



Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Efavirenz (EFV, Sustiva) (Last updated November 1, 2012; last reviewed November 1, 2012)

For additional information see Drugs@FDA: <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>

Formulations

Capsules: 50 mg, 200 mg

Tablets: 600 mg

Combination Tablets:

- With emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF):
FTC 200 mg + TDF 300 mg + EFV 600 mg (Atripla)

Dosing Recommendations

Neonate/infant dose:

- EFV is not approved for use in neonates/infants.

Pediatric dose:

- *Children aged <3 years:*
No data are currently available on the appropriate EFV dosage for children aged <3 years.
- *Children aged ≥3 years and body weight ≥10 kg:*
Administer EFV once daily:

Weight (kg)	EFV dose (mg)*†
10 to <15	200
15 to <20	250
20 to <25	300
25 to <32.5	350
32.5 to <40	400
≥40	600

* The dose in mg can be dispensed in any combination of capsule strengths.

† Some experts recommend a dose of 367 mg/m² of body surface area (maximum dose 600 mg) because of concern for underdosing, especially at the upper end of each weight band (see *Pediatric Use* for details).

Adolescent (body weight ≥40 kg)/adult dose:

- 600 mg once daily.

Selected Adverse Events

- Rash
- Central nervous system (CNS) symptoms such as dizziness, somnolence, insomnia, abnormal dreams, impaired concentration, psychosis, seizures
- Increased transaminases
- False-positive with some cannabinoid and benzodiazepine tests
- **Potentially** teratogenic
- Lipohypertrophy, although a causal relationship has not been established and this adverse event may be less likely than with the boosted protease inhibitors.

Special Instructions

- Administer EFV on an empty stomach, preferably at bedtime. Avoid administration with a high-fat meal because of potential for increased absorption.
- Administer Atripla on an empty stomach.
- Bedtime dosing is recommended, particularly during the first 2 to 4 weeks of therapy, to improve tolerability of CNS side effects.
- EFV should be used with caution in **female adolescents and adults with reproductive potential** because of the **potential** risk of teratogenicity.

Metabolism

- Cytochrome P450 3A4 (CYP3A4) inducer/inhibitor (more inducer than inhibitor).

Atripla

- Atripla should not be used in pediatric patients <40 kg where the EFV dose would be excessive.
- *Adult dose:* One tablet once daily
- CYP3A4 and CYP2B6 substrate.
- Dosing of EFV in patients with hepatic impairment: No recommendation is currently available; use with caution in patients with hepatic impairment.
- Adult dose of Atripla in patients with renal impairment: Because Atripla is a fixed-dose combination product, it should not be used in patients with creatinine clearance (CrCl) of <50 mL/minute or in patients on dialysis.
- Interpatient variability in EFV exposure can be explained in part by polymorphisms in CYP450 with slower metabolizers having higher risk of toxicity. (See text for information about therapeutic drug monitoring [TDM] for management of mild or moderate toxicity.)

Drug Interactions: (see also the [Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents](#)):

- *Metabolism:* Mixed inducer/inhibitor of CYP3A4 enzymes; concentrations of concomitant drugs can be increased or decreased depending on the specific enzyme pathway involved. There are multiple drug interactions. **Importantly, dosage adjustment or the addition of ritonavir may be necessary when efavirenz is used in combination with atazanavir, fosamprenavir, indinavir, lopinavir/ritonavir, or maraviroc.**
- Before efavirenz is administered, a patient's medication profile should be carefully reviewed for potential drug interactions with efavirenz.

Major Toxicities:

- *More common:* Skin rash, increased transaminase levels. Central nervous system (CNS) abnormalities, such as dizziness, somnolence, insomnia, abnormal dreams, confusion, abnormal thinking, impaired concentration, amnesia, agitation, depersonalization, hallucinations, euphoria, seizures, primarily reported in adults.
- *Rare:* Prenatal efavirenz exposure has been associated with CNS congenital abnormalities in the offspring of cynomolgus monkeys. Based on these data and retrospective reports in humans of an unusual pattern of severe CNS defects in five infants after first-trimester exposure to efavirenz-containing regimens (three meningomyelocoeles and two Dandy-Walker malformations), efavirenz has been classified as Food and Drug Administration (FDA) Pregnancy Class D, **which means that there is positive evidence of human fetal risk based on studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.** Because of the potential for teratogenicity, pregnancy should be avoided in women receiving efavirenz, and treatment with efavirenz should be avoided during the first trimester (the primary period of fetal organogenesis) whenever possible. Women of childbearing potential should undergo pregnancy testing before initiation of efavirenz and should be counseled about the potential risk to the fetus and desirability of

avoiding pregnancy. Alternate antiretroviral (ARV) regimens that do not include efavirenz should be strongly considered in women who are planning to become pregnant or who are sexually active and not using effective contraception (if such alternative regimens are acceptable to provider and patient and will not compromise the woman's health).

Resistance: The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://www.iasusa.org/resistance_mutations/index.html) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see <http://hivdb.stanford.edu/pages/GRIP/EFV.html>).

