AIDSinfo

Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States

Teratogenicity (Last updated December 7, 2018; last reviewed December 7, 2018)

Panel's Recommendations

- All cases of antiretroviral (ARV) drug exposure during pregnancy should be reported to the Antiretroviral Pregnancy Registry **(AIII)**.

- Based on the preponderance of studies indicating no difference in rates of birth defects for first-trimester exposure compared with later ARV drug exposures, women can be counseled that ARV therapy during pregnancy generally does not increase the risk of birth defects **(BIII)**, with the possible exception of dolutegravir.

Interim Panel Recommendations Regarding the Use of Dolutegravir at the Time of Conception and During Pregnancy:[a]

- Dolutegravir **is not recommended for use in nonpregnant women who are trying to conceive or during the first trimester of pregnancy**,[b,c] due to concerns about a possible increased risk of neural tube defects (NTDs) **(AIII)**.

- Clinicians should discuss the possible increased risk of NTDs with women of childbearing potential who are currently receiving dolutegravir as part of their ART or who wish to be started on dolutegravir **(AIII)**.

- A pregnancy test should be performed prior to the initiation of dolutegravir **(AIII)**.

- Women who want to become pregnant or who cannot consistently use effective contraception should not initiate a dolutegravir-based regimen **(AIII)**.

- For pregnant women who are receiving dolutegravir and who present to care during the first trimester,[b,c] provide counseling about the risks and benefits of continuing dolutegravir or switching to another ARV regimen **(AIII)**. The following considerations should be addressed:

    - NTDs may have already occurred;

    - Depending on the current gestational age, the additional risk of NTDs developing during the remaining time in first trimester may be small;

    - There is a background risk of NTDs regardless of antiretroviral treatment (ART) regimen or HIV status (this risk ranges from 0.05% to 0.1% for women without HIV, and women with HIV who are receiving ART that does not include dolutegravir); *and*

    - Changes in ART, even in the first trimester, are often associated with viral rebound that may increase the risk of perinatal HIV transmission.

- Dolutegravir is a preferred integrase strand transfer inhibitor for use in pregnant women after the first trimester;[b] this designation is based on available PK, safety, and efficacy data **(AII)**.

- When dolutegravir use is continued after delivery, clinicians should recommend the use of postpartum contraception and discuss contraceptive options with patients **(AIII)**.

- For additional information, see Interim Recommendations about the Use of Dolutegravir in Pregnancy in Recommendations for the Use of Antiretroviral Drugs During Pregnancy and the Adult and Adolescent Antiretroviral Guidelines.

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

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

[a] These are intended to be conservative, interim recommendations and will be revised, if indicated, as additional data become available in 2019.

[b] The first trimester is less than 14 weeks (up to 13 6/7 weeks) gestational age by last menstrual period. The term "12 weeks post-conception," used in the Adult and Adolescent ARV Guidelines, is consistent with the first trimester.

[c] Although dolutegravir is not Food and Drug Administration-approved for use in the first trimester, some Perinatal Panel members would consider using dolutegravir at 12 weeks gestational age by last menstrual period on an individual patient basis.

First-Trimester Exposure and Birth Defects

In general, reports of birth defects in fetuses and infants of women enrolled in observational studies who receive antiretroviral (ARV) regimens during pregnancy are reassuring and find no difference in rates of birth defects between first-trimester drug exposures and later exposures.[1-4] The Antiretroviral Pregnancy Registry conducted 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 2.7 per 100 live births among women with a first-trimester exposure to any ARV drug (244 of 8,909 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).[5]

