



**Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States**

Downloaded from <http://aidsinfo.nih.gov/guidelines> on 12/21/2016

Visit the *AIDSinfo* website to access the most up-to-date guideline.

Register for e-mail notification of guideline updates at <http://aidsinfo.nih.gov/e-news>.

Panel's Recommendations
<ul style="list-style-type: none"><li>All cases of antiretroviral (ARV) drug exposure during pregnancy should be reported to the Antiretroviral Pregnancy Registry (see <a href="http://www.APREgistry.com">http://www.APREgistry.com</a>) (AIII).</li><li>Based on the preponderance of studies indicating no difference in rates of birth defects for first-trimester compared with later ARV exposures, women can be counseled that antiretroviral therapy during pregnancy generally does not increase the risk of birth defects. (BIII).</li></ul>
<b>Rating of Recommendations:</b> A = Strong; B = Moderate; C = Optional
<b>Rating of Evidence:</b> 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

### First-Trimester Exposure 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; the interaction 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 drugs in pregnancy is derived from animal toxicity data, anecdotal experience, registry data, and clinical trials. Drug choice should be individualized and must be based on discussion with the woman and 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. For example, of approximately 1,200 known animal teratogens, only about 30 are known to be teratogenic in humans.<sup>1</sup> Limited data exist regarding placental passage, pharmacokinetics and safety in pregnancy, and long-term safety in exposed infants of Food and Drug Administration-approved antiretroviral (ARV) drugs (see [Supplement: Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy](#)).

In general, reports of birth defects in fetuses/infants of women enrolled in observational studies who receive ARV regimens during pregnancy are reassuring and find no difference in rates of birth defects for first-trimester compared with later exposures.<sup>2-5</sup> In the primary analysis by the Antiretroviral Pregnancy Registry of prospective cases of ARV exposure during pregnancy provided by health care providers, prevalence of birth defects was 2.9 per 100 live births among women with a first-trimester exposure to any ARV (221 of 7,738 exposures; 95% confidence interval [CI], 2.5–3.3). The prevalence of defects is not significantly different from that in women with an initial exposure during the second and/or third trimester (2.8 per 100 live births) (prevalence ratio 1.02; 95% CI, 0.86–1.22).<sup>6</sup>

Some individual reports have raised concerns regarding specific ARV agents. Most studies evaluating a possible association between ARV 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.<sup>7</sup> 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.<sup>8</sup> Maternal tobacco and alcohol use may also serve as confounders.<sup>9</sup>

### Specific Drugs

#### *Efavirenz*

Efavirenz use during pregnancy has received increased scrutiny because of the results of a small study in non-human primates. Significant malformations were observed in 3 of 20 infant cynomolgus monkeys

receiving efavirenz from gestational days 20 to 150 at a dose resulting in plasma concentrations comparable to systemic human exposure at therapeutic dosage.<sup>10</sup> The malformations included anencephaly and unilateral anophthalmia in one, 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, without any such increase detected; a single case of myelomeningocele and one case of anophthalmia have been prospectively reported in live births.<sup>6</sup> In retrospective reports to the Antiretroviral Pregnancy Registry, there have been six cases of central nervous system defects, including meningomyelocele, with first trimester exposure. However, retrospective reports can be biased toward reporting of more unusual and severe cases and are less likely to be representative of the general population experience.

Two publications have reported higher rates of congenital birth defects with first trimester efavirenz exposure. The PACTG protocols 219 and 219C studies reported a higher defect rate in infants with first-trimester exposure to efavirenz compared with those without first-trimester efavirenz exposure (AOR 4.31; 95% CI, 1.56–11.86). However, only 32 infants had efavirenz exposure.<sup>11</sup> PACTG protocol P1025 is a companion study of PACTG 219 with considerable overlap in cases enrolled. Although P1025 reports a significant increased risk of congenital anomalies in infants born between 2002 and 2007 with first-trimester exposure to efavirenz,<sup>3</sup> there is overlap in the defect cases between the two studies and only 41 infants with efavirenz exposure are included in this analysis. There was no specific pattern of anomalies specific to efavirenz described by these studies: 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.<sup>12</sup> However, in a secondary analysis using 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 defects were neural tube defects, and none of the defects had common embryology.<sup>13</sup> A meta-analysis including data from 23 studies reporting on 2,026 first-trimester exposures found no increased risk of overall birth defects in infants born to women on efavirenz during the first trimester compared with those on other ARV drugs during the first trimester (relative risk 0.78; 95% CI, 0.56–1.08). One neural tube defect was observed, giving an incidence of 0.05% (95% CI, <0.01 to 0.28).<sup>14</sup> The number of reported first-trimester efavirenz exposures is currently sufficient to rule out a 2-fold increase in low-incidence birth defects such as neural tube defects (incidence of neural tube defects in the general U.S. population is 0.02% to 0.2%).<sup>15</sup>

In prior Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in The United States (Perinatal Guidelines), efavirenz use was not recommended before 8 weeks' gestational age, because of concerns regarding potential teratogenicity. Although this caution remains in the package insert, the large meta-analysis above has been reassuring that risks of neural tube defects after first trimester efavirenz exposure are not greater than those in the general population.<sup>7,10,16</sup> As a result, the current Perinatal Guidelines do not include the restriction of use before 8 weeks' gestation, consistent with both the British HIV Association and World Health Organization guidelines for use of ARV drugs in pregnancy (which note that efavirenz can be used throughout pregnancy).<sup>17,18</sup> Importantly, women who become pregnant on suppressive efavirenz-containing regimens should continue their current regimens.

