Non-Nucleoside Reverse Transcriptase Inhibitors

<table>
<thead>
<tr>
<th>Glossary of Terms for Supplement</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Carcinogenic:</strong> Producing or tending to produce cancer</td>
</tr>
<tr>
<td>• Some agents, such as certain chemicals or forms of radiation, are both mutagenic and clastogenic.</td>
</tr>
<tr>
<td>• Genetic mutations and/or chromosomal damage can contribute to cancer formation.</td>
</tr>
<tr>
<td><strong>Clastogenic:</strong> Causing disruption of or breakages in chromosomes</td>
</tr>
<tr>
<td><strong>Genotoxic:</strong> Damaging to genetic material such as DNA and chromosomes</td>
</tr>
<tr>
<td><strong>Mutagenic:</strong> Inducing or capable of inducing genetic mutation</td>
</tr>
<tr>
<td><strong>Teratogenic:</strong> Interfering with fetal development and resulting in birth defects</td>
</tr>
</tbody>
</table>

Five non-nucleoside analogue reverse transcriptase inhibitors (NNRTIs) are currently U.S. Food and Drug Administration (FDA) approved: delavirdine, efavirenz, etravirine, nevirapine, and rilpivirine. Delavirdine is no longer available in the United States.

**Efavirenz (Sustiva, EFV)**

*(Last updated November 14, 2017; last reviewed November 14, 2017)*

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 review of updated evidence, do not include a restriction on use of efavirenz in pregnant women or in women planning to become pregnant, consistent with both the British HIV Association 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 evaluating 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 approximately 1.7-fold higher than in humans receiving standard therapeutic doses, no increase in tumor incidence above background was observed in male mice, but in female mice, an increase 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 drug exposures lower than that in humans receiving 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 rats at efavirenz doses that produced peak plasma concentrations and area under the curve (AUC) values in female rats ≤ those achieved in humans at the recommended human dose (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 3 of 20 infants born to pregnant cynomolgus monkeys receiving efavirenz from gestational days 20 to 150 at a dose of 60 mg/kg/day (resulting in plasma concentrations 1.3 times that of systemic human therapeutic exposure, with fetal umbilical venous drug concentrations 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 receiving efavirenz during the third trimester, efavirenz clearance was slightly increased and trough levels were decreased compared with levels measured postpartum.\(^4\) These differences are not of sufficient magnitude to warrant dose adjustment during pregnancy. A review of this study plus four others that measured single 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 regimens.\(^5\)

In a pharmacogenomics study, non-pregnant individuals with the CYP2B6 516 TT genotype had more than 3-fold increases in both short-term and long-term efavirenz exposure, as measured by plasma and hair drug levels, suggesting there could be significant variation in drug levels with CYP2B6 polymorphisms.\(^6\) The frequency of this allele varies between different ethnic populations, ranging from 3.4% in white, 6.7% in Hispanic, and 20% in African Americans.\(^4\)

**Placental and Breast Milk Passage**

In a study of 25 mother-infant pairs, median efavirenz cord blood/maternal blood concentration 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 (mean breast milk to mean maternal plasma concentration ratio 0.54) and higher in skim breast milk than in infant plasma (mean skim breast milk to mean newborn plasma concentration ratio 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 8 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 receiving efavirenz 600 mg daily, the median (range) milk/maternal plasma ratio was 0.82 (0.51–1.1) and the median (range) infant efavirenz concentration was 178 (88–340) ng/mL.\(^8\) In a study of plasma and hair drug concentration in 56 mother-infant pairs receiving efavirenz-based therapy during pregnancy and breastfeeding, infant plasma levels at delivery and hair levels at age 12 weeks suggested moderate in utero transfer during pregnancy and breastfeeding, with approximately one-third of transfer occurring postpartum (40% cumulative with 15% during breastfeeding). 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 2017 birth defects were observed in 22 of 978 live births with first-trimester exposure (2.2%, 95% CI, 1.4% to 3.4%).\(^10\) Although these data provide sufficient numbers of first-trimester exposures to rule out a 2-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, anophthalmia, and amniotic band. An undefined abnormality of the
cerebral vermis was seen on ultrasound and reported in 2014; however, at birth and with follow-up, the infant is noted to be developing normally as per the parents, who have also declined further testing. Among retrospective cases, there are six reports of CNS defects, including three cases of meningomyelocele in infants born to mothers receiving efavirenz during the first trimester. 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.

In an updated meta-analysis of 23 studies (including Antiretroviral Pregnancy Registry data) reporting on birth outcomes among women exposed to efavirenz during the first trimester, there were 44 infants with birth defects among 2,026 live births to women receiving first-trimester efavirenz (rate of overall birth defects (1.63%, 95% CI, 0.78% to 2.48%). The rate of overall birth defects was similar among women exposed to efavirenz-containing regimens and non-efavirenz-containing regimens 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), 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 using the European Surveillance of Congenital Anomalies (EUROCAT) classification system, no increase in birth defects after first-trimester efavirenz exposure was detected compared to those without efavirenz exposure in pregnancy (adjusted odds ratio 1.16, 95% CI, 0.73–1.85). In a secondary analysis using 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 after first-trimester efavirenz exposure, or an analysis of a national cohort in Italy that included 1,257 pregnancies, 80 after first-trimester efavirenz exposure.

Although two small studies (PACTG protocol 219/219C and PACTG protocol P1025) reported a higher rate of birth defects among infants with first-trimester exposure to efavirenz compared with those without exposure, the number of exposures was small (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 risk of neural tube defects is elevated.

The FDA advises women to avoid becoming pregnant while taking efavirenz and health care providers to avoid administration in the first trimester of pregnancy as fetal harm may occur. Although the limited data on first-trimester efavirenz exposure cannot rule out a 2- or 3-fold increased incidence of a rare outcome, such as neural tube defects, the available data from the meta-analysis on more than 2,000 births suggest that there is not a large increase (e.g., a 10-fold increase to a rate of 1%) in the risk of neural tube defects with first-trimester exposure. As a result, the current Perinatal Guidelines do not include the restriction of use of efavirenz in pregnancy or in women planning pregnancy, consistent with both the British HIV Association and WHO guidelines for use of ARV drugs in pregnancy (which note that efavirenz can be used throughout pregnancy). Efavirenz should be continued in pregnant women receiving a virologically suppressive, efavirenz-based regimen, because ARV drug changes during pregnancy may be associated with loss of viral control and 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, potentially affecting 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 among 15 (12.4%) of 115 women on efavirenz using Jadelle, compared to no pregnancies among 208 women on

Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States G-53
nevirapine-based regimens and no pregnancies among 13 women on lopinavir/ritonavir-based regimens ($P < 0.001$) (see Preconception Counseling and Care). In a prospective clinical trial by Scarsi et al., 3 out of 20 (15%) Ugandan women became pregnant between 36 and 48 weeks with the combination of levonorgestrel and efavirenz-based antiretroviral therapy (ART) regimen. In comparison to the ART-naive women, the women on efavirenz-based regimens had lower levonorgestrel PK.\(^{27}\)

**Interaction between the etonogestrel-releasing implant and three ARV drug regimens (atazanavir/ritonavir, lopinavir/ritonavir, efavirenz) in postpartum women who chose an etonogestrel implant for contraception** were evaluated in P1026s. 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.\(^{28}\) Thus, women receiving efavirenz and using combined oral contraceptive pills, progestin-only pills, 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 by concomitant efavirenz may also be considered. A study evaluating 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.\(^{29}\) 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) would be expected to maintain efficacy.

**Excerpt from Table 9**

<table>
<thead>
<tr>
<th>Generic Name (Abbreviation)</th>
<th>Formulation</th>
<th>Dosing Recommendations</th>
<th>Use in Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efavirenz</strong> (EFV) Sustiva (EFV/TDF/FTC) Atripla</td>
<td>EFV (Sustiva)(^a) Capsules: • 50 mg • 200 mg Tablet: • 600 mg Atripla: • EFV 600 mg plus TDF 300 mg plus FTC 200 mg tablet</td>
<td>Standard Adult Dose EFV (Sustiva): • 600 mg once daily at or before bedtime, on empty stomach to reduce side effects Atripla: • 1 tablet once daily at or before bedtime, on empty stomach to reduce side effects PK in Pregnancy: • AUC decreased during third trimester, compared with postpartum, but nearly all third-trimester participants exceeded target exposure. Dosing in Pregnancy: • No change in dose indicated.</td>
<td>Moderate placental transfer to fetus.(^b) Potential fetal safety concern: The FDA advises women to avoid becoming pregnant while taking EFV and advises health care providers to avoid administration in the first trimester of pregnancy as fetal harm may occur. Although the limited data on first-trimester EFV exposure cannot rule out a 2- or 3-fold increased incidence of a rare outcome, such as neural tube defects, the available data from a meta-analysis on more than 2,000 births suggest that there is not a large increase (e.g., a 10-fold increase to a rate of 1%) in the risk of neural tube defects with first-trimester exposure. As a result, the current Perinatal Guidelines do not include a restriction of use of EFV in pregnant women or in women planning to become pregnant, consistent with both the British HIV Association and WHO guidelines for use of ARV drugs in pregnancy. EFV should be continued in pregnant women receiving a virologically suppressive EFV-based regimen, because ARV drug changes during pregnancy may be associated with loss of viral control and increased risk of perinatal transmission (see Pregnant Women Living with HIV Who are Currently Receiving Antiretroviral Therapy).</td>
</tr>
</tbody>
</table>

\(^{a}\) Individual ARV drug dosages may need to be adjusted in renal or hepatic insufficiency (for details, see Adult and Adolescent Guidelines, Appendix B, Table 7).

\(^{b}\) Placental transfer categories—Mean or median cord blood/maternal delivery plasma drug ratio:

- **High:** >0.6
- **Moderate:** 0.3–0.6
- **Low:** <0.3

\(^{c}\) See Teratogenicity for discussion of EFV and risks in pregnancy.

\(^{d}\) Only indicated for use in chronic hepatitis B virus infection in adults.

\(^{e}\) Generic formulation available

**Key to Abbreviations:** ARV = antiretroviral; AUC = area under the curve; EFV = efavirenz; FDA = Food and Drug Administration; FTC = emtricitabine; PK = pharmacokinetic; TDF = tenofovir disoproxil fumarate; WHO = World Health Organization
References