Use of Dolutegravir at the Time of Conception and 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 neural tube defects (NTDs) among infants born to 426 women (0.94%) who became pregnant while receiving a dolutegravir-based regimen.[6] These data were updated in a planned analysis in July 2018. No new NTDs were observed in infants born to women who received preconception dolutegravir, leading to an updated prevalence of dolutegravir exposure at conception (4/596 women [0.67%]) and a revised risk of NTDs (95% CI, 0.26% to 1.7%).[7] This risk remains higher than the risk observed among women receiving preconception efavirenz-based ART (0.05%) or any preconception ART regimen that does not contain dolutegravir (0.12%) and among women without HIV (0.09%). Importantly, in an earlier publication about outcomes among women from Botswana who started dolutegravir-based ART or efavirenz-based ART during pregnancy, investigators reported that the rate of birth defects was 0 among infants born to 280 women who started dolutegravir during the first trimester. All the women initiated the regimen at >4 weeks gestational age, and most of them initiated the regimen at >6 weeks gestational age. In addition, there were 0 birth defects among infants born to the 729 women who started dolutegravir during the second or third trimesters.[8] As of the July 2018 update, one NTD was observed among infants born to 3,104 women who started dolutegravir at any time during pregnancy (0.03%); in this case, dolutegravir was initiated at 8 weeks gestational age. **Note:** The study is ongoing, and it is anticipated that data from this study and other investigations will provide more information about the safety of *in utero* exposure to dolutegravir in 2019.

The neural tube closes by approximately 4 weeks post-conception, or approximately 6 weeks after the last menstrual period in women with regular menses. The early data from Botswana suggest that two of the four observed defects may be defects that can occur during the first trimester, after the neural tube has closed (post-neurulation events). If a causal relationship exists between the use of dolutegravir and NTDs, it remains unknown

- What the mechanism of this effect may be,

- Whether folic acid is a mediating factor (and thus whether risk would be reduced by folic acid supplementation), *and*

- Whether this risk may exist for other integrase inhibitors.

The Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission (the Panel) encourages all providers to prospectively report the pregnancy exposures of individuals with HIV who are receiving ART to the Antiretroviral Pregnancy Registry.

The Panel has developed interim recommendations regarding the use of dolutegravir during pregnancy and at the time of conception in coordination with the Panel on Antiretroviral Guidelines for Adults and Adolescents (see Recommendations for the Use of Antiretroviral Drugs during Pregnancy, Preconception Counseling and Care for Women of Childbearing Age Living with HIV, and the Adult and Adolescent Antiretroviral Guidelines). The Panel conservatively recommends that dolutegravir not be initiated during the first trimester (less than 14 weeks [up to 13 6/7 weeks] gestational age by last menstrual period) as an interim recommendation pending additional data. For additional guidance, please contact the Perinatal HIV Hotline at (888) 448-8765.

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; the interactions with other agents to which the fetus is exposed; and, to an unknown extent, the genetic makeup of 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 must also 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 regarding placental passage, pharmacokinetics, safety in pregnancy, and long-term safety in infants exposed to Food and Drug Administration (FDA)-approved ARV drugs continue to be collected. However, the data remains somewhat limited, especially for newer drugs (see Supplement: Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy). For analysis of 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. The general U.S. population birth defect prevalence is 2.8%.[5] However, data from a larger number of infants is required to detect an increased risk of specific birth defects with lower frequencies of occurrence, with the required number of infants exposed to an ARV drug increasing as the frequency of the defect in an unexposed population decreases.[9]

A population-based prospective cohort study that used data from 214,240 pregnancies in the Quebec Pregnancy Cohort found no increased risk in overall birth defects among 198 infants with first-trimester ARV exposure when compared to the risk of birth defects in the general population (10.3% vs. 8.6%, *P* = 0.41).[10] Of note, the median time to diagnosis of birth defects was similar in both groups (53 days), suggesting that many asymptomatic defects were detected during follow-up. The distribution of defects noted among exposed infants was similar to that in the unexposed population.

Some individual reports have raised concerns regarding specific ARV agents. Most studies that evaluate a possible association between ARV drug exposure and birth defects do not evaluate maternal folate use or levels. Folate antagonists (e.g., trimethoprim-sulfamethoxazole), which have been associated with an increased risk of birth defects with first-trimester use in some, but not all, studies, may be prescribed to women with advanced HIV disease.[11] Therefore, it may be important to consider the role of folate antagonists as well as folic acid supplementation when evaluating any potential association between ARV drugs and birth defects.[12] Maternal tobacco and alcohol use may also serve as confounders.[13]

Specific Drugs

Efavirenz

Efavirenz 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 efavirenz from gestational days 20 to 150 at a dose that produced plasma concentrations comparable to those seen with systemic exposure in humans at therapeutic dose.[14] The malformations included anencephaly and unilateral anophthalmia in one monkey, microphthalmia in another, and cleft palate in the third. In humans, sufficient numbers of first-trimester exposures to efavirenz have been monitored in the Antiretroviral Pregnancy Registry to detect at least a two-fold increase in the risk of overall birth defects; however, no such increase has been detected. Twenty-two infants out of 990 infants (2.2%) with first-trimester exposures to efavirenz were found to have birth defects, including a single case of myelomeningocele and one case of anophthalmia.[5]

