Efavirenz (Sustiva, EFV)

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Animal Studies

Carcinogenicity

Efavirenz (EFV) was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests. A study that evaluated the genotoxicity of EFV 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.[1] Long-term animal carcinogenicity studies with EFV have been completed in mice and rats. No increase in tumor incidence above background was observed in male mice at systemic drug exposures that were approximately 1.7-fold higher than the exposures seen in humans who received standard therapeutic doses. In female mice, an increase in tumor incidence above background was seen for 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 EFV exposures that were lower than those seen in humans who received therapeutic doses.[2]

Reproduction/Fertility

EFV has had no observable effects on reproduction or fertility in rodents.[2]

Teratogenicity/Adverse Pregnancy Outcomes

An increase in fetal resorption was observed in female rats at EFV doses that produced peak plasma concentrations and area under the curve (AUC) values less than or equal to those in humans who received the recommended dose of EFV 600 mg once daily. EFV produced no reproductive toxicities when given to pregnant rabbits at doses that produced peak plasma concentrations similar to those achieved in humans who received EFV 600 mg once daily. AUC values in these rabbits were approximately half of the values seen in humans who received EFV 600 mg once daily.[2]

Central nervous system malformations and cleft palate were observed in 3 of 20 infant monkeys born to pregnant cynomolgus monkeys that received EFV between gestational day 20 and gestational day 150 at a dose of EFV 60 mg/kg per 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.[2]

A study in pregnant and lactating rats exposed to EFV found that perinatal exposure to EFV provoked cell death, significant changes in cytoarchitecture, and disturbances in serotonergic and dopaminergic innervation in the medial prefrontal cortex of adult offspring.[4]

Placental and Breast Milk Passage

EFV readily crosses the placenta in rats, rabbits, and primates, producing cord blood concentrations that are similar to the concentrations observed in maternal plasma. Maternal and fetal blood concentrations in pregnant rabbits and cynomolgus monkeys are equivalent, while fetal concentrations in rats exceeded maternal concentrations.[2]

Human Studies in Pregnancy

Pharmacokinetics/Pharmacogenomics

In an intensive sampling pharmacokinetic (PK) study of 25 pregnant women who received EFV during the third trimester, EFV clearance was slightly increased and trough levels were decreased compared with levels measured postpartum.[5] These differences are not of sufficient magnitude to warrant dose adjustment during

pregnancy. A review of this study and four others that measured EFV concentrations in pregnant women found that EFV concentrations were not significantly affected by pregnancy and that high rates of HIV RNA suppression at delivery were achieved with EFV-based regimens.[6]

In a PK study of 42 pregnant women who received EFV 600 mg once daily, EFV exposure was similar during pregnancy and postpartum. EFV PK data were available for 15 women during their second trimester, 42 women during their third trimester, and 40 women postpartum. EFV AUC during the third trimester (60 mcg•h/mL) was similar to the AUC observed in nonpregnant adults (58 mcg•h/mL). EFV drug levels in the second trimester were lower than postpartum values, but they remained within 80% to 125% of postpartum values. Viral loads at delivery were <400 copies/mL and <50 copies/mL for 96.7% and 86.7% of women, respectively.[7]

In an open-label, two-center study in the United Kingdom and Uganda, 25 pregnant women with HIV who were virally suppressed (defined as a viral load <50 copies/mL) on a regimen that included EFV 600 mg once daily had their dose reduced to EFV 400 mg in the third trimester. PK parameters, AUC, and plasma concentrations at 24 hours postdose were slightly lower in the third trimester than during the postpartum period but generally remained within the therapeutic range; all participants maintained viral suppression.[8]

