



Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Efavirenz (EFV, Sustiva) (Last updated April 27, 2017; last reviewed April 27, 2017)

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

Formulations

Capsules: 50 mg, 200 mg

Tablets: 600 mg

Fixed-Dose Combination Tablets:

- [Atripla] Efavirenz 600 mg plus emtricitabine 200 mg plus tenofovir disoproxil fumarate (TDF) 300 mg

Dosing Recommendations

Neonatal Dose:

- Efavirenz is not approved for use in neonates.

Pediatric Dose:

Infants and Children Aged 3 Months to <3 Years and Weighing ≥ 3 kg:

- The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) recommends that efavirenz generally not be used in children aged 3 months to <3 years. If use of efavirenz is unavoidable due to the clinical situation, the Panel suggests the use of investigational doses of efavirenz in this age group. See text for investigational dosing tables; evaluation of CYP 2B6 genotype is required prior to use. Therapeutic drug monitoring should be considered with an efavirenz plasma concentration measured 2 weeks after initiation; some experts would also measure at age 3 years after making the transition to the new dose (see text under therapeutic drug monitoring at the bottom of this section). For dose adjustment based on efavirenz concentrations, consultation with an expert is recommended.

Children Aged ≥ 3 Years and Weighing ≥ 10 kg:

Note: See Tables 1a and 1b in text for recommended dosing if EFV must be used in children aged <3 years

Selected Adverse Events

- Rash, which is generally mild and transient, and appears to be more common in children than in adults
- Central nervous system symptoms such as fatigue, poor sleeping patterns, vivid dreams, impaired concentration, agitation, seizures, depression, suicidal ideation
- False-positive with some cannabinoid and benzodiazepine tests
- Gynecomastia
- Hepatotoxicity
- QTc prolongation has been observed with the use of efavirenz. Consider alternatives to efavirenz when co-administered with a drug with known risk of *Torsades de Pointes* or when administered to patients at higher risk of *Torsades de Pointes*

Special Instructions

- Efavirenz can be swallowed as a whole capsule or tablet or administered by sprinkling the contents of an opened capsule on food as described below.
- Administer whole capsule or tablet of Atripla on an empty stomach. Avoid administration with a high-fat meal because of potential for increased absorption.
- Bedtime dosing is recommended, particularly during the first 2 to 4 weeks of therapy, to improve tolerability of central nervous system side effects.
- Efavirenz should be used with caution in female adolescents and adults with reproductive potential because of the potential risk of teratogenicity.

Administer Efavirenz Once Daily

Weight (kg)	Efavirenz Dose (mg) ^{a,b}
10 kg to <15 kg	200 mg
15 kg to <20 kg	250 mg
20 kg to <25 kg	300 mg
25 kg to <32.5 kg	350 mg
32.5 kg to <40 kg	400 mg
≥40 kg	600 mg

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

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

Adolescent (Weighing ≥40 kg) and Adult Dose:

- 600 mg once daily

[Atripla] Efavirenz plus Emtricitabine plus TDF

- Atripla should not be used in pediatric patients <40 kg as the efavirenz dose of 600 mg would be excessive.

Adult Dose:

- One tablet once daily

Instructions for Use of Capsule as a Sprinkle Preparation with Food or Formula:

- Hold capsule horizontally over a small container and carefully twist to open to avoid spillage.
- Gently mix capsule contents with 1–2 teaspoons of an age-appropriate soft food (e.g., applesauce, grape jelly, yogurt), or reconstituted infant formula at room temperature.
- Administer infant formula mixture using a 10-mL syringe.
- After administration, an additional 2 teaspoons of food or infant formula must be added to the container, stirred, and dispensed to the patient.
- Administer within 30 minutes of mixing and do not consume additional food or formula for 2 hours after administration.

Metabolism/Elimination

- Cytochrome P450 3A (CYP3A) and CYP2B6 inducer *in vivo* and CYP2C9, 2C19, and 3A4 isozyme inhibitor *in vitro*.
- Dosing of efavirenz 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 and TDF and emtricitabine require dose adjustment based on renal function, Atripla should not be used in patients with creatinine clearance <50 mL/minute or in patients on dialysis.
- Interpatient variability in efavirenz exposure can be explained in part by polymorphisms in CYP450 with slower metabolizers at higher risk of toxicity (see text for information about therapeutic drug monitoring 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](#) and <http://www.hiv-druginteractions.org/>)

- **Metabolism:** Co-administration of efavirenz with drugs primarily metabolized by CYP2C9, CYP2C19, CYP2B6, or CYP3A isozymes may result in altered plasma concentrations of the co-administered drugs. Drugs that induce CYP3A and CYP2B6 activity would be expected to increase the clearance of efavirenz resulting in lower plasma concentrations. 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, ritonavir-boosted lopinavir (LPV/r), or maraviroc.
- Before efavirenz is administered, a patient's medication profile should be carefully reviewed for potential drug interactions with efavirenz.

