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

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Efavirenz (Sustiva, EFV)

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The Food and Drug Administration (FDA) cautions that efavirenz should not be used in the first trimester of pregnancy because of the potential risk of neural tube defects, which have been observed among children exposed to efavirenz in utero and in animal studies.¹

However, the current Perinatal Guidelines, based on a review of updated evidence, do not include a restriction on the use of efavirenz in pregnant women or in women who are planning to become pregnant. This is consistent with both the British HIV Association guidelines and World Health Organization (WHO) guidelines for use of antiretroviral (ARV) drugs in pregnancy.

Animal Studies

Carcinogenicity

Efavirenz was neither mutagenic nor clastogenic in a series of in vitro and animal in vivo screening tests. A study that evaluated the genotoxicity of efavirenz in mice noted DNA damage in brain cells after daily dosing for 36 days; no damage was seen in liver, heart, or peripheral blood cells.² Long-term animal carcinogenicity studies with efavirenz have been completed in mice and rats. At systemic drug exposures that were approximately 1.7-fold higher than the exposures seen in humans who received standard therapeutic doses, no increase in tumor incidence above background was observed in male mice. In female mice, an increase in tumor incidence above background was seen in hepatocellular adenomas and carcinomas and pulmonary alveolar/bronchiolar adenomas. No increase in tumor incidence above background was observed in male and female rats with systemic efavirenz exposures that were lower than those seen in humans who received therapeutic doses.¹

Reproduction/Fertility

No effect of efavirenz on reproduction or fertility in rodents has been seen.¹

Teratogenicity/Adverse Pregnancy Outcomes

An increase in fetal resorption was observed in female rats at efavirenz doses that produced peak plasma concentrations and area under the curve (AUC) values that were less than or equal to those achieved in humans who received the recommended dose of efavirenz 600 mg once daily. Efavirenz produced no reproductive toxicities when given to pregnant rabbits at doses that produced peak plasma concentrations similar to and AUC values approximately half of those achieved in humans administered efavirenz (600 mg once daily).¹

Central nervous system (CNS) malformations and cleft palate were observed in three of 20 infants born to pregnant cynomolgus monkeys that received efavirenz between gestational day 20 and gestational day 150 at a dose of efavirenz 60 mg/kg/day. This dose resulted in plasma concentrations that were 1.3 times that of systemic human therapeutic exposure, with fetal umbilical venous drug concentrations that were approximately 0.7 times the maternal values.³ The malformations included anencephaly and unilateral anophthalmia in one fetus, microphthalmia in another fetus, and cleft palate in a third fetus.¹

Placental and Breast Milk Passage

Efavirenz readily crosses the placenta in rats, rabbits, and primates, producing cord blood concentrations similar to concentrations in maternal plasma. Maternal and fetal blood concentrations in pregnant rabbits and cynomolgus monkeys are equivalent, while fetal concentrations in rats exceeded maternal concentrations.¹

Human Studies in Pregnancy

Pharmacokinetics/Pharmacogenomics

In an intensive sampling pharmacokinetic (PK) study of 25 pregnant women who received efavirenz during the third trimester, efavirenz clearance was slightly increased and trough levels were decreased compared with levels measured postpartum.¹ These differences are not of sufficient magnitude to warrant dose adjustment during pregnancy. A review of this study plus four others that measured efavirenz concentrations in pregnant
women found that efavirenz concentrations were not significantly affected by pregnancy and that high rates of HIV RNA suppression at delivery were achieved with efavirenz-based regimens.\(^5\)

In a pharmacogenomics study, nonpregnant individuals with the cytochrome P (CYP) 2B6 516 TT genotype had >3-fold increases in both short-term and long-term efavirenz exposure, as measured by plasma and hair drug levels. This suggests that there could be significant variation in drug levels with CYP2B6 polymorphisms.\(^6\) The frequency of this allele varies between different ethnic populations, with a prevalence of 3.4% in white people, 6.7% in Hispanic people, and 20% in African Americans.\(^4\)

