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

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Teratogenicity (Last updated July 31, 2012; last reviewed July 31, 2012)

Panel's Recommendations
• All cases of antiretroviral (ARV) drug exposure during pregnancy should be reported to the Antiretroviral Pregnancy Registry (see details at http://www.APRegistry.com) **(AIII)**.
• Non-pregnant women of childbearing potential should undergo pregnancy testing before initiation of efavirenz and receive counseling about the potential risk to the fetus and desirability of avoiding pregnancy while on efavirenz-containing regimens **(AIII)**. o Alternate ARV regimens that do not include efavirenz should be strongly considered in women who are (1) planning to become pregnant or (2) sexually active and not using effective contraception, assuming these alternative regimens are acceptable to the provider and are not thought to compromise the woman's health **(BIII)**.
• Because the risk of neural tube defects is restricted to the first 5 to 6 weeks of pregnancy and pregnancy is rarely recognized before 4 to 6 weeks of pregnancy, and unnecessary changes in ARV drugs during pregnancy may be associated with loss of viral control and increased risk of perinatal transmission, efavirenz can be continued in pregnant women receiving an efavirenz-based regimen who present for antenatal care in the first trimester, provided the regimen produces virologic suppression (see HIV-Infected Pregnant Women Who are Currently Receiving Antiretroviral Treatment) **(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 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. Data are limited for antiretroviral (ARV) drugs, particularly when used in combination therapy. Drug choice should be individualized and must be based on discussion with a 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.[1] Limited data exist regarding placental passage, pharmacokinetics and safety in pregnancy, and long-term safety for exposed infants for the Food and Drug Administration (FDA)-approved 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.[2-4] However, concerns have been raised about the risk of several ARV agents.

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.[5] The malformations included anencephaly and unilateral anophthalmia in one, microphthalmia in another, and cleft palate in the third. Among pregnancies prospectively reported to the Antiretroviral Pregnancy Registry through January 2012 that had exposure to efavirenz-based regimens, a

2.7% incidence of overall birth defects was seen with first-trimester exposure, a proportion not significantly different from that observed among U.S. births in the general population.[6] Defects reported prospectively included 1 report of myelomeningocele and a separate report of anophthalmia. The case of anophthalmia included severe oblique facial clefts and amniotic banding that is known to be associated with anophthalmia.[6] In addition, 6 cases of central nervous system defects, including myelomeningocele, have been retrospectively reported in infants born to mothers receiving efavirenz during the first trimester.[5] 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.

A meta-analysis including data from 9 cohorts with prospective reporting on 1,132 first-trimester exposures did not find an 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 [RR] 0.87; 95% confidence interval [CI], 0.61–1.24).[7] One neural tube defect occurred among 1,256 live births. An update to the meta-analysis included 181 additional live births with first-trimester efavirenz exposure and had similar results; the RR of overall birth defects on efavirenz versus non-efavirenz regimens was 0.85 (95% CI, 0.61–1.20), and 1 neural tube defect (the same as previous) was observed, giving an incidence of 0.07% (95% CI, 0.002–0.39).[8] However, the number of reported first-trimester efavirenz exposures still remains insufficient to rule out a significant 2- to 3-fold increase in low-incidence birth defects (incidence of neural tube defects in the general U.S. population is 0.02–0.2%).

In contrast to the meta-analysis, the Pediatric AIDS Clinical Trials Protocols (PACTG) 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 (adjusted odds ratio 4.31; 95% CI, 1.56–11.86). However, only 32 infants had efavirenz exposure. 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, there is overlap in the defect cases between the 2 studies and only 42 infants are included in this analysis. Thus, additional data are needed on first-trimester efavirenz exposures to be able to more conclusively determine if risk of neural tube defects or other malformations is elevated.

Although a causal relationship has not been established between these events and the use of efavirenz, in light of similar findings in primates, efavirenz has been classified as FDA Pregnancy Category D. Because of the potential for teratogenicity, pregnancy should be avoided in women receiving efavirenz, and treatment with efavirenz should be avoided during the first trimester (the primary period of fetal organogenesis) whenever possible. Women of childbearing potential should undergo pregnancy testing before initiation of efavirenz and should be counseled about the potential risk to the fetus and desirability of avoiding pregnancy while on efavirenz-containing regimens. Alternate ARV regimens that do not include efavirenz should be strongly considered in women who are planning to become pregnant or who are sexually active and not using effective contraception if such alternative regimens are acceptable to provider and patient and will not compromise the woman's health. However, the Panel now recommends that efavirenz can be continued in women who present for care in the first trimester and are receiving efavirenz-based ARV therapy that is effective in suppressing viral replication. This is because the neural tube closes at 36 to 39 days after the last menstrual period; hence the risk of neural tube defects is restricted to the first 5 to 6 weeks of pregnancy (and pregnancy is rarely recognized before 5–6 weeks of pregnancy), and unnecessary changes in ARV drugs during pregnancy may be associated with a loss of virologic control and, thus, increased risk of transmission to the infant.[9] For more details, see HIV-Infected Pregnant Women Who are Currently Receiving Antiretroviral Treatment.

