Efavirenz (EFV)

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Summary

- Standard adult dosing (600 mg daily) is recommended for efavirenz (EFV) in pregnancy. Reduced EFV doses (i.e., 400 mg daily) may not provide therapeutic drug levels due to the induction of cytochrome P450 2B6 (CYP2B6) during pregnancy.
- First-trimester exposure to EFV is not associated with increased risk of neural tube defects or other congenital anomalies. The Perinatal Guidelines support the use of EFV in the preconception period and during pregnancy (see Table 7).
- Newer data are concerning for increased incidence of microcephaly and neurodevelopmental delay in infants exposed to EFV *in utero*.

Human Studies in Pregnancy

Pharmacokinetics/Pharmacogenomics

A 2014 review of five pharmacokinetic (PK) studies of EFV during pregnancy found that EFV concentrations were not affected significantly by pregnancy and that high rates of HIV RNA suppression at birth were achieved with EFV-based regimens.[1] Two additional studies demonstrated commensurate pregnancy and postpartum EFV exposure. In an analysis of International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) 1026s and Pharmacokinetics of Newly Developed Antiretroviral Agents in HIV-infected Pregnant Women (PANNA) PK data from 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 area under the curve (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 birth were <400 copies/mL and <50 copies/mL for 96.7% and 86.7% of women, respectively.[2,3] A study in 19 pregnant women in Ghana similarly found that PK parameters—specifically, maximum (peak) plasma drug concentration (C_{max}), minimum plasma drug concentration (C_{min}), area under the plasma concentration-time curve from 0 to 24 hours ($AUC_{0–24h}$), and apparent clearance (CL/F)—were similar in pregnancy and postpartum. Pregnancy and postpartum geometric mean ratios for EFV C_{max}, C_{min}, $AUC_{0–24h}$, and CL/F were 1.10 (95% confidence interval [CI], 0.93–1.31), 0.88 (95% CI, 0.67–1.17), 0.84 (95% CI, 0.71–0.98), and 1.20 (95% CI, 1.02–1.40), respectively.[4]

In an open-label, two-center study in the United Kingdom and Uganda, 25 pregnant women with virally suppressed HIV (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, $AUC_{0–24h}$, 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.[5]

Although the prospective data with reduced EFV are reassuring, a PK modeling study using pooled data from seven studies of women who were taking regimens that included EFV raises significant concerns regarding the adequacy of exposure due to a variation in CYP2B6 metabolism. 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 12-hour concentrations during the third trimester that were 91% and 87% of the values observed among nonpregnant women, respectively.[6] A more recent physiologically based pharmacokinetic modeling study evaluated EFV exposure in the third trimester in women with extensive, intermediate, and poor 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.[7] 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 American people.[3] Additional modeling data suggest increased EFV clearance with cigarette smoking.[8]

Placental and Breast Milk Passage

EFV crosses the placenta and also is excreted into breast milk. Low levels of EFV are found in the serum of some breastfed infants but do not appear to affect the growth and development of breastfed infants without HIV.[9] 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 with available washout data, median elimination half-life was 65.6 hours (interquartile range, 40.6–129 hours).[2] An older study of 25 mother–infant pairs similarly found that the median EFV cord blood–to–maternal blood concentration ratio was 0.49 (range 0.37–0.74).[3]

In a study of 13 women in Rwanda, EFV was given during the third trimester and for 6 months after birth.[10] 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 less than the minimum therapeutic concentration of 1,000 ng/mL that is recommended for the treatment of adults with HIV.

In a study of 134 women in Nigeria who received EFV 600 mg once daily, the median milk-to–maternal plasma concentration ratio was 1.10 (range 0.57–1.71), and the median infant EFV concentration was 157 ng/mL (range 28.6–1360 ng/mL).[11] 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 birth 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).[12] 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.

Teratogenicity/Adverse Pregnancy Outcomes

The Antiretroviral Pregnancy Registry (APR) provides updated birth defect data for EFV and other antiretroviral (ARV) drugs twice a year through an interim report released in June and December. The APR has monitored sufficient numbers of first-trimester exposures to EFV to detect at least a 1.5-fold increase in the risk of overall birth defects and at least a twofold increase in the risk of

cardiovascular and genitourinary defects (which are the more common classes of birth defects in the general population). No such increase in the risk of birth defects has been observed with EFV. Figure 1. Summary of Birth Defects Among First Trimester Exposures in the APR interim report provides a summary of the number and prevalence of birth defects per live births among cases of first-trimester exposure to EFV and other ARV drugs reported to the APR where there are sufficient data to determine 95% CIs. The data in Figure 1 can be compared with the prevalence in the U.S. population (2.72 birth defects per 100 live births) based on the Centers for Disease Control and Prevention surveillance system (The Metropolitan Atlanta Congenital Defects Program [MACDP]) and with the Texas Birth Defects Registry ([TBDR] 5.07 per 100 live births).