**Placental and Breast Milk Passage**

In a study of 25 mother-infant pairs, the median efavirenz cord blood/maternal blood concentration ratio was 0.49 (range 0.37–0.74).\(^4\) In a study of 13 women in Rwanda, efavirenz was given during the last trimester of pregnancy and for 6 months after delivery.\(^7\) Efavirenz concentrations were measured in maternal plasma, breast milk, and infant plasma. Efavirenz concentration was significantly higher in maternal plasma than in skim breast milk (with a mean breast milk to mean maternal plasma concentration ratio of 0.54) and higher in skim breast milk than in infant plasma (with a mean skim breast milk to mean newborn plasma concentration ratio of 4.08). Mean infant plasma efavirenz concentrations were 860 ng/mL, and the mean infant plasma efavirenz concentration was 13.1% of maternal plasma concentrations. All infants had detectable plasma concentrations of efavirenz, and eight of 13 newborns had plasma efavirenz concentrations below the minimum therapeutic concentration of 1,000 ng/mL recommended for treatment of adults with HIV. In a study of 51 women in Nigeria who received efavirenz 600 mg daily, the median milk/maternal plasma concentration ratio was 0.82 (range 0.51–1.1) and the median (range) infant efavirenz concentration was 178 ng/mL (range 88–340 ng/mL).\(^8\) In a study of 56 mother-infant pairs in which the mothers received efavirenz-based therapy during pregnancy and breastfeeding, infant plasma drug concentration levels at delivery and hair drug concentration levels at age 12 weeks suggested moderate *in utero* transfer of efavirenz during pregnancy and breastfeeding, with approximately one-third of transfer occurring postpartum (40% cumulative transfer, with 15% of transfer occurring during breastfeeding).\(^9\) All mothers and infants had detectable efavirenz plasma levels at 0, 8, and 12 weeks, and mean infant-to-maternal hair concentration at 12 weeks postpartum was 0.40 for efavirenz. No data currently are available about the safety and PK of efavirenz in neonates.

**Teratogenicity/Adverse Pregnancy Outcomes**

In pregnancies with prospectively reported exposure to efavirenz-based regimens in the Antiretroviral Pregnancy Registry through January 2018 birth defects were observed in 24 of 1,024 live births with first-trimester exposure (2.35%, 95% CI, 1.51% to 3.47%).\(^10\) Although these data provide sufficient numbers of first-trimester exposures to rule out a 1.5-fold or greater increase in the risk of overall birth defects, the low incidence of neural tube defects in the general population means that a larger number of exposures are still needed to be able to definitively rule out an increased risk of this specific defect. Prospective reports to the Antiretroviral Pregnancy Registry of defects after first-trimester efavirenz exposure have documented one neural tube defect case (sacral aplasia, myelomeningocele, and hydrocephalus with fetal alcohol syndrome) and one case of bilateral facial clefts in infants born to mothers who received efavirenz during the first trimester.\(^1\) Retrospective reports can be biased toward reporting of more unusual and severe cases and are less likely to be representative of the general population’s experience.

In an updated meta-analysis of 23 studies (including Antiretroviral Pregnancy Registry data), there were 44 infants with birth defects among 2,026 live births to women who received efavirenz during the first trimester. The rate of overall birth defects was 1.63% (95% CI, 0.78% to 2.48%).\(^11\) The rate of overall birth defects was similar among women who received efavirenz-containing regimens and women who received regimens that did not contain efavirenz during the first trimester (pooled relative risk [RR] 0.78; 95% CI, 0.56–1.08). Across all births, one neural tube defect (myelomeningocele) was observed, giving a point prevalence of 0.05% (95% CI, <0.01 to 0.28), which is within the range reported in the general population. However, the number of reported
first-trimester efavirenz exposures remains insufficient to rule out a significant increase in low-incidence birth defects (incidence of neural tube defects in the general U.S. population is 0.02% to 0.2%).

