Teratogenicity

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

Panel's Recommendations
• All cases of antiretroviral (ARV) drug exposure during pregnancy should be reported to the Antiretroviral Pregnancy Registry **(AIII)**. • Based on multiple studies indicating no difference in rates of total birth defects for first-trimester exposure compared with later ARV drug exposures, women can be counseled that ARV drugs during pregnancy generally do not increase the risk of birth defects **(BIII)**; a possible exception is a very small potentially increased risk of neural tube defects (NTDs) with dolutegravir (DTG) use during the periconception period. Providers should be aware that data on the risks of birth defects for many ARV drugs are limited and evolving. • Currently, in the United States there are not enough data to determine the risk of NTDs with preconception use of many of the *Preferred* and *Alternative* regimens, including DTG. • DTG exposure around the time of conception has been associated with a small but significant increase in the prevalence of infant NTDs in Botswana, where food is not routinely fortified with folate. Although this prevalence of NTDs with periconception DTG (0.19%) was higher than the prevalence for NTDs in infants born to women who were receiving efavirenz (0.07%) and women without HIV (0.07%), the risk was not significantly increased compared to women with HIV receiving any non-DTG ARV regimen at conception (0.11%, risk difference [0.09% difference; 95% CI 0.03%, 0.30%]). • Based on the available evidence, the Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission (the Panel) recommends DTG as a Preferred drug for pregnant women, irrespective of trimester **(AII)**, and for women who are trying to conceive **(AIII)**. • The Panel emphasizes the importance of counseling and informed decision-making regarding all ARV regimens for people with HIV (AIII). For additional information, see Appendix C: Antiretroviral Counseling Guide for Health Care Providers: Pregnant Women and Women who are Trying to Conceive. • Clinicians should discuss future reproductive plans and timing, as well as the risks and benefits of conceiving on specific ARV medications and the use of appropriate contraceptive options to prevent unintended pregnancy **(AIII)**. • Folic acid is known to prevent NTDs in the general population. All pregnant women and women who might conceive should take at least 400 mcg of folic acid daily **(AI)**. For additional information, see Recommendations for Use of Antiretroviral Drugs During Pregnancy, Preconception Counseling and Care for Women of Childbearing Age with HIV, Pregnant Women with HIV Who Are Currently Receiving Antiretroviral Therapy.
Rating of Recommendations: A = Strong; B = Moderate; C = Optional **Rating of Evidence:** I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion

Antiretroviral Pregnancy Registry Reporting

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

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

Antiretroviral Drugs and Birth Defects

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

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

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

It is important to consider potential confounding factors in studies of ARV drugs and birth defects. Several factors that are associated with HIV also may increase the risk of birth defects, such as exposure to folate antagonists (e.g., trimethoprim-sulfamethoxazole),[3] nutritional and folate status,[4] and tobacco and alcohol use.[5] Clinicians also should be aware of indication bias, which can occur when a patient's reason for taking a particular ARV drug is associated with an increased risk of birth defects, such as older age or more advanced disease.

Several studies of birth defects in fetuses and infants of women who received various ARV regimens during observational studies found no difference in rates of total birth defects between first-trimester drug exposures and later exposures.[6–10] The APR conducts a primary analysis of prospective cases of ARV drug exposure during pregnancy provided by health care providers. In this analysis, the prevalence of birth defects was 2.8 per 100 live births among women with a first-trimester exposure to any ARV drug (271 of 9,854 exposures; 95% CI, 2.4–3.1). The prevalence of defects is not significantly different from that seen in women with an initial exposure during the second and/or third trimester (2.8 per 100 live births; prevalence ratio 0.99, 95%

CI, 0.83–1.18).[1] Although these studies are reassuring, an increased risk of specific abnormalities, particularly rare abnormalities, would not necessarily be detectable when looking only at the total number of birth defects. Furthermore, risk may be underestimated when defects are ascertained only after live births, because this does not include more severe defects that result in stillbirths and terminations. Another limitation is that an increased risk that is associated with a specific ARV drug may be obscured when the analysis unit combines all ARV drugs together.