- QTc prolongation has been observed with the use of efavirenz.^{1,2} Consider alternatives to efavirenz when coadministered with a drug with known risk of *Torsades de Pointes* or when administered to patients at higher risk of *Torsades de Pointes*.

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:* QTc prolongation has been observed with the use of efavirenz.^{1,2} A case report associated efavirenz use with marked QT prolongation and *Torsades de Pointes*.³ An association between efavirenz and suicidal ideation, suicide, and attempted suicide (especially among those with a history of mental illness or substance abuse) was found in one retrospective analysis of four comparative trials in adults. This association, however, was not found in analyses of two large observational cohorts.
- *Potential risk of teratogenicity:* For discussion, see Pediatric Use section below; see also [Efavirenz](#) in the [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](#) (Perinatal Guidelines).

Resistance

The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://iasusa.org/sites/default/files/tam/october_november_2015.pdf#page=10) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see <http://hivdb.stanford.edu/DR/>).

Pediatric Use

Approval

Efavirenz is Food and Drug Administration (FDA)-approved for use as part of antiretroviral therapy in children aged ≥ 3 months who weigh at least 3.5 kg.

Efficacy in Clinical Trials

In clinical trials in adults and children with HIV, efavirenz in combination with 2 nucleoside reverse transcriptase inhibitors (NRTIs) has been associated with excellent virologic response.

- Efavirenz-based regimens have proven virologically superior or non-inferior to a variety of regimens in adults including those containing LPV/r, nevirapine, rilpivirine, atazanavir, elvitegravir, raltegravir, and maraviroc.⁴⁻¹⁰
- Efavirenz proved inferior to dolutegravir in the SINGLE trial in adults, which compared virologic response of dolutegravir in combination with abacavir and lamivudine to efavirenz combined with tenofovir disoproxil fumarate and emtricitabine at weeks 48 and 144. The differences were most likely due to more drug discontinuations in the efavirenz group.¹¹
- Efavirenz in combination with two NRTIs or with a NRTI and a protease inhibitor has been studied in children with virologic potency and safety comparable to what is seen in adults.¹²⁻¹⁸

Pharmacokinetics: Pharmacogenomics

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 CYP 2B6 516 T/T genotype (which has an allele frequency of 20% in African Americans) have reduced metabolism resulting in higher efavirenz levels compared with those with the G/G or G/T genotype.¹⁹⁻²² IMPAACT P1070 has shown that aggressive dosing with approximately 40 mg/

kg using opened capsules resulted in therapeutic efavirenz concentrations in 68% of children aged <3 years with G/G or G/T genotype but excessive exposure in those with T/T genotype.²¹ Optimal dosing may require pretreatment CYP2B6 genotyping in children aged <3 years (see discussion below).^{21,23} Additional variant CYP2B6 alleles and variant CYP2A6 alleles have been found to influence efavirenz concentrations in adults and children.²⁴⁻²⁸