A French study of 13,124 live births between 1994 and 2010 included an analysis of 372 infants born after first-trimester efavirenz exposure. In the primary analysis that used the European Surveillance of Congenital Anomalies (EUROCAT) classification system, no increase in the incidence of birth defects was detected among infants with first-trimester efavirenz exposure compared to those without efavirenz exposure in pregnancy (adjusted odds ratio 1.16; 95% CI, 0.73–1.85). In a secondary analysis that used the modified Metropolitan Atlanta Congenital Defect Program classification used by the Antiretroviral Pregnancy Registry, an association was found between first-trimester efavirenz exposure and neurologic defects. However, none of the four defects (ventricular dilatation with anomalies of the white substance, partial agenesis of the corpus callosum, subependymal cyst, and pachygyria) were neural tube defects, and none of the defects had common embryology. First-trimester efavirenz exposure was not associated with an increased risk of defects in a Pediatric HIV/AIDS Cohort Study analysis that included 2,580 live births, 94 of which involved first-trimester efavirenz exposure, or an analysis of a national cohort in Italy that included 1,257 pregnancies, 80 of which involved first-trimester efavirenz exposure. Thus, additional data are needed on first-trimester efavirenz exposures to more conclusively determine if the risk of neural tube defects is elevated.

The FDA advises women to avoid becoming pregnant while taking efavirenz and advises health care providers to avoid administration during the first trimester of pregnancy, as fetal harm may occur. Although the limited data on first-trimester efavirenz exposure cannot rule out a two- or three-fold increased incidence of a rare outcome, such as neural tube defects, the available data from the meta-analysis on >2,000 births suggest that there is no large increase in the risk of neural tube defects with first-trimester exposure (e.g., a 10-fold increase to a rate of 1%). As a result, the current Perinatal Guidelines do not restrict the use of efavirenz in pregnancy or in women who are planning to become pregnant; this is consistent with the British HIV Association guidelines and WHO guidelines for use of ARV drugs in pregnancy, both of which note that efavirenz can be used throughout pregnancy. Efavirenz should be continued in pregnant women who are receiving a virologically suppressive, efavirenz-based regimen, because ARV drug changes during pregnancy may be associated with loss of viral control and an increased risk of perinatal transmission.

**Additional Information**

PK interactions between efavirenz and some hormonal contraceptives have been reported, with the potential for failure of the progesterone component. This may potentially affect the efficacy of emergency contraception, combined oral contraceptive pills, progestin-only pills, and progestin implants. A retrospective chart review study suggests that efavirenz may decrease the efficacy of levonorgestrel implants (e.g., Jadelle). Pregnancy occurred in 15 of 115 women (12.4%) who were on efavirenz and using Jadelle; no pregnancies occurred among 208 women who were on nevirapine-based regimens, and no pregnancies occurred among 13 women who were on lopinavir/ritonavir (LPV/r)-based regimens (P < 0.001) (see Preconception Counseling and Care). In a prospective clinical trial by Scarsi et al., three out of 20 Ugandan women (15%) became pregnant between 36 and 48 weeks with the combination of levonorgestrel and an efavirenz-based antiretroviral therapy (ART) regimen. When compared to ART-naive women, the women on efavirenz-based regimens had lower levonorgestrel PKs.

P1026s evaluated the interaction between the etonogestrel-releasing implant and three ARV drug regimens (atazanavir/ritonavir, LPV/r, efavirenz) in postpartum women who chose an etonogestrel implant for contraception. There was no significant change in the concentration levels of the ARV drugs after insertion of...
Dosing Recommendations

Use in Pregnancy

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

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Excerpt from Table 10a

Individual ARV drug doses may need to be adjusted in patients with renal or hepatic insufficiency (for details, see the Adult and Adolescent
Guidelines, Appendix B, Table 8).

b Placental transfer categories are determined by mean or median cord blood/maternal delivery plasma drug ratio:

<table>
<thead>
<tr>
<th>Category</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>&gt; 0.6</td>
</tr>
<tr>
<td>Moderate</td>
<td>0.3–0.6</td>
</tr>
<tr>
<td>Low</td>
<td>&lt; 0.3</td>
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</tbody>
</table>

d Generic formulation is available.

Key to Acronyms: 3TC = lamivudine; ARV = antiretroviral; AUC = area under the curve; EFV = efavirenz; FDA = Food and Drug Administration; FDC = fixed-dose combination; FTC = emtrictabine; PK = pharmacokinetic; TDF = tenofovir disoproxil fumarate; WHO = World Health Organization

References