Tenofovir has not demonstrated teratogenicity in rodents or monkeys. In infant monkeys with *in utero* exposure to tenofovir at maternal doses resulting in levels approximately 25 times those used in humans, low

birth weights and reductions in fetal bone porosity were seen. Chronic administration of tenofovir to immature animals of multiple species has resulted in reversible bone abnormalities; these effects were dose, exposure, age, and species specific. Data from the Antiretroviral Pregnancy Registry show a birth defect incidence of 2.3% in 1,370 women with first-trimester tenofovir exposure, similar to that in the general population.[6] An Italian study assessed growth patterns, bone health, and markers of bone metabolism in 33 infants with *in utero* exposure to tenofovir and found no difference compared with infants born to HIV-infected women who had not been exposed to tenofovir.[10] A larger study from the United States included 2,029 HIV-exposed but uninfected infants, 449 (21%) of whom had *in utero* exposure to tenofovir.[11] Although there were no differences in anthropomorphic parameters at birth, at age 1 year, infants exposed to tenofovir-based regimens had slight but significantly lower adjusted mean length and head circumference for age z-score than those without exposure to tenofovir. Because of the limited data on use in human pregnancy and concern regarding potential fetal bone effects and potential nephrotoxicity, tenofovir is recommended as an alternative rather than a preferred drug for use in pregnancy unless a pregnant woman is HIV/hepatitis B coinfected (see Table 5).

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).[6] The lower bound of the CI for didanosine and nelfinavir (2.8%) is 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 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 to obtain detailed information on individual drugs.

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. 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*. Jul 13 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*. Mar 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*. Feb 2012;31(2):164-170. Available at http://www.ncbi.nlm.nih.gov/pubmed/21983213.
4. Joao EC, Calvet GA, Krauss MR, et al. Maternal antiretroviral use during pregnancy and infant congenital anomalies: the NISDI perinatal study. *J Acquir Immune Defic Syndr.* Feb 2010;53(2):176-185. Available at http://www.ncbi.nlm.nih.gov/pubmed/20104119.
5. Bristol-Myers Squibb. Sustiva drug label, 11/30/2010. http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021360s024lbl.pdf. Accessed July 6, 2012.
6. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral pregnancy registry international interim report for 1 Jan 1989 - 31 January 2012. Wilmington, NC: Registry Coordinating Center; 2012. Available at http://www.APRegistry.com.
7. Ford N, Mofenson L, Kranzer K, et al. Safety of efavirenz in first-trimester of pregnancy: a systematic review and meta-analysis of outcomes from observational cohorts. *AIDS*. Jun 19 2010;24(10):1461-1470. Available at http://www.ncbi.nlm.nih.gov/pubmed/20479637.
8. Ford N, Calmy A, Mofenson L. Safety of efavirenz in the first trimester of pregnancy: an updated systematic review and meta-analysis. *AIDS*. Nov 28 2011;25(18):2301-2304. Available at http://www.ncbi.nlm.nih.gov/pubmed/21918421.
9. Floridia M, Ravizza M, Pinnetti C, et al. Treatment change in pregnancy is a significant risk factor for detectable HIV-1 RNA in plasma at end of pregnancy. *HIV Clin Trials*. Nov-Dec 2010;11(6):303-311. Available at http://www.ncbi.nlm.nih.gov/pubmed/21239358.
10. Vigano A, Mora S, Giacomet V, et al. *In utero* exposure to tenofovir disoproxil fumarate does not impair growth and bone health in HIV-uninfected children born to HIV-infected mothers. *Antivir Ther*. 2011;16(8):1259-1266. Available at http://www.ncbi.nlm.nih.gov/pubmed/22155907.
11. Siberry GK, Williams PL, Mendez H, et al. Safety of tenofovir use during pregnancy: early growth outcomes in HIV-exposed uninfected infants. *AIDS*. Jun 1 2012;26(9):1151-1159. Available at http://www.ncbi.nlm.nih.gov/pubmed/22382151.