A PK modeling study was conducted using pooled data from seven studies of women who were taking regimens that included EFV. The study included an analysis of 1,968 PK samples, 774 of which were collected during pregnancy. This analysis predicted that the reduced EFV dose of 400 mg would generate median EFV AUC_{24h} and C_{12h} during the third trimester that were 91% and 87%, respectively, of the values observed among nonpregnant women.[9] A more recent physiologically based pharmacokinetic (PBPK) modeling study evaluated EFV exposure in the third trimester in women with extensive, intermediate, and poor cytochrome P450 2B6 (CYP2B6) metabolism. The model predicted about a twofold increase in drug clearance in the third trimester when compared with clearance prior to pregnancy—resulting in subtherapeutic concentrations of EFV in the third trimester in 57% of extensive metabolizers. These results suggest that the recommended reduction in EFV dose from 600 mg to 400 mg may not provide therapeutic drug levels in extensive metabolizers during the third trimester and that clinical trials to evaluate the effectiveness of a 400 mg dose of EFV in the third trimester, especially in extensive metabolizers, are indicated prior to a dose adjustment in pregnancy.[10]

In a pharmacogenomics study, nonpregnant individuals with the CYP2B6 516 TT genotype had greater than threefold increases in both short-term and long-term EFV exposure, as measured by drug levels in plasma and hair. This suggests that drug levels could vary significantly with CYP2B6 polymorphisms.[11,12] The frequency of this allele varies among different ethnic populations, with a prevalence of 3.4% in white people, 6.7% in Hispanic people, and 20% in African Americans.[5]

Placental and Breast Milk Passage

In a PK study of 42 pregnant women who received EFV 600 mg once daily, EFV readily crossed the placenta, and infant elimination half-life was more than twice that of maternal participants. The cord blood-to-maternal-plasma concentration ratio was 0.67 (range 0.36–0.95). Among 23 infants for whom washout data were available, median elimination half-life was 65.6 hours (interquartile range, 40.6–129 hours). Viral loads at delivery were <400 copies/mL and <50 copies/mL for 96.7% and 86.7% of women, respectively.[7]

In a study of 25 mother–infant pairs, the median EFV cord blood-to-maternal-blood concentration ratio was 0.49 (range 0.37–0.74).[5] In a study of 13 women in Rwanda, EFV was given during the third trimester and for 6 months after delivery.[13] EFV concentrations were measured in maternal plasma, breast milk, and infant plasma. EFV concentration was significantly higher in maternal plasma than in skim breast milk (with a mean breast milk-to-maternal-plasma concentration ratio of 0.54) and higher in skim breast milk than in infant plasma (with a mean skim breast-milk-to-newborn-plasma concentration ratio of 4.08). The mean infant plasma EFV

concentration was 860 ng/mL, 13.1% of mean maternal plasma concentrations. All infants had detectable plasma concentrations of EFV, and 8 of 13 newborns had plasma EFV concentrations that were below the minimum therapeutic concentration of 1,000 ng/mL that is recommended for treatment of adults with HIV.

In a study of 51 women in Nigeria who received EFV 600 mg once daily, the median milk-to-maternal-plasma concentration ratio was 0.82 (range 0.51–1.1) and the median infant EFV concentration was 178 ng/mL (range 88–340 ng/mL).[14] In a study of 56 mother–infant pairs in which the mothers received EFV-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 EFV during pregnancy and breastfeeding, with approximately one-third of transfer occurring postpartum (40% cumulative transfer, with 15% of transfer occurring during breastfeeding).[15] All mothers and infants had detectable EFV plasma levels at 0, 8, and 12 weeks, and mean infant-to-maternal-hair concentration at 12 weeks postpartum was 0.40 for EFV. No data are currently available about the safety and PK of EFV in neonates.

Teratogenicity/Adverse Pregnancy Outcomes

In pregnancies with prospectively reported exposure to EFV-based regimens in the Antiretroviral Pregnancy Registry through January 2020, birth defects were observed in 27 of 1,142 live births with first-trimester exposure (2.4%; 95% confidence interval [CI], 1.6% to 3.4%).[16] 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 and a twofold increase in cardiovascular and genitourinary defects, the low incidence of neural tube defects (NTDs) 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 EFV exposure have documented one NTD case (0.9%), which is consistent with the expected background prevalence.[16]