### *Tenofovir Disoproxil Fumarate*

Tenofovir disoproxil fumarate (TDF) has not demonstrated teratogenicity in rodents or monkeys. Data from the Antiretroviral Pregnancy Registry show a birth defect incidence of 2.3% (60/2608) women with first-trimester TDF exposure, similar to that in the general population.<sup>6</sup>

Administration of TDF at high doses to pregnant monkeys (exposure resulting in drug levels 25 times the

area under the curve achieved with therapeutic dosing in humans), was associated with maternal toxicity, 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 scans within 4 weeks of birth among 74 infants exposed to more than 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 ( $P = 0.004$ ) as was the whole-body-less-head BMC (-2.6 g,  $P = 0.056$ ). However, the duration and clinical significance of these findings require further longitudinal evaluation. In contrast, in a study evaluating fetal long bone (femur and humerus) growth by serial ultrasound in women who received different durations of TDF antiretroviral therapy during pregnancy (<10 weeks, 10–24 weeks, >25 weeks) found no association between duration of *in utero* TDF disoproxil fumarate exposure per week and change in femur and humerus length z-score ( $P = 0.51$  and  $P = 0.40$ , respectively).<sup>19</sup> No clinical studies have examined the clinical outcomes of maternal usage of tenofovir alafenamide (TAF) on newborn outcomes.

### Other Drugs

In a study from France that included 13,124 live births that occurred between 1994 and 2010; 5,388 (42%) had first-trimester exposure to ARV drugs. 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 HIV-exposed infants, and spontaneous closure of ventricular septal defects after birth is common, the clinical significance of the cardiac findings is uncertain.<sup>13</sup> In contrast to the French study, an analysis of 16,304 prospectively reported pregnancies to assess the risk of ventricular septal defects and congenital heart defects comparing exposure between zidovudine-containing regimens and non-zidovudine ART regimens did not find significant differences between the two groups.<sup>20</sup> Additionally, in a comparison between 417 HIV- and ARV-exposed, uninfected infants and unexposed controls tested at ages 2 to 7 years, no clinically significant differences were found in echocardiographic parameters of left ventricular function and structure.<sup>9</sup>

In an analysis from PHACS that included 2,580 live births, first-trimester ARV exposure overall was not associated with an increased risk of birth defects.<sup>21</sup> In adjusted analyses, the only individual ARV drug for which first-trimester exposure was associated with birth defects was atazanavir, primarily skin and musculoskeletal defects. However, in the Antiretroviral Pregnancy Registry, there was no increase in birth defects with first-trimester atazanavir exposure among 1,093 births.<sup>6</sup>

In the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposures have been monitored to detect at least a 2-fold increase in risk of overall birth defects for abacavir, darunavir, didanosine, efavirenz, indinavir, and stavudine; no such increases have been detected to date. For 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 2-fold increase in risk of birth defects in the more common classes, 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 compared with the U.S. population-based Metropolitan Atlanta Congenital Defects Program (MACDP) surveillance data.<sup>6</sup> The lower bounds of the confidence intervals for didanosine and nelfinavir (2.9% and 2.8%, respectively) are slightly above the higher bound (2.76%) for the MACDP rate. No specific pattern of defects has been detected with 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 Drugs in Pregnancy](#) for detailed information on individual drugs.

## Antiretroviral Pregnancy Registry Reporting

Health care providers who are caring for HIV-infected pregnant women and their newborns are strongly advised to report instances of prenatal exposure to ARV drugs (either alone or in combination) 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>

