced pup survival.

Abortions, embryotoxicity, and maternal toxicity were observed in rabbits at doses approximately 6 times human therapeutic exposure.

Placental and Breast Milk Passage

Whether delavirdine crosses the placenta is unknown. Delavirdine is excreted in the milk of lactating rats; however, it is unknown if the drug is excreted in human breast milk.

Human Studies in Pregnancy

Delavirdine has not been evaluated in HIV-infected pregnant women. In premarketing clinical studies, the outcomes of seven unplanned pregnancies were reported: three resulted in ectopic pregnancies, three resulted in healthy live births, and one infant was born prematurely with a small muscular ventricular septal defect to a patient who received approximately 6 weeks of treatment with delavirdine and zidovudine early in the course of pregnancy.

Didanosine (Videx, ddI)

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

Didanosine is classified as Food and Drug Administration (FDA) Pregnancy Category B.[1]

Didanosine **is not recommended** for use in pregnant women with HIV due to its toxicity.

Animal Studies

Carcinogenicity

Didanosine is both mutagenic and clastogenic in several *in vitro* and *in vivo* assays. Long-term animal carcinogenicity screening studies of 0.7 times to 1.7 times human exposure in mice and 3 times human exposure in rats have been negative.[1]

Reproduction/Fertility

At approximately 12 times the estimated human exposure, didanosine was slightly toxic to female rats and their pups during mid and late lactation. These rats showed reduced food intake and body weight gains; however, the physical and functional development of the offspring was not impaired and there were no major changes in the F2 generation.

Teratogenicity/Adverse Pregnancy Outcomes

No evidence of teratogenicity or toxicity was observed in pregnant rats and rabbits with exposures of didanosine that were 12 times and 14 times, respectively, the exposures seen in humans.

Placental and Breast Milk Passage

A study in rats showed that didanosine and/or its metabolites are transferred to the fetus through the placenta.

Human Studies in Pregnancy

Pharmacokinetics

A Phase 1 study (PACTG 249) of didanosine was conducted in 14 pregnant women with HIV who were enrolled at gestational age 26 to 36 weeks and treated through 6 weeks postpartum.[2] The drug was well tolerated during pregnancy by the women and the fetuses. Pharmacokinetic (PK) parameters after oral administration were not significantly affected by pregnancy, and dose modification from the usual adult dosage is not needed.

Placental and Breast Milk Passage

Placental transfer of didanosine was low-moderate in a Phase 1/2 safety and PK study.[2] This was confirmed in a study of 100 pregnant women with HIV who were receiving nucleoside reverse transcriptase inhibitors (NRTIs), generally as part of a two- or three-drug combination antiretroviral (ARV) regimen. At the time of delivery, cord-to-maternal-blood ratio for didanosine (n = 10) was 0.38 (range 0.0–2.0). In 15 of 24 samples (62%), cord blood concentrations for didanosine were below the limits of detection.[3]

It is not known whether didanosine is excreted in human breast milk.

Teratogenicity/Adverse Pregnancy Outcomes

The French Perinatal Cohort reported that head and neck birth defects were associated with first-trimester exposure to didanosine (0.5%, adjusted odds ratio [aOR] 3.4, 95% CI, 1.1–10.4, $P = 0.04$).[4] Though the PHACS/SMARTT cohort found no association between any individual NRTIs and birth defects, after adjusting for birth cohort and other factors, didanosine administered in combination with stavudine was associated with an overall increase in congenital abnormalities;[5] it should be noted that the combination of didanosine and stavudine **should not be used** in pregnant women with HIV (or anyone with HIV) because of a higher risk of toxicity. Among 897 births to women with HIV in a Spanish cohort, there was no significant difference between the rate of birth defects after first-trimester exposure and the rate of birth defects after second- and third-trimester exposure (odds ratio [OR] 0.61, 95% CI, 0.16–2.27).[6] In the Antiretroviral Pregnancy Registry, sufficient

numbers of first-trimester exposures to didanosine in humans have been monitored to be able to detect at least a 2-fold increase in the risk of overall birth defects.[7] Among cases of first-trimester didanosine exposure reported to the Antiretroviral Pregnancy Registry, prevalence of birth defects was 4.68% (20 of 427 births; 95% CI, 2.88% to 7.14%) compared with 2.72% in the U.S. population, based on Centers for Disease Control and Prevention surveillance.[7] All defects were reviewed in detail by the Registry, and no pattern of defects was discovered. The rate and types of defects will continue to be closely monitored.

Safety

Lactic acidosis, fatal in some cases, has been described in pregnant women receiving the combination of didanosine and stavudine along with other ARV agents;[8-10] the FDA and Bristol-Myers Squibb have issued a warning to health care professionals that pregnant women may be at increased risk of fatal lactic acidosis when prescribed didanosine and stavudine in combination.