Pharmacokinetics and Dosing: Infants and Children Aged <3 Years

The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) **recommends that efavirenz generally not be used in children aged 3 months to <3 years.** Limited pharmacokinetic (PK) data in children aged <3 years or weighing <13 kg have shown that it is difficult to achieve target trough concentrations in this age group.^{21,29} Hepatic enzyme activity is known to change with age. Using a pharmacometric model, the increase in oral clearance of efavirenz as a function of age is predicted to reach 90% of mature value by age 9 months.²² This maturation of oral clearance is postulated to result from an increase in the expression of CYP 2B6 with age.²² CYP 2B6-516-G/G genotype is associated with the greatest expression of hepatic CYP 2B6 when compared with the CYP 2B6-516-G/T or -T/T genotype.¹⁹ In children with CYP 2B6-516-G/G genotype, the oral clearance rate has been shown to be higher in children aged <5 years than in older children.¹⁹ Efficacy data for opened capsules with contents used as sprinkles suggest acceptable palatability and bioavailability for infants and children aged <3 years. IMPAACT study P1070, an ongoing study of children with HIV and HIV/tuberculosis coinfection aged <3 years, using efavirenz dosed by weight band based on CYP2B6 GG/GT versus T/T genotype (see Tables 1a and 1b below), resulted in HIV RNA <400 copies/mL in 61% by intent to treat analysis at 24 weeks.²¹ When used without regard to genotype, doses higher than the FDA-approved doses resulted in therapeutic efavirenz concentrations in an increased proportion of study participants with G/G or G/T genotypes but excessive exposure in a high proportion of those with T/T genotypes.²¹ Therefore, dosing tables have been modified so that infants and young children with T/T genotype will receive a reduced dose. Additional subjects will be studied to confirm that this dose is appropriate for this subset of patients. The modified doses listed in Tables 1a and 1b are under investigation.

Investigational Dosing for Children Aged 3 Months to <3 Years Based on CYP 2B6 Genotype

Table 1a. Protocol P1070 Dosing for Patients with CYP 2B6 516 GG and GT Genotypes (Extensive Metabolizers [EM])^a

Weight (kg)	Efavirenz Dose (mg)
3 kg to <5 kg	200 mg
5 kg to <7 kg	300 mg
7 kg to <14 kg	400 mg
14 kg to <17 kg	500 mg
≥17 kg	600 mg

Table 1b. Protocol P1070 Dosing for Patients with CYP 2B6 516 TT Genotype (Slow Metabolizers [SM])^a

Weight (kg)	Efavirenz Dose (mg)
3 kg to <7 kg	50 mg
7 kg to <14 kg	100 mg
14 kg to <17 kg	150 mg
≥17 kg	150 mg

^a Investigational doses are based on IMPAACT study P1070.²¹ Evaluation of CYP 2B6 genotype is required. Therapeutic drug level monitoring is recommended with a trough measured 2 weeks after initiation and at age 3 years for possible dose adjustment.

The FDA has approved efavirenz for use in infants and children aged 3 months to <3 years at doses derived from a population PK model based on data from older subjects in PACTG 1021 and PACTG 382, and AI266-922, which is a study assessing the PK, safety, and efficacy of capsule sprinkles in children aged 3 months to 6 years (see Table 2).

Table 2: FDA-Approved Dosing for Children Aged 3 Months to <3 Years (Without Regard to CYP 2B6 Genotype)

Weight (kg)	Efavirenz Dose (mg)
3.5 kg to <5 kg	100 mg
5 kg to <7.5 kg	150 mg
7.5 kg to <15 kg	200 mg
15 kg to <20 kg	250 mg

The FDA-approved doses are lower than the CYP 2B6 extensive metabolizer doses and higher than the CYP 2B6 slow metabolizer doses currently under study in P1070. Further studies are needed to determine if the FDA dosing can achieve therapeutic levels for the group aged 3 months to 3 years. There is concern that FDA-approved doses may result in frequent under-dosing in CYP 2B6 extensive metabolizers. Estimates of efavirenz area under the curve (AUC) for FDA dosing using P1070 data are given in Table 3.²³ Estimates were calculated as follows: P1070 observed AUC X (FDA dose/P1070 CYP 2B6 genotype-directed study dose). A high initial dose of efavirenz in the first version of the P1070 protocol was used to produce a target AUC of 35 to 180 mcg*h/mL, a systemic exposure similar to that shown to be safe and effective in older children and adults.²³ Estimates indicate that FDA-recommended doses of efavirenz will produce excessive efavirenz AUCs in 67% of slow metabolizer (SM) and sub-therapeutic AUCs in 33% of extensive metabolizer (EM) children aged <3 years, whereas CYP 2B6 genotype-directed dosing resulted in achievement of target AUCs in 83% of EM children and 89% of SM children.

Table 3: Estimated Efavirenz AUC for FDA Dosing Compared with AUC for P1070 Dosing^a

Metabolizer Phenotype	Median AUC (mcg*h/mL) [95% CI]	Number with Estimated Plasma AUC <35 mcg*h/mL	Number with Estimated Plasma AUC 35–180 mcg*h/mL	Number with Estimated Plasma AUC >180 mcg*h/mL
EM (CYP2B6 516 GG/GT) n = 30				
P1070 Dosing ^b	105.