## References

1. Mills JL. Protecting the embryo from X-rated drugs. *N Engl J Med*. 1995;333(2):124-125. Available at <http://www.ncbi.nlm.nih.gov/pubmed/7777019>.
2. Watts DH, Huang S, Culnane M, et al. Birth defects among a cohort of infants born to HIV-infected women on antiretroviral medication. *J Perinat Med*. 2011;39(2):163-170. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21142844>.
3. Knapp KM, Brogly SB, Muenz DG, et al. Prevalence of congenital anomalies in infants with in utero exposure to antiretrovirals. *Pediatr Infect Dis J*. 2012;31(2):164-170. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21983213>.
4. daCosta TP, Machado ES, et al. Malformations among HIV vertically exposed newborns—results from a Brazilian cohort study. Presented at: 6th IAS Conference on HIV Pathogenesis and Treatment and Prevention. 2011. Rome, Italy.
5. Floridia M, Mastroiacovo P, Tamburrini E, et al. Birth defects in a national cohort of pregnant women with HIV infection in Italy, 2001–2011. *BJOG*. 2013;120(12):1466-1475. Available at <http://www.ncbi.nlm.nih.gov/pubmed/23721372>.
6. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral Pregnancy Registry international interim report for 1 January 1989–31 July 2015. Wilmington, NC: Registry Coordinating Center. 2015. Available at <http://www.apregistry.com/>.
7. Ford N, Shubber Z, Jao J, Abrams EJ, Frigati L, Mofenson L. Safety of cotrimoxazole in pregnancy: a systematic review and meta-analysis. *J Acquir Immune Defic Syndr*. 2014. Available at <http://www.ncbi.nlm.nih.gov/pubmed/24853309>.
8. Jungmann EM, Mercey D, DeRuiter A, et al. Is first trimester exposure to the combination of antiretroviral therapy and folate antagonists a risk factor for congenital abnormalities? *Sex Transm Infect*. 2001;77(6):441-443. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11714944>.
9. Lipshultz SE, Williams PL, Zeldow B, et al. Cardiac effects of in-utero exposure to antiretroviral therapy in HIV-uninfected children born to HIV-infected mothers. *AIDS*. 2015;29(1):91-100. Available at <http://www.ncbi.nlm.nih.gov/pubmed/25562493>.

10. Efavirenz [package insert]. Food and Drug Administration. 2016. Available at [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2016/020972s049-021360s038lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020972s049-021360s038lbl.pdf). Accessed August 12, 2016.
11. Brogly SB, Abzug MJ, Watts DH, et al. Birth defects among children born to human immunodeficiency virus-infected women: pediatric AIDS clinical trials protocols 219 and 219C. *Pediatr Infect Dis J*. 2010;29(8):721-727. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20539252>.
12. Sibiude J, Mandelbrot L, Blanche S, et al. Association between prenatal exposure to antiretroviral therapy and birth defects: an analysis of the French perinatal cohort study (ANRS CO1/CO11). *PLoS Med*. 2014;11(4):e1001635. Available at <http://www.ncbi.nlm.nih.gov/pubmed/24781315>.
13. Mofenson LM, Watts DH. Safety of pediatric HIV elimination: the growing population of HIV- and antiretroviral-exposed but uninfected infants. *PLoS Med*. 2014;11(4):e1001636. Available at <http://www.ncbi.nlm.nih.gov/pubmed/24781352>.
14. Ford N, Mofenson L, Shubber Z, et al. Safety of efavirenz in the first trimester of pregnancy: an updated systematic review and meta-analysis. *AIDS*. 2014;28 Suppl 2:S123-131. Available at <http://www.ncbi.nlm.nih.gov/pubmed/24849471>.
15. Watts DH. Teratogenicity risk of antiretroviral therapy in pregnancy. *Curr HIV/AIDS Rep*. 2007;4(3):135-140. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17883999>.
16. Ford N, Calmy A, Mofenson L. Safety of efavirenz in the first trimester of pregnancy: an updated systematic review and meta-analysis. *AIDS*. 2011;25(18):2301-2304. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21918421>.
17. de Ruiter A, Taylor GP, Clayden P, et al. British HIV Association guidelines for the management of HIV infection in pregnant women 2012 (2014 interim review). *HIV Med*. 2014;15 Suppl 4:1-77. Available at <http://www.ncbi.nlm.nih.gov/pubmed/25604045>.
18. World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection—recommendations for a public health approach; second edition 2016. 2016; <http://www.who.int/hiv/pub/arv/arv-2016/en/>.
19. Jao J, Abrams EJ, Phillips T, Petro G, Zerbe A, Myer L. *In utero* tenofovir exposure is not associated with fetal long bone growth. *Clin Infect Dis*. 2016. Available at <http://www.ncbi.nlm.nih.gov/pubmed/27009251>.
20. Vannappagari V, Albano JD, Koram N, Tilson H, Scheuerle AE, Napier MD. Prenatal exposure to zidovudine and risk for ventricular septal defects and congenital heart defects: data from the Antiretroviral Pregnancy Registry. *Eur J Obstet Gynecol Reprod Biol*. 2016;197:6-10. Available at <http://www.ncbi.nlm.nih.gov/pubmed/26687320>.
21. Williams PL, Crain MJ, Yildirim C, et al. Congenital anomalies and *in utero* antiretroviral exposure in human immunodeficiency virus-exposed uninfected infants. *JAMA Pediatr*. 2015;169(1):48-55. Available at <http://www.ncbi.nlm.nih.gov/pubmed/25383770>.