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

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

In May 2018, an unplanned interim evaluation of a National Institutes of Health–funded observational surveillance study of birth outcomes among pregnant women on antiretroviral therapy (ART) in Botswana revealed four cases of NTDs among infants born to 426 women (0.94%) who became pregnant while receiving a DTG-based regimen.[12] These data were updated in a planned analysis in March 2019 and again in April 2020. In the most recent analysis of the Tsepamo study in Botswana, seven NTDs were identified (0.19%) among 3,591 deliveries to women who were taking DTG around the time of conception; the defects included three instances of myelomeningocele, one of anencephaly, two of encephalocele, and one of iniencephaly. In comparison, 21 NTDs were found among 19,361 deliveries (0.11%) in which the mother was taking any ART that did not include DTG at conception, eight NTDs were found among 10,958 deliveries (0.07%) in which the mother was taking efavirenz (EFV) at conception, two NTDs were found among 4,581 deliveries (0.04%) in which the mother started treatment with DTG during pregnancy, and 87 NTDs were found among 119,630 deliveries (0.07%) to mothers without HIV.[13] The risk of NTDs in infants who were exposed to DTG around the time of conception (0.19%) remains significantly higher than among infants exposed to EFV (0.07%) and infants born to women without HIV (0.07%) but is no longer significantly elevated compared to infants exposed to any non-DTG ARV (0.11%, risk difference 0.09%, 95% CI -0.03%, 0.30%) around conception. Although some increased risk of NTDs with DTG exposure in early pregnancy in the setting without folate food supplementation continues to be noted, the risk is lower than originally observed.

Although there are limited data on the association between NTDs and DTG exposure, two studies that included an internal comparator group and assessments of NTDs in stillbirths and terminations have evaluated NTDs in infants who were exposed to DTG at conception in addition to the Botswana study. The first was a prospective study by the Ministry of Health and the Centers for Disease Control and Prevention at 22 additional sites in Botswana that were not included in the Tsepamo study. This study identified one NTD among infants born to 152 women (0.66%) who were receiving DTG at conception, compared to no NTDs among infants born to 381 women who were receiving other ARV drugs at conception and two NTDs among infants born to 2,328 women who did not have HIV (0.09%).[14] The second study included prospective data from the APR, and it is worth noting that 75% of the data in the registry comes from North America, Europe, and Latin America, where most countries require folate fortification for food. The study found one case of an NTD among 382 live births (0.26%) of infants with periconception DTG exposure and no NTDs among 298 live births of infants with periconception elvitegravir (EVG) exposure and 327 live births of infants with periconception raltegravir (RAL) exposure.[1] An additional retrospective study that did not include evaluation of defects in stillbirths or terminations evaluated infants born to women with periconception ARV drug exposure in a national cohort in Brazil. No NTDs were observed among 384 pregnancies in which infants were exposed to DTG (95% CI, 0.0–0.0099) or among 1,109 pregnancies in which infants were exposed to EFV or RAL (95% CI, 0.0–0.003).[15] Unlike Brazil and the United States, Botswana does not have mandated food folate fortification, which can

decrease NTD prevalence by half. More data are needed to delineate the risks of NTDs among infants born to women on integrase inhibitors periconceptionally in other geographical regions and countries with mandated food folate fortification.

No mechanism has been identified to explain the observed association between DTG exposure and NTDs, although several studies have evaluated the role of folate. A substudy of the ADVANCE trial evaluated serum folate levels among women by randomized arm and found that folate deficiency occurred less often in women who were receiving DTG, with 13.7% of women in the DTG plus tenofovir disoproxil fumarate (TDF) plus emtricitabine (FTC) arm and 5.4% of women in the DTG plus tenofovir alafenamide (TAF) plus FTC arm experiencing folate deficiency compared with 30% of those who received EFV ($P < 0.001$).[16] Studies that have evaluated folate receptor antagonism by DTG in animal models and cell models have had conflicting results, and the clinical implications of these results are unclear.[17,18] Additional studies are needed to clarify the role of folate and to explore other potential mechanisms.

