Teratogenicity

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Panel's Recommendations
• All cases of antiretroviral (ARV) drug exposure during pregnancy should be reported to the Antiretroviral Pregnancy Registry (AIII). • Based on multiple studies indicating no difference in rates of total birth defects for first-trimester exposure compared with later ARV drug exposures, people should be counseled that ARV drugs during pregnancy generally do not increase the risk of birth defects (BIII). Providers should be aware that data on the risks of birth defects for many ARV drugs are limited and evolving (see Appendix B: Supplement: Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy). • All pregnant people with HIV should initiate antiretroviral therapy (ART) as early in pregnancy as possible (AI). Pregnant people with HIV should not delay initiating ART due to concerns about teratogenicity with first-trimester exposure (AIII). • The Panel on Treatment of HIV During Pregnancy and Prevention of Perinatal Transmission emphasizes the importance of counseling and informed decision-making regarding all ARV regimens for people with HIV (AIII). For additional information, see Appendix C: Antiretroviral Counseling Guide for Health Care Providers. • Clinicians should discuss future reproductive plans and timing, as well as the risks and benefits of conceiving on specific ARV medications, and the use of appropriate contraceptive options to prevent unplanned pregnancies (AIII). See Prepregnancy Counseling and Care for Persons of Childbearing Age with HIV, Introduction to the Selection of Antiretroviral Drugs In Pregnancy, People with HIV Who are Trying to Conceive, and Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs in Pregnant People and Nonpregnant People Who Are Trying to Conceive.
Rating of Recommendations: A = Strong; B = Moderate; C = Optional *Rating of Evidence: I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

Antiretroviral Pregnancy Registry Reporting

Health care providers who are caring for pregnant people with HIV are advised strongly to report instances of prenatal exposure to antiretroviral (ARV) drugs (either single-drug exposure or exposure to a combination of ARV drugs) to the Antiretroviral Pregnancy Registry as early in pregnancy as possible. The purpose of the Antiretroviral Pregnancy Registry is to detect any major teratogenic effect involving any of the registry drugs to which pregnant people are exposed. Registry data are used to supplement animal toxicology studies and assist clinicians in weighing the potential risks and benefits of treatment for individual patients. The Antiretroviral Pregnancy Registry is a collaborative project of pharmaceutical manufacturers with an advisory committee that includes a teratologist; an infectious disease specialist; an epidemiologist; a biostatistician; and a group of obstetric, maternal–fetal medicine, and pediatric providers. This prospective registry does not use patient names, and registry staff obtain birth outcome follow-up information from the reporting health care provider.

Referrals should be directed to—

Antiretroviral Pregnancy Registry
Research Park
301 Government Center Drive
Wilmington, NC 28403
Telephone: 1-800-258-4263
Fax: 1-800-800-1052
Email: SM_APR@APRegistry.com

Antiretroviral Drugs and Birth Defects

The potential harm to the fetus from birthing parent's ingestion of a specific drug depends not only on the drug itself, but also on the dose ingested; the gestational age of the fetus at exposure; the duration of exposure; interactions with other agents to which the fetus is exposed; and, to an unknown extent, the genetic makeup of the birthing parent and fetus. Information regarding the safety of using certain drugs during pregnancy is derived from multiple sources, including animal reproductive/developmental toxicity data, anecdotal experience, registry data, randomized clinical trials, and observational studies.

Drug choice should be individualized and discussed with people who are pregnant or are trying to conceive before treatment begins. Clinicians also must consider available data from preclinical and clinical testing of the individual drugs. Preclinical data include results of *in vitro* and animal *in vivo* screening tests for carcinogenicity, clastogenicity/mutagenicity, and reproductive and teratogenic effects. However, the predictive value of such tests for adverse effects in humans is unknown. When considering whether a pregnant person should continue an effective antiretroviral regimen when they present in early pregnancy, the potential risk of viral rebound with switching regimens must be considered, as well as the specific or unknown risks for birth defects of the current drug regimen and stage of gestation.[1] For additional information, see People with HIV Who Are Taking Antiretroviral Therapy When they Become Pregnant.