In a meta-analysis of 23 studies that was designed to update the 2013 World Health Organization (WHO) guidelines for antiretroviral therapy (ART) in low- and middle-income countries, there were 44 infants with birth defects among 2,026 live births to women who received EFV during the first trimester. The pooled proportion of overall birth defects was 1.63% (95% CI, 0.78% to 2.48%).[17] The rate of overall birth defects was similar among women who received EFV-containing regimens and women who received regimens that did not contain EFV during the first trimester (pooled relative risk [RR] 0.78; 95% CI, 0.56–1.08). Across all births, one NTD (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 EFV exposures was insufficient to rule out a significant increase in low-incidence birth defects, such as NTDs. The incidence of NTDs in the general U.S. population is 0.06% to 0.07%.[18]

A French study of 13,124 live births between 1994 and 2010 included an analysis of 372 infants born after first-trimester exposure to EFV.[19] In the primary analysis, which used the European Surveillance of Congenital Anomalies and Twins (EUROCAT) classification system, no increase in the incidence of birth defects was detected among infants with first-trimester EFV exposure compared to those without exposure to EFV during pregnancy (adjusted odds ratio 1.16; 95% CI, 0.73–1.85). A secondary analysis that used the modified Metropolitan Atlanta Congenital Defect Program classification (used by the Antiretroviral Pregnancy Registry), found an association between first-trimester EFV exposure and neurologic defects, but none of the four defects that were reported during this study (ventricular dilatation with anomalies of the white substance, partial agenesis of the corpus callosum, subependymal cyst, and pachygyria) were NTDs, and none had similar embryologic origins.[20]

Recently, Zash et al. reported on the outcomes of a large birth surveillance study in Botswana. Among 7,959 deliveries to women who were taking EFV around the time of conception, there were three NTDs

(0.04%; 95% CI, 0.01% to 0.11%), which is similar to the rate of NTDs that was observed among infants born to 89,372 women without HIV (0.08%; 95% CI, 0.06% to 0.10%).[21] This study adds to available data on first-trimester EFV exposures, providing strong evidence against an elevated risk of NTDs in infants who were exposed to EFV. The South African Pregnancy Exposure Registry similarly found no association between first-trimester use of EFV-based ART regimens and congenital malformations.[22]

The Food and Drug Administration continues to advise women to avoid becoming pregnant while taking EFV and to advise health care providers to avoid administering EFV during the first trimester, because fetal harm may occur. However, the data on more than 7,900 periconception exposures to EFV from Botswana are sufficient to rule out a threefold or greater increased risk of NTDs with the use of EFV. As a result, the Perinatal Guidelines do not restrict the use of EFV during pregnancy or in women who are planning to conceive; this is consistent with the British HIV Association guidelines and WHO guidelines for use of antiretroviral (ARV) drugs in pregnancy, both of which note that EFV can be used throughout pregnancy.[23–25] EFV should be continued in pregnant women who are receiving 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 HIV transmission.[26]

A recent report from the Surveillance Monitoring for ART Toxicities (SMARTT) study of the Pediatric HIV/AIDS Cohort Study (PHACS) network detected an increased rate of microcephaly in HIV-exposed but uninfected children with *in utero* EFV exposure. The relative risk of microcephaly in infants with *in utero* EFV exposure was 2.56 (95% CI, 1.22–5.37). In this study, microcephaly was defined as a z-score of less than −2 between 6 and 36 months of age or head size below the second percentile after 36 months.[27] Only 4.7% of children had been exposed to EFV *in utero*. The relative risk of microcephaly was higher among children who had been exposed to EFV plus zidovudine and lamivudine than among those who had been exposed to EFV plus tenofovir disoproxil fumarate and emtricitabine. Children with microcephaly had lower scores on neurodevelopmental assessments at ages 1 year and 5 years and a higher rate of neurodevelopmental impairment than those without microcephaly. Additional evaluation of the association between microcephaly and *in utero* EFV exposure is needed (see the Teratogenicity section).