Pediatric Use: Efavirenz is FDA-approved for use as part of antiretroviral therapy in children aged 3 years or older who weigh at least 10 kg. Limited pharmacokinetic (PK) data in children younger than age 3 or who weigh less than 13 kg have shown that it is difficult to achieve target trough concentrations in this age group, even with very high (>30 mg/kg) doses of an investigational liquid formulation.¹ Thus, efavirenz is not recommended for use in children younger than age 3 years at this time, and no liquid formulation is commercially available. Additional studies are required to determine the appropriate dose of efavirenz in infants and young children. P1070 is an ongoing study collecting data on efavirenz dosing in HIV-infected and HIV/tuberculosis-co-infected children younger than age 3 years. In addition, efavirenz should be used with caution in adolescent women of childbearing age because of the **potential** risk of teratogenicity.

Efavirenz metabolism is controlled by enzymes that are polymorphically expressed and result in large interpatient variability in drug exposure. CYP2B6 is the primary enzyme for efavirenz metabolism, and pediatric patients with the 516 T/T or G/T genotype have reduced metabolism and higher efavirenz levels compared with those with the G/G genotype.^{2,3} Additional variant CYP2B6 alleles and variant CYP2A6 alleles have been found to influence efavirenz concentrations in adults.^{4,5}

Long-term HIV RNA suppression has been associated with maintenance of trough efavirenz concentrations greater than 1 mcg/mL in adults.⁶ Early HIV RNA suppression in children has also been seen with higher drug concentrations. Higher efavirenz troughs of 1.9 mcg/mL were seen in subjects with HIV RNA levels less than or equal to 400 copies/mL versus efavirenz troughs of 1.3 mcg/mL in subjects with detectable virus (>400 copies/mL).⁷ In a West African pediatric study, ANRS 12103, early reduction in viral load (by 12 weeks) was greater in children with efavirenz minimum plasma concentration (C_{\min}) levels greater than 1.1 mcg/mL or area under the curve (AUC) greater than 51 mcg*h/mL.⁸ Even with the use of FDA-approved pediatric dosing, efavirenz concentrations can be suboptimal.^{2,8-11} Therefore, some experts recommend therapeutic drug monitoring with efavirenz and possibly use of higher doses in young children, especially in select clinical situations such as virologic rebound or lack of response in an adherent patient. In one study in which the efavirenz dose was adjusted in response to measurement of the AUC, the median administered efavirenz dose was 13 mg/kg (367 mg/m²) and the range was from 3 to 23 mg/kg (69–559 mg/m²).⁷ A PK study in 20 children aged 10 to 16 years treated with the combination of lopinavir/ritonavir 300 mg/m² twice daily plus efavirenz 350 mg/m² once daily showed adequacy of the lopinavir trough values but suggested that the efavirenz trough was lower than PK targets. The authors therefore recommended that higher doses of efavirenz might be needed when these drugs are used together.¹² Therapeutic drug monitoring can be considered when using efavirenz in combinations with potentially complex drug interactions.

The toxicity profile for efavirenz differs for adults and children. A side effect commonly seen in children is rash, which was reported in up to 40% of children compared with 27% of adults. The rash is usually maculopapular, pruritic, and mild to moderate in severity and rarely requires drug discontinuation. Onset

is typically during the first 2 weeks of treatment.¹³ Although severe rash and Stevens-Johnson syndrome (SJS) have been reported, they are rare. In adults, CNS symptoms have been reported in more than 50% of patients.¹⁴ These symptoms usually occur early in treatment and rarely require drug discontinuation, but they can sometimes occur or persist for months. Bedtime efavirenz dosing appears to decrease the occurrence and severity of these neuropsychiatric side effects. **Ensuring that efavirenz is taken on an empty stomach also reduces the occurrence of neuropsychiatric adverse effects.** In several studies, the incidence of such adverse effects was correlated with efavirenz plasma concentrations and the symptoms occurred more frequently in patients receiving higher concentrations.^{6, 15-18} In patients with pre-existing psychiatric conditions, efavirenz should be used cautiously for initial therapy. Adverse CNS effects occurred in 14% of children receiving efavirenz in clinical studies¹³ and in 30% of children with efavirenz concentrations greater than 4 mcg/mL.³ CNS adverse effects may be harder to detect in children because of the difficulty in assessing neurologic symptoms such as impaired concentration, sleep disturbances, or behavior disorders in these patients.

Therapeutic drug monitoring (TDM) can be considered for children with mild or moderate toxicity possibly attributable to a particular ARV agent (see [Role of Therapeutic Drug Monitoring in Management of Treatment Failure](#)). In that situation, it is reasonable for a clinician to use therapeutic drug monitoring to determine whether the toxicity is due to an efavirenz concentration in excess of the normal therapeutic range.^{19, 20} This is the only setting in which dose reduction would be considered appropriate management of drug toxicity and, even then, it should be used with caution.

Efavirenz should not be used by women who desire to become pregnant or who do not use effective, consistent contraception. Efavirenz should not be used throughout the first trimester of pregnancy because of the potential risk of teratogenicity²¹ (see [Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States](#)²²). Alternative ARV regimens **that do not include efavirenz should be strongly considered** for use in sexually active adolescent females because of the potential for **inconsistent** use of contraception and the high risk of unintended pregnancy.

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