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

Data on Other Integrase Strand Transfer Inhibitors

Limited data are available on the association between other integrase strand transfer inhibitors and birth defects. A retrospective case series evaluated data from nine institutions on 140 pregnancies in which the woman received EVG during pregnancy, including 82 women who received the drug before conception and during the first trimester.[19] Two defects were noted: one case of hydronephrosis in which exposure began before conception, and one case of an encephalocele in which a woman with periconceptional exposure to TDF plus FTC plus darunavir/ritonavir (DRV/r) was switched to atazanavir (ATV) plus EVG/cobicistat/FTC/TDF at 9 weeks because of drug side effects. Among 33 women who were exposed to EVG during the first trimester in the United Kingdom and Ireland, no defects were noted in 31 liveborn infants.[20] In the APR, defects were reported in 11 of 323 infants (3.4%; 95% CI, 1.7% to 6.0%) born after first-trimester exposure to EVG; this does not represent an increased risk compared to the overall rate of defects in the Registry.[1] A review of the Gilead safety database, which included an earlier data set from the APR, reported 155 prospective periconception exposures to EVG with no NTDs.[21] Review of a surveillance database in Canada found no NTDs among 28 infants with first-trimester exposures.[10]

Surveillance data from the United Kingdom and Ireland included 882 live births of infants with exposure to RAL, and birth defects were reported in 23 infants, a rate of 2.59% (95% CI, 1.65% to 3.86%); this rate is similar to that in the general population. No NTDs were reported.[20] Among the 222 infants with periconception exposure to RAL, five defects were noted, including two heart defects, two limb defects, and one unspecified defect. In the APR, birth defects were reported in 13 of 422 infants (3.1%; 95% CI, 1.7% to 5.2%) with first-trimester exposure to RAL. This incidence is similar to the incidence seen in the overall population reported to the APR. A review performed by Merck researchers that included data from the company database, the previously noted APR data, and data from the United Kingdom, Ireland, and French pregnancy cohorts reported

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

The Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission continues to review and update its recommendations regarding the use of ARV drugs during pregnancy and at the time of conception (see Recommendations for Use of Antiretroviral Drugs During Pregnancy, Preconception Counseling and Care for Women of Childbearing Age with HIV, and the Adult and Adolescent Antiretroviral Guidelines). The benefits and risks of ARV drugs, including the potential risk of NTDs, the benefits and risks of changing antiretroviral therapy should be discussed with women who need to initiate ART during the first trimester or who are planning to become pregnant or are currently taking ART (see Appendix C: Antiretroviral Counseling Guide for Health Care Providers: Pregnant Women and Women who are Trying to Conceive). For additional guidance, please contact the National Perinatal HIV Hotline (1-888-448-8765).

Specific Drugs

Efavirenz

EFV use during pregnancy has received increased scrutiny because of the results of a small study in nonhuman primates. Significant malformations were observed in three of 20 infant cynomolgus monkeys that received EFV from gestational days 20 to 150 at a dose similar to human therapeutic exposures.[23] The malformations included anencephaly and unilateral anophthalmia in one monkey, microphthalmia in another, and cleft palate in the third.

Increased scrutiny of outcomes after EFV exposure has provided reassuring data. Sufficient numbers of first-trimester exposures to EFV have been monitored in the APR to rule out at least a 1.5-fold increase in the risk of overall birth defects and a twofold increase in risk of birth defects in the cardiovascular and genitourinary systems. Twenty-seven of 1,142 infants (2.4%) with first-trimester exposures to EFV were found to have birth defects, including a single case of myelomeningocele and one case of anophthalmia and amniotic bands.[1] A meta-analysis that included data from 23 studies reporting on 2,026 first-trimester exposures to ARV drugs found no increased risk of overall birth defects for infants born to women who were on EFV during the first trimester compared with those who were on other ARV drugs during the first trimester (relative risk [RR] 0.78; 95% CI, 0.56–1.08). One NTD was observed, giving an incidence of 0.05% (95% CI, <0.01 to 0.28).[24] The number of reported first-trimester EFV exposures in this meta-analysis is sufficient to rule out a twofold increase in low-incidence birth defects, such as NTDs. Incidence of NTDs in the general U.S. population is 0.02% to 0.2%.[2,24] A recent report from a South African pregnancy exposure registry of births at a single hospital found no increase in risk of congenital malformations with EFV exposure at conception (1/297, 0.3%) compared with infants born to women without HIV (29/7,532, 0.4%).[25]

The Tsepamo study discussed above found eight NTDs among 10,958 live births and stillbirths (0.07%) to women who were on EFV at conception, which was identical to the prevalence of NTDs among infants born to women without HIV.[26] The study also found no increased risk of total major abnormalities identified on infant surface exam among women who were taking EFV around the time of conception compared with women without HIV (0.68% vs. 0.59%).[26] In addition, a birth defect surveillance program in Uganda that used methods that were similar to those used in the Tsepamo study reported an NTD prevalence of 0.059% (95% CI, 0.001% to 0.118%) among infants born to women with HIV, 80% of whom were on EFV, and an NTD prevalence of 0.092% (95% CI, 0.068% to 0.116%) among infants born to women without HIV.[27] Thus, the findings in monkeys have not been confirmed by human data, underscoring the need for well-designed studies to rapidly provide data on the safety of new drugs for use in pregnancy.