Two publications that had overlapping data sets and investigated small numbers of pregnancies exposed to efavirenz have reported higher than background rates of congenital birth defects with first-trimester efavirenz exposure.[2,15] In these studies, there was no pattern of anomalies specific to efavirenz: patent foramen ovale (n = 1), gastroschisis (n = 1), polydactyly (n = 1), spina bifida cystica (n = 1), plagiocephaly (n = 1), Arnold Chiari malformation (n = 1), and talipes (n = 1).

In a report from the French Perinatal Cohort on 5,388 births with first-trimester exposure to ARV drugs, first-trimester efavirenz use was not associated with an increase in defects in the primary analysis using

the European Surveillance of Congenital Abnormalities birth defect classification system.[16] However, in a secondary analysis that used the Metropolitan Atlanta Congenital Defects Program (MACDP) birth defect classification (the system used by the Antiretroviral Pregnancy Registry), an association was found between first-trimester efavirenz exposure and neurologic defects. However, none of the four neurologic defects reported in the analysis were NTDs, and none of the defects had common embryology.[17] Antiretroviral Pregnancy Registry data through January 2018 includes defects in 24 of 1,023 infants with first-trimester exposure to ARV drugs (2.35%; 95% CI, 1.51–3.47) and in three of 194 infants with later exposure (1.5%; 95% CI, 0.3–4.5).[5] A meta-analysis that included data from 23 studies reporting on 2,026 first-trimester exposures found no increased risk of overall birth defects for infants born to women on efavirenz during the first trimester compared with those 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).[18] The number of reported first-trimester efavirenz exposures in this meta-analysis is sufficient to rule out a two-fold increase in low-incidence birth defects, such as NTDs. Incidence of NTDs in the general U.S. population is 0.02% to 0.2%.[9,18]

In prior Perinatal Guidelines, use of efavirenz was not recommended before 8 weeks gestational age because of concerns regarding potential teratogenicity. On the basis of the data summarized above, the current Perinatal Guidelines do not restrict the use of efavirenz before 8 weeks' gestation, consistent with both the British HIV Association and World Health Organization guidelines for use of ARV drugs in pregnancy.[19,20] Importantly, women who become pregnant on efavirenz-containing regimens that are suppressive and tolerated should continue those regimens.

Tenofovir Disoproxil Fumarate

Tenofovir disoproxil fumarate (TDF) has not demonstrated teratogenicity in rodents or monkeys. Data from the Antiretroviral Pregnancy Registry showed that 76 of 3,342 infants born to women with first-trimester TDF exposure had birth defects. That means the birth defect incidence for infants exposed to TDF during the first trimester is 2.3%, similar to the incidence in the general population.[5] A recent comprehensive review of the use of TDF in pregnant women for treatment of HIV or hepatitis B or for pre-exposure prophylaxis found no evidence of an increased risk of pregnancy loss, stillbirth, preterm birth, infants that are small for their gestational age, or infant mortality compared to similar women receiving placebo or other ARV drug regimens.[21] A more recent meta-analysis of TDF use among women with HIV found no increase in congenital anomalies associated with the use of TDF (RR 1.03; 95% CI, 0.83–1.28).[22]

Administration of TDF at high doses to pregnant monkeys, which resulted in drug levels that were 25 times the area under the curve achieved with therapeutic dosing in humans, was associated with maternal toxicity and resulted in lower fetal circulating insulin-like growth factor (IGF)-1, higher IGF binding protein-3 levels, and lower body weights in infant monkeys. A slight reduction in fetal bone porosity was also observed. In human neonates, a study evaluated whole-body dual-energy X-ray absorptiometry (DXA) scans within 4 weeks of birth among 74 infants who were exposed to >8 weeks of TDF *in utero* and 69 infants with no TDF exposures. The adjusted mean whole-body bone mineral content (BMC) was significantly lower in the TDF group by 6.3 g ($P = 0.004$); the whole-body-less-head BMC was also significantly lower in the TDF group (-2.6 g, $P = 0.056$).[23] A subsequent DXA study evaluated infants born to women who were randomized to receive TDF-containing ART, ART that did not contain TDF, or zidovudine plus single-dose nevirapine. Infants in both ART arms had significantly lower whole-body BMC than those in the zidovudine plus nevirapine arm; however, there were no differences in whole-body BMC between the ART arms. No significant differences were seen among the arms when comparing lumbar spine BMC.[24]