The PHACS/SMARTT cohort found that after adjusting for birth cohort and other factors, didanosine administered in combination with stavudine was associated with the occurrence of neurodevelopmental disability. However, there was no increase in the likelihood of adverse events in the following domains with didanosine alone: metabolic, growth and development, cardiac, neurological, neurodevelopmental, behavior, language, and hearing.[11,12] As noted above, the combination of didanosine and stavudine should not be used in pregnant women with HIV (or anyone with HIV) because of a high risk of toxicity.

In a multivariate analysis of the association between *in utero* ARV exposure and risk of cancer in HIV-exposed, uninfected infants, the French Perinatal Study reported a 5.5-fold (95% CI, 2.1–14.4) increase in cancer incidence with first-trimester didanosine exposure.[13]

Excerpt from Table 8[a]

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations	Use in Pregnancy
Didanosine (ddI) *Videx* *Videx EC*	ddI (Videx) *Buffered Tablets (Non-EC):* • No longer available *Solution:* • 10 mg/mL oral solution Videx EC (EC Beadlets) Capsules: • 125 mg • 200 mg • 250 mg • 400 mg Generic Delayed-Release Capsules: • 200 mg • 250 mg • 400 mg	Standard Adult Doses *Body Weight ≥60 kg:* • ddI 400 mg once daily *With TDF:* • ddI 250 mg once daily; take 1/2 hour before or 2 hours after a meal. *Body Weight <60 kg:* • ddI 250 mg once daily *With TDF:* • ddI 200 mg once daily; take 1/2 hour before or 2 hours after a meal. Note: Preferred dosing with oral solution is twice daily (total daily dose divided into 2 doses). Take 1/2 hour before or 2 hours after a meal. Dosing in Pregnancy: • No change in dose indicated. PK in Pregnancy: • PK is not significantly altered in pregnancy.	ddI is not recommended for pregnant women. Low-moderate placental transfer to fetus.[b] ddI should not be used with d4T. Lactic acidosis, sometimes fatal, has been reported in pregnant women receiving ddI and d4T together.

[a] Individual ARV drug dosages may need to be adjusted in patients with renal or hepatic insufficiency (for details, see the Adult and Adolescent Guidelines. Appendix B, Table 10).

[b] Placental transfer categories are determined by mean or median cord blood/maternal delivery plasma drug ratio:

High: >0.6 Moderate: 0.3–0.6 Low: <0.3

Key to Acronyms: ARV = antiretroviral; d4T = stavudine; ddI = didanosine; EC = enteric coated; FDC = fixed-dose combination; PK = pharmacokinetic; TDF = tenofovir disoproxil fumarate

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Enfuvirtide (Fuzeon, T-20)

(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 pregnancy 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 pregnancy 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).

[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 pregnancy compared to exposures in 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).

[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: June 12, 2025
Reviewed: June 12, 2025

Decision-Making About Antiretroviral Drugs During Pregnancy or When 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 antiretroviral therapy (ART) options during pregnancy or when trying to conceive.

During pregnancy or when 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) when ART for HIV is initiated prior to conception and sustained viral suppression to undetectable levels throughout pregnancy has been achieved. See Use of Antiretroviral Drugs to Prevent Perinatal HIV Transmission and Improve Health During Pregnancy.

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 During Pregnancy or When Trying to Conceive

- As part of shared decision-making, information should be provided during pregnancy or when trying to conceive to help the understanding and consideration of 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 birth, birth defects). For additional information, refer to Table 6. What to Start: Initial Antiretroviral Regimens During Pregnancy When Antiretroviral Therapy Has Never Been Received, Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs During Pregnancy and When Trying to Conceive , Teratogenicity, and Antiretroviral Drug Regimens and Pregnancy Outcomes.
- When trying to conceive, information should be provided about the use of specific ARV regimens during pregnancy to enable informed decisions before pregnancy occurs.
- 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 (APR) prospectively collects and reviews data about birth defects in order to detect any major teratogenic effect(s) involving ARV drug exposure during

pregnancy. Clinicians are encouraged to report all cases of ARV drug exposure during pregnancy or when conception occurred while receiving ARV drugs to the Antiretroviral Pregnancy Registry. The APR provides updated birth defect data for ARV drugs twice a year through an interim report released in June and December.

  - 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 the HIV status during pregnancy. Most NTDs occur before the neural tube closes at 4 weeks post-conception (approximately 6 weeks after the last menstrual period), often before pregnancy is known. After 6 weeks' gestation, the additional risk of NTDs developing is thought to be much less likely. Folic acid supplementation should always be encouraged when trying to conceive and in early pregnancy (see Prepregnancy Counseling and Care).
  - 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.
  - The Antiretroviral Pregnancy Registry report has monitored sufficient numbers of first-trimester exposures to bictegravir (BIC) 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 when conception occurred while receiving ARV drugs to the APR.