A recent report from the Surveillance Monitoring for ART Toxicities (SMARTT) study of the Pediatric HIV/AIDS Cohort Study (PHACS) network detected an increased rate of microcephaly in HIV-exposed but uninfected children with *in utero* EFV exposure. The relative risk of microcephaly in infants with *in utero*

EFV exposure was 2.56 (95% CI, 1.22–5.37). In this study, microcephaly was defined as a z-score of less than -2 between 6 and 36 months of age or head size below the second percentile after 36 months.[28] Only 4.7% of children had been exposed to EFV *in utero*. The relative risk of microcephaly was higher among children who had been exposed to EFV plus zidovudine (ZDV) and lamivudine (3TC) than among those who had been exposed to EFV plus TDF and FTC. Children with microcephaly had lower scores on neurodevelopmental assessments at ages 1 year and 5 years and a higher rate of neurodevelopmental impairment than those without microcephaly. Additional evaluation of the association between microcephaly and *in utero* EFV exposure is needed.

The EFV package insert advises women to avoid becoming pregnant while taking EFV and advises health care providers to avoid administering EFV during the first trimester of pregnancy, because fetal harm may occur. However, with the data from Botswana on nearly 11,000 periconception exposures, we can now rule out a threefold or more increase in the risk of NTDs in infants who were exposed to EFV. As a result, the Perinatal Guidelines do not restrict the use of EFV in pregnancy or in women who are planning to become pregnant; this is consistent with the British HIV Association and World Health Organization guidelines for use of ARV drugs in pregnancy, both of which note that EFV can be used throughout pregnancy.[29] Importantly, women who become pregnant on EFV-containing regimens that are suppressive and tolerated should continue using those regimens.

Tenofovir Disoproxil Fumarate

TDF has not demonstrated teratogenicity in rodents or monkeys. Data from the APR showed that 91 of 3,851 (2.4%) infants born to women with first-trimester TDF exposure had birth defects, which is similar to the incidence in the general population.[1] A more recent meta-analysis of TDF use among women with HIV found no increase in the risk of congenital anomalies associated with the use of TDF (RR 1.03; 95% CI, 0.83–1.28).[30]

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

Zidovudine

In a study from France that included 13,124 live births that occurred between 1994 and 2010, first-trimester ARV drug exposure was found in 5,388 infants (42%). The authors reported a significant adjusted association between first-trimester ZDV exposure and congenital heart defects, primarily ventricular (58%) and atrial (18%) septal defects (adjusted odds ratio [aOR] 2.2; 95% CI, 1.3–3.7). Because fetal ultrasounds were conducted on all infants who were exposed to HIV, and because spontaneous closure of ventricular septal defects after birth is common, the clinical significance of the cardiac findings is uncertain.[31] An analysis of 16,304 prospectively reported pregnancies compared the risk of ventricular septal defects and congenital heart defects in infants with prenatal exposure to ZDV-containing regimens and infants with prenatal exposure to ART regimens that did not contain ZDV. In contrast to the French study, this analysis found that the risk of these defects was similar between the two groups.[32] A recent study that combined a meta-analysis and data from a Medicaid database of ART prescriptions and infant outcomes did not detect a significant increase in overall defects or heart defects among infants who had first-trimester ZDV exposure compared with infants who had exposure to other ART regimens during the first trimester (odds ratio [OR] for overall defects 1.11; 95% CI, 0.80–1.55; OR for cardiac defects 1.30; 95% CI, 0.63–2.71).[33] Additionally, one study investigated echocardiographic parameters of left ventricular function and structure in 417 infants. Some of the infants had been exposed to HIV and ARV drugs but had not contracted HIV, while others had not been exposed to either HIV or ARV drugs. When these children were tested at ages 2 to 7 years, no clinically significant differences in left ventricular function and structure were found between the exposed and unexposed groups.[5]

Atazanavir

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

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

Rilpivirine

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

Other Antiretroviral Drugs

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

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

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