Data continue to be collected on the placental passage, pharmacokinetics, and safety of U.S. Food and Drug Administration (FDA)–approved ARV drugs administered during pregnancy, in addition to data on the long-term safety in infants who were exposed to these drugs *in utero*. However, the data remain somewhat limited, especially for newer drugs (see Appendix B: Supplement: Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy). The Antiretroviral Pregnancy Registry has predefined analytical methods and criteria for recognizing a potential signal. When analyzing registry data, data on birth outcomes from 200 infants who were exposed to an ARV drug during the first trimester are viewed as sufficient to detect a doubling of the risk of overall birth defects associated with that drug compared to the general population. A cohort of 1,000 is sufficient to detect a 1.5-fold increase in the risk of overall birth defects. The general U.S. population birth defect prevalence is 2.72% as determined by the Metropolitan Atlanta Congenital Defect Program, the Centers for Disease Control and Prevention's population-based surveillance system for birth defects.[2] Table 8 below summarizes Antiretroviral Pregnancy Registry risk assessment for individual ARV drugs and points out that risk assessment is not available when pregnancy exposures are not reported. Detailed information about Antiretroviral Pregnancy Registry data for individual drugs is available in Appendix B: Supplement: Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy.

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

ARV Drug	Level of Risk Assessment	Risk Assessment Outcome
BIC, COBI, DRV, d4T, ddI, DTG, EVG, IDV, RAL, RPV, and TAF	Sufficient numbers of first-trimester exposures have been monitored to detect at least a 2-fold increase in the risk of overall birth defects.	No such increases detected.
3TC, ABC, ATV, EFV, FTC, LPV/r, NFV, NVP, RTV, TDF, and ZDV	Sufficient numbers of first-trimester exposures have been monitored to detect at least a 1.5-fold increase in the risk of overall birth defects and a twofold increase in the risk of birth defects in cardiovascular and genitourinary systems.	No such increases detected.
CAB, DOR, ETR, FTR, LEN, and T-20	Insufficient numbers of exposures reported to assess the level of risk.	Not available.

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

For individual birth defects, the power of the Antiretroviral Pregnancy Registry to find an increased risk will vary depending upon the frequency of the defect in the population. However, data from a larger number of infants are required to detect an increased risk of specific birth defects with lower frequencies of occurrence, with the required number of infants who were exposed to an ARV drug increasing as the frequency of the defect in an unexposed population decreases. Thus, large numbers of cases are required to detect increased risk of rare but serious defects, underscoring the need for providers to report all ARV exposures prospectively to the Antiretroviral Pregnancy Registry.[3]

It is important to consider potential confounding factors in studies of ARV drugs and birth defects. Several factors that are associated with HIV also may increase the risk of birth defects, such as exposure to folate antagonists (e.g., trimethoprim-sulfamethoxazole),[4] nutritional and folate status,[5] and tobacco and alcohol use.[6] Clinicians also should be aware of indication bias, which can occur when a patient's reason for taking a particular ARV drug is associated with an increased risk of birth defects, such as older age or more advanced disease. Additionally, clinicians should consider all medications used in early pregnancy. According to a 2018 study involving 9,546 pregnant people, 97.1% reported taking at least one medication during their pregnancy.[7] In the last decade, 89.3% of the 290 therapeutics submitted to the FDA between 2010 and 2019 lacked human data related to pregnancy.[8] Thus, it is important to know of any and all medication exposures in pregnancy when evaluating risk of birth defects in relation to ARV drugs.

Several studies of birth defects in fetuses and infants of women who received various ARV regimens during observational studies found no difference in rates of total birth defects between first-trimester drug exposures and later exposures.[9-13] The Antiretroviral Pregnancy Registry conducts a primary analysis of prospective cases of ARV drug exposure during pregnancy provided by health care providers. In the current analysis through January 31, 2023, the prevalence of birth defects was 3.0 per 100 live births among women with a first-trimester exposure to any ARV drug (348 of 11,767 exposures; 95% confidence interval [CI], 2.7–3.3). The prevalence of defects is not significantly different from that seen in women with an initial exposure during the second and/or third trimester (2.8 per 100 live births; prevalence ratio 1.04; 95% CI, 0.89–1.21).[2] Although these

data are reassuring, an increased risk of specific abnormalities—particularly rare abnormalities—would not necessarily be detectable when looking only at the total number of birth defects. Furthermore, risk may be underestimated when defects are ascertained only after live births because this does not include more severe defects that result in stillbirths and terminations. Another limitation is that an increased risk that is associated with a specific ARV drug may be obscured when the analysis unit combines all ARV drugs together.

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

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