- The risk of other adverse pregnancy outcomes, many of which are more common than birth defects, also should be discussed. Some ARV regimens may increase the risk of preterm birth (see Antiretroviral Drug Regimens and Pregnancy Outcomes).
- In most cases, the Panel recommends continuing the current regimen during pregnancies impacted by HIV, 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.
  - When ARVs that are not *Preferred* or *Alternative* options for use during pregnancy are being taken, counsel about the benefits and risks of continuing the current ART or switching to another ARV regimen.
  - When ARVs for which data about use in pregnancy are insufficient (e.g., long-acting cabotegravir [CAB-LA], doravirine) or ARVs with pharmacokinetic (PK) changes that could lead to lower drug levels and loss of viral suppression (e.g., cobicistat-boosted regimens) are being taken, 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 in the context of ART experience, ARV drugs that have insufficient data regarding use in pregnancy or are not recommended for use in pregnancy except in special circumstances may need to be taken.
- For additional information, see Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs During Pregnancy and When Trying to Conceive and Antiretroviral Therapy Use During Prepregnancy and Early Pregnancy.

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 during pregnancy and in nonpregnant adults. The Panel requires adequate PK, dosing, and teratogenicity data during pregnancy to categorize a drug as *Preferred* or *Alternative* for use in pregnancy or when trying to conceive. ARV drugs are assigned to one of the five categories (see Recommendations for the Use of Antiretroviral Drugs During Pregnancy: Overview).
- ARV regimens for treating HIV-2 mono-infection or HIV-1/HIV-2 coinfection should include drugs that are active against HIV-2 (see HIV-2 Infection and Pregnancy).
- 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 regimens include DTG or BIC used in combination with two nucleoside reverse transcriptase inhibitors (NRTIs).
  - DTG plus tenofovir alafenamide (TAF) or tenofovir disoproxil fumarate (TDF) plus emtricitabine (FTC) or lamivudine (3TC)
  - Fixed-dose combination of BIC/FTC/TAF
- DTG- and BIC-based regimens are *Preferred* for treating early (acute or recent) HIV infection during pregnancy unless there is a history of prior exposure to CAB-LA for pre-exposure prophylaxis. After CAB-LA 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 that includes integrase resistance testing. For additional information, see Early (Acute and Recent) HIV Infection.
- Raltegravir, atazanavir/ritonavir (ATV/r), DRV/r, efavirenz, rilpivirine (RPV), and the NRTI abacavir 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 and RPV with antacids or divalent cation–containing vitamins, avoiding proton pump inhibitors and spacing administration of H2 blockers with ATV/r and RPV). See Appendix B: 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. When the decision is made to continue one of these regimens, more frequent viral load monitoring (i.e., every 1 to 2 months) should be performed.
- 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 When Antiretroviral Therapy Has Never Been Received and Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs During Pregnancy and When 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 the Use of Antiretroviral Drugs During Pregnancy: Overview, Table 6. What to Start: Initial Antiretroviral Regimens During Pregnancy When Antiretroviral Therapy Has Never Been Received, Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs During Pregnancy and When Trying to Conceive, and Appendix B: 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 Infants With *In Utero*, Intrapartum, or Breastfeeding Exposure to 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 24 months (26% efficacy).

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
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, $P = 0.11$).
PHPT-1; Thailand;[13] Formula feeding	4 ZDV regimens with different durations of AP	Long (from 28 weeks) or short (from 36 weeks)	Long (6 weeks) or short (3 days); infant only	Perinatal transmission rate was 10.5% in the short-short arm. This

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
	and infant PP administration; no placebo	Oral IP		arm was stopped at interim analysis. Perinatal transmission at 6 months was 6.5% in long-long arm vs. 4.7% in long-short arm and 8.6% in short-long arm (no statistical difference). *In utero* transmission was significantly higher with short vs. long maternal therapy regimens (5.1% vs. 1.6%).
PACTG 316 Trial; Bahamas, Belgium, Brazil, France, Germany, Italy, Spain, Sweden, Switzerland, United Kingdom, United States;21 Formula feeding	SD NVP vs. placebo among women already receiving ZDV alone (23%) or ZDV plus other ARV drugs (77% combination therapy)	Nonstudy ARV regimen Oral IP • Placebo vs. SD NVP plus IV ZDV	Placebo vs. SD NVP within 72 hours of birth plus nonstudy ARV drugs (ZDV); infant only	77% of women received dual- or triple-combination ARV regimens during pregnancy. Trial stopped early because of very low perinatal transmission in both arms: 1.4% in SD NVP arm vs. 1.6% in placebo arm (53% of perinatal transmission was *in utero*).
PHPT-2; Thailand;[40] Formula feeding	ZDV alone vs. ZDV plus maternal and infant SD NVP vs. ZDV plus maternal SD NVP	ZDV from 28 weeks Oral IP • ZDV alone, *or* • ZDV plus SD NVP	ZDV for 1 week with or without SD NVP; infant only	ZDV-alone arm was stopped because the rate of perinatal transmission was higher in this arm than in the ZDV/NVP arm (6.3% vs. 1.1%, respectively). In arms in which the mother received SD NVP, the perinatal transmission rate did not differ significantly whether the infant received SD NVP or not (2.0% vs. 2.8%, respectively).

