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.

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. 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.

*Reproduction/Fertility*

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

*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).

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. The malformations included anencephaly and unilateral anophthalmia in one fetus, microphthalmia in another fetus, and cleft palate in a third fetus.

*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.

**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. 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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).\textsuperscript{4} In a study of 13 women in Rwanda, efavirenz was given during the last trimester of pregnancy and for 6 months after delivery.\textsuperscript{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).\textsuperscript{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).\textsuperscript{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%).\textsuperscript{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.\textsuperscript{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%).\textsuperscript{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.

Although two studies (Pediatric AIDS Clinical Trials Group [PACTG] protocol 219/219C and PACTG protocol P1025) reported a higher rate of birth defects among infants with first-trimester exposure to efavirenz than among those without exposure, the number of exposures was small in both studies (35 exposures in PACTG 219/219C and 42 in P1025), and there is overlap in defect cases between the two studies. 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
the etonogestrel implant. However, of the three ARV drug regimens, efavirenz use was associated with greatly decreased etonogestrel concentrations, to levels that could impair contraceptive efficacy.\[^{28}\] A nonrandomized parallel group study in Ugandan women with HIV characterized the PKs of etonogestrel released from a contraceptive implant. Women who were receiving either efavirenz-based regimens or nevirapine-based regimens were compared to women who were ART-naive and not receiving ART. At 24 weeks, etonogestrel concentrations were 82% lower in women who were taking efavirenz than in ART-naive women. No significant changes in etonogestrel concentration were observed when etonogestrel was combined with nevirapine.\[^{29}\] An ACTG study (A5316) evaluated pharmacokinetic interactions between etonogestrel and ethinyl estradiol from a vaginal ring and efavirenz or atazanavir/ritonavir (ATV/r). When compared to women who had yet to start an ART regimen, women in the efavirenz group had etonogestrel levels that were 76% to 79% lower and ethynyl estradiol plasma concentrations that were 53% to 57% lower over 21 days.\[^{30}\] Thus, women receiving efavirenz and using combined oral contraceptive pills, progestin-only pills, the contraceptive vaginal ring, or progestin implants should be informed of the possible decreased effectiveness of these contraceptive methods and strongly advised to also use barrier contraception.

Alternative contraceptive regimens for which efficacy is not reduced while using concomitant efavirenz may also be considered. A study that evaluated the interaction between efavirenz and depot medroxyprogesterone acetate (DMPA) in 17 women found no change in the PK profile of either efavirenz or DMPA with concomitant use.\[^{31}\] DMPA levels remained above the level needed for inhibition of ovulation throughout the dosing interval. In addition, intrauterine devices (both copper-containing and levonorgestrel-containing devices) would be expected to maintain efficacy when used with efavirenz-based regimens.

Excerpt from Table 10\[^{a}\]

Note: When using FDCs, refer to other sections in Appendix B and Table 10 for information about the dosing and safety of individual drug components of the FDC during pregnancy.

<table>
<thead>
<tr>
<th>Generic Name (Abbreviation) Trade Name</th>
<th>Formulation</th>
<th>Dosing Recommendations</th>
<th>Use in Pregnancy</th>
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</table>
| Efavirenz (EFV) Sustiva | EFV (Sustiva)\[^{a}\]: Capsules: • 50 mg • 200 mg Tablet: • 600 mg EFV/FTC/TDF (Atripla): • EFV 600 mg plus FTC 200 mg tablet TDF 300 mg plus EFV/3TC/TDF (Symfli): • EFV 600 mg plus 3TC 300 mg plus TDF 300 mg tablet EFV/3TC/TDF (Symfli Lo): • EFV 400 mg plus 3TC 300 mg plus TDF 300 mg tablet | Standard Adult Doses
EFV (Sustiva): • EFV 600 mg once daily at or before bedtime, on an empty stomach to reduce side effects
EFV/FTC/TDF (Atripla): • 1 tablet once daily at or before bedtime, on an empty stomach to reduce side effects
EFV/3TC/TDF (Symfli or Symfli Lo): • 1 tablet once daily on an empty stomach and preferably at bedtime | Moderate placental transfer to fetus.\[^{a}\]

The FDA advises women to avoid becoming pregnant while taking EFV and advises healthcare providers to avoid administration during the first trimester of pregnancy, as fetal harm may occur. Although the limited data on first-trimester EFV exposure cannot rule out a 2-fold or 3-fold increased incidence of a rare outcome such as neural tube defects, the available data from a meta-analysis of >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 EFV in pregnant women or in women who are planning to become pregnant. This is consistent with both the British HIV Association and WHO guidelines for use of ARV drugs in pregnancy.

EFV should be continued in pregnant women who are on a virologically suppressive, EFV-based regimen, because ARV drug changes during pregnancy may be associated with loss of viral control and an increased risk of perinatal transmission (see Pregnant Women Living with HIV Who are Currently Receiving Antiretroviral Therapy).
Excerpt from Table 10a

a 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:

High: > 0.6  Moderate: 0.3–0.6  Low: < 0.3
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 = emtricitabine; PK = pharmacokinetic; TDF = tenofovir disoproxil fumarate; WHO = World Health Organization

References