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, 44 infants with birth defects among 2,026 live births to women who received EFV during the first trimester were observed. The pooled proportion of overall birth defects was 1.63% (95% CI, 0.78% to 2.48%).[13] 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 0.78; 95% CI, 0.56–1.08). Across all births, one neural tube defect (NTD) (myelomeningocele) was observed, giving a point prevalence of 0.05% (95% CI, <0.01–0.28), 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%.[14]

A contemporary French study of 13,124 live births between 1994 and 2010 included an analysis of 372 infants born after first-trimester exposure to EFV.[15] 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). Similarly, a secondary analysis that used the modified Metropolitan Atlanta Congenital Defect Program classification (used by the APR) 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.[16]

More recently, Zash et al. reported on the outcomes of a large birth surveillance study in Botswana. Among 7,959 births to women who were taking EFV around the time of conception, three NTDs were observed (0.04%; 95% CI, 0.01% to 0.11%), which is similar to the rate of NTDs observed among infants born to 89,372 women without HIV (0.08%; 95% CI, 0.06% to 0.10%).[17] 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.[18]

The U.S. 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 when planning to conceive; this is consistent with the British HIV Association guidelines and WHO guidelines for use of ARV drugs in pregnancy, both of which note that EFV can be used throughout pregnancy.[19-21] EFV should be continued in pregnancy when a virologically

suppressive, EFV-based regimen is being received because ARV drug changes during pregnancy may be associated with loss of viral control and an increased risk of perinatal HIV transmission.[22]

A 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 children who were HIV-exposed but uninfected 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. Only 4.7% of children had been exposed to EFV *in utero*.[23] 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.[23]

A study of Botswanan children who were HIV-exposed but uninfected 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 worse 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; $P = 0.05$); Developmental Milestones Checklist (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 better 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, children who were HIV-exposed but uninfected exposed *in utero* to EFV-based ART may be at higher risk for neurodevelopmental and social-emotional deficits than children who were HIV-exposed but uninfected exposed to non-EFV-based ART.[24] An additional prospective study of a cohort of 3,747 children who were HIV-exposed but uninfected found that children exposed to EFV at any time during pregnancy had a higher risk of neurodevelopmental abnormalities (adjusted relative risk 1.53; 95% CI, 0.94–2.51). This association was stronger when comparing EFV exposure at conception to no exposure during pregnancy (adjusted relative risk 1.92; 95% CI, 1.09–3.36) and considering follow-up and case diagnosis only through age 2 (adjusted relative risk 2.14; 95% CI, 1.11–4.12).[25]

Safety

The Promoting Maternal and Infant Survival Everywhere (PROMISE) trial randomized ART-naive antepartum and postpartum women with HIV, CD4 >350 cells/μL, and median alanine aminotransferase <2.5 the upper limit of normal 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.[26]

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.[27-31] (see Prepregnancy Counseling and Care and Table 3).

Animal Studies

Carcinogenicity

EFV was neither mutagenic nor clastogenic in the majority 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.[32] Long-term animal carcinogenicity studies with EFV have been completed in mice and rats. In female mice, an increase in tumor incidence was seen for hepatocellular adenomas and carcinomas and pulmonary alveolar/bronchiolar adenomas.[33]

Reproduction/Fertility

EFV has had no observable effects on reproduction or fertility in rodents.[33]

Teratogenicity/Adverse Pregnancy Outcomes

Animal data, specifically NTD in cynomolgus monkeys, set off concern for potential risk of human teratogenicity; however, the same malformations have not been observed in human fetuses. 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.[34] The malformations included anencephaly and unilateral anophthalmia in one fetus, microphthalmia in another fetus, and cleft palate in a third fetus.[33]

Additionally, an increase in fetal resorption was observed in female rats at EFV doses that produced peak plasma concentrations and AUC values less than or equal to those in humans who received the recommended dose of EFV 600 mg once daily.[33] An additional 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.[35]

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.[33]

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.[33]

Excerpt From Table 14

Note: When using fixed-dose combination (FDC) tablets, refer to other sections in Appendix B and Table 14 in the Perinatal Guidelines 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) (EFV/FTC/TDF) (EFV/3TC/TDF) *Symfi or generic* **Note:** Generic products are available for some formulations.	**EFV** *Capsules* • 50 mg • 100 mg • 200 mg *Tablet* • 600 mg **EFV/FTC/TDF** • 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** • EFV 400-mg/3TC 300-mg/TDF 300-mg tablet	**Pregnancy** *PK 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. For guidance about the use of combination products in pregnancy, please see the specific sections on other components (i.e., 3TC, FTC, TDF). **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* • One tablet once daily at or before bedtime • Take on an empty stomach to reduce side effects. *EFV/3TC/TDF (Symfi or FDC containing EFV 400-mg/3TC/TDF)* • One tablet once daily on an empty stomach and preferably at bedtime	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 because 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 during pregnancy or when 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 pregnancy when a virally suppressive, EFV-based regimen is being received because ARV drug changes during pregnancy may be associated with loss of viral control and an increased risk of perinatal transmission (see When Antiretroviral Therapy is Being Taken When Pregnancy Occurs). **Note:** Please see FDA label for full list of drugs

Excerpt From Table 14

Generic Name (Abbreviation) *Trade Name*	**Formulation**	**Dosing Recommendations**[a]	**Use in Pregnancy**
			with potential interactions and drugs for which administration with EFV is contraindicated.

[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).

[b] Placental transfer categories are determined by mean or median cord blood–to–maternal plasma drug ratio:

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

Key: 3TC = lamivudine; ARV = antiretroviral; AUC = area under the curve; EFV = efavirenz; FDA = U.S. Food and Drug Administration; FTC = emtricitabine; NTD = neural tube defect; PK = pharmacokinetics; TDF = tenofovir disoproxil fumarate; WHO = World Health Organization

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