A study that evaluated fetal long bone (femur and humerus) growth using serial ultrasounds in women who received different durations of TDF-containing ART during pregnancy (<10 weeks, 10–24 weeks, and ≥25 weeks) found no association between the duration of *in utero* TDF exposure and change in femur and humerus length z-score ($P = 0.51$ and $P = 0.40$, respectively).[25] A follow-up study evaluated linear growth in this same cohort of infants. The study found no association between linear growth during the first year

of life and *in utero* TDF exposure.[26] In a meta-analysis, anthropometric measures at birth and weight for age at 1 year were evaluated for infants who were exposed to TDF-containing regimens and infants who were exposed to regimens that did not contain TDF; no differences in these measures were found between these two groups.[22] One study reported that infants who were exposed to TDF-containing regimens *in utero* had lower scores for length and head circumference at 1 year of age than infants with exposures to other ART regimens.[27] Studies that compared child growth through 2 years of age[23] and 5 years of age[28] found no significant differences in growth between children who were exposed to TDF *in utero* and children who were not exposed to TDF. Taken together, current data do not suggest that exposure to TDF-containing regimens during pregnancy has a significant effect on bone density or growth.

No clinical studies have reported newborn outcomes associated with maternal use of tenofovir alafenamide (TAF).

Other Drugs

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 zidovudine 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.[17] 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 zidovudine-containing regimens and infants with prenatal exposure to non-zidovudine ART regimens. In contrast to the French study, this analysis found that the risk of these defects was similar between the two groups.[29] 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 zidovudine exposure compared to infants with exposure to other ART regimens during the first trimester (OR for overall defects 1.11; 95% CI, 0.80–1.55; odds ratio for cardiac defects 1.30; 95% CI, 0.63–2.71).[30] 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.[13]

In an analysis from the Pediatric HIV/AIDS Cohort Study that included 2,580 live births, first-trimester ARV drug exposure overall was not associated with an increased risk of birth defects.[31] In adjusted analyses, atazanavir was the only individual ARV drug for which first-trimester exposure was associated with birth defects, primarily skin and musculoskeletal defects. However, in the Antiretroviral Pregnancy Registry, there was no increase in birth defects with first-trimester atazanavir exposure among 1,235 births.[5]

In the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposures have been monitored to detect at least a two-fold increase in risk of overall birth defects for darunavir, didanosine, efavirenz, indinavir, raltegravir, rilpivirine, and stavudine; however, no such increases have been detected to date. For abacavir, atazanavir, emtricitabine, lamivudine, lopinavir, nelfinavir, nevirapine, ritonavir, TDF, and zidovudine, sufficient numbers of first-trimester exposures have been monitored to detect at least a 1.5-fold increase in risk of overall birth defects and a two-fold increase in 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 didanosine and nelfinavir is observed when data from the Antiretroviral Pregnancy Registry are compared with the U.S. population-based MACDP surveillance data.[5] The lower bounds of the confidence intervals for didanosine and nelfinavir (2.9% and 2.8%, respectively) are slightly above the higher bound (2.72%) for the MACDP rate, but rates are not elevated compared to the Texas Birth Defect Registry rate of 4.17%, an additional comparator now included in the Antiretroviral Pregnancy Registry. No specific pattern of defects has been detected with the use of either didanosine or

nelfinavir, and the clinical relevance of this statistical finding is unclear. The Antiretroviral Pregnancy Registry will continue to monitor didanosine and nelfinavir 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.

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 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. This registry is an epidemiologic project to collect observational, nonexperimental data regarding ARV 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 Antiretroviral Pregnancy Registry is a collaborative project of pharmaceutical manufacturers with an advisory committee of obstetric and pediatric practitioners. The registry does not use patient names, and registry staff obtain birth outcome follow-up information from the reporting physician.

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

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