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
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 HIV at birth were 6.5% and 16.9%, respectively.

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
Post-Exposure Infant Prophylaxis; South Africa;[9] Breastfeeding and formula feeding	Neonatal SD NVP vs. ZDV for 6 weeks	No AP or IP ARV drugs	SD NVP vs. ZDV for 6 weeks	For formula-fed infants only, perinatal transmission at 6 weeks was 14.3% in SD NVP arm vs. 14.1% in ZDV arm (not significant, *P* = 0.30). For breastfed infants only, perinatal transmission was 12.2% in SD NVP arm vs. 19.6% in ZDV arm (*P* = 0.03).
Mashi; Botswana;[41,42] Breastfeeding and formula feeding	Initial • Short-course ZDV with/without maternal and infant SD NVP and with/without breastfeeding Revised • Short-course ZDV plus infant SD NVP with/without maternal SD NVP and with/without breastfeeding; women with CD4 counts <200 cells/mm^3 received combination therapy.	First Randomization • ZDV from 34 weeks Oral IP • ZDV plus either SD NVP or placebo	Second Randomization • Breastfeeding plus ZDV (infant) 6 months plus SD NVP; infant only, vs. • Formula feeding plus ZDV (infant) 4 weeks plus SD NVP; infant only	Initial Design • In formula-feeding arm, perinatal transmission at 1 month was 2.4% in maternal and infant SD NVP arm vs. 8.3% in placebo arm (*P* = 0.05). • In breastfeeding plus infant ZDV arm, perinatal transmission at 1 month was 8.4% in SD NVP arm vs. 4.1% in placebo arm (difference not statistically significant). Revised Design • Perinatal transmission at 1 month was 4.3% in maternal plus infant SD NVP arm vs. 3.7% in maternal placebo plus infant SD NVP arm (no significant difference; no interaction with mode of infant feeding). Perinatal transmission at 7 months was 9.1% in

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
				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. 2 extended infant regimens (NVP or NVP/ZDV) for 14 weeks	No AP ARV drugs Oral IP • SD NVP (if mother presents in time)	Infant SD NVP plus ZDV for 1 week (control) vs. Control plus NVP for 14 weeks vs.	Postnatal Infection in Infants Without HIV at Birth • Perinatal transmission at 6 weeks was 5.1% in control arm vs. 1.7% in extended NVP arm (67% efficacy) and 1.6% in

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
			Control plus NVP/ZDV for 14 weeks	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

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	Arm 2 (P = 0.009 vs. control), and 1.7% in infant NVP Arm 3 (P < 0.001 vs. control). • Perinatal transmission at 48 weeks was 7.0% in control Arm 1, 4.0% in maternal triple-drug prophylaxis Arm 2 (P = 0.0273 vs. control), and 4% in infant NVP Arm 3 (P =0.0027 vs. control). No significant difference between maternal triple-drug prophylaxis (Arm 2) and infant NVP (Arm 3) (P = 0.12 at 28 weeks and P = 0.426 at 48 weeks).
HPTN 046; South Africa, Tanzania, Uganda, Zimbabwe;[38,44] Breastfeeding	Postpartum prophylaxis to prevent breast milk transmission of HIV with 6 weeks of infant NVP vs. 6 months of infant NVP	AP drugs allowed if required for maternal health	All infants received daily NVP from birth through age 6 weeks. Arm 1 • Daily infant NVP from 6 weeks through 6 months Arm 2 • Daily infant placebo from 6 weeks through 6 months	In infants without HIV at age 6 weeks, the 6-month infant HIV infection rate was 1.1% (0.3% to 1.8%) in the extended NVP arm vs. 2.4% (1.3% to 3.6%) in the placebo arm (P = 0.048). 18-month postnatal infection rates were 2.2% (1.1% to 3.3%) in the extended NVP arm vs. 3.1% (1.9% to 4.4%) in the placebo arm (P = 0.28). HIV infection and mortality rates did not differ between arms at any age through 18 months. At infant randomization at age 6 weeks, 29% of

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'	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
		gestation and 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;

Supplemental Table 1. Results of Major Studies on Antiretroviral Interventions to Prevent Perinatal HIV Transmission

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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