A study of Botswana HIV-exposed but uninfected children evaluated the association between neurodevelopmental deficits and the timing of initial *in utero* EFV exposure. Adjusted mean scores for the 126 children in the EFV-exposed group were lower than for the 367 children in the EFV-unexposed group on Bayley Scales of Infant and Toddler Development, Third Edition (BSID III) Receptive Language (21.5 vs. 22.5; $P = 0.05$); DMC Locomotor (30.7 vs. 32.0; $P < 0.01$) and Fine Motor scales (17.8 vs. 19.2; $P < 0.01$); and Profile of Social Emotional Development (PSED) (11.7 vs. 9.9; $P = 0.02$); however, scores for the first group were higher on the DMC Language scale (17.6 vs. 16.5; $P = 0.01$). Earlier (vs. later) EFV exposure was associated with lower scores on the BSID III Receptive Language scale (20.7 vs. 22.2; $P = 0.02$). Consistent with findings from other trials, HIV-exposed but uninfected children exposed *in utero* to EFV-based ART may be at higher risk for neurodevelopmental and social-emotional deficits than HIV-exposed but uninfected children exposed to non-EFV-based ART.[28] An additional prospective study of a cohort of 3,747 HIV-exposed but uninfected children found that children exposed to EFV at any time during pregnancy had a higher risk of neurodevelopmental abnormalities (adjusted relative risks [aRR] 1.53; 95% CI, 0.94–2.51). This association was stronger when comparing EFV exposure at conception to no exposure during pregnancy (aRR 1.92; 95% CI, 1.09–3.36) and considering follow-up and case diagnosis only through age 2 (aRR 2.14; 95% CI, 1.11–4.12).[29]

Safety

The Promoting Maternal and Infant Survival Everywhere (PROMISE) trial randomized ART naive antepartum and postpartum women with HIV, CD4 >350, and ALT <2.5 ULN to different ART regimens. The study found

that 2.5% of the 2,435 women randomized to EFV-based regimens developed severe hepatotoxicity, and 3% of women with severe hepatotoxicity developed liver-related mortality.[30]

Drug–Drug Interactions

PK interactions between EFV and the progestin component of some hormonal contraceptives may decrease the efficacy of emergency contraception, combined oral contraceptive pills, progestin-only pills, and progestin implants and may increase the risk of contraceptive failure.[31–35] (see Preconception Counseling and Care for Women of Childbearing Age Living with HIV and Table 3).

Excerpt from Table 10

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

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations[a]	Use in Pregnancy
Efavirenz (EFV) *Sustiva* (EFV/FTC/TDF) *Atripla* (EFV/3TC/TDF) *Symfi* (EFV/3TC/TDF) *Symfi Lo* **Note:** Generic products are available for some formulations.	**EFV (Sustiva)[d]** *Capsules:* • *50 mg* • *200 mg* *Tablet:* • *600 mg* **EFV/FTC/TDF (Atripla):** • EFV 600 mg/FTC 200 mg/TDF 300 mg tablet **EFV/3TC/TDF (Symfi):** • EFV 600 mg/3TC 300 mg/TDF 300 mg tablet **EFV/3TC/TDF (Symfi Lo):** • EFV 400 mg/3TC 300 mg/TDF 300 mg tablet	**Standard Adult Doses** *EFV (Sustiva):* • EFV 600 mg once daily at or before bedtime • Take on an empty stomach to reduce side effects. *EFV/FTC/TDF (Atripla)*: • One tablet once daily at or before bedtime • Take on an empty stomach to reduce side effects. *EFV/3TC/TDF (Symfi or Symfi Lo):* • One tablet once daily on an empty stomach and preferably at bedtime **Pregnancy** *PKs in Pregnancy:* • AUC is decreased during the third trimester compared with postpartum, but nearly all third trimester participants exceeded target exposure. *Dosing in Pregnancy:* • No change in dose is indicated.	Moderate placental transfer to fetus.[b] The FDA advises women to avoid becoming pregnant while taking EFV and advises health care providers to avoid administration during the first trimester of pregnancy, as fetal harm may occur. However, the data on more than 7,900 periconception EFV exposures from Botswana rule out a threefold or greater increased risk of NTDs. 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

		For guidance about the use of combination products in pregnancy, please see the specific sections on other components (i.e., 3TC, FTC, TDF).	in pregnant women who are on a virally 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).

[a] Individual ARV drug doses may need to be adjusted in patients with renal or hepatic insufficiency (for details, see the Adult and Adolescent Antiretroviral Guidelines, Appendix B, Table 10).
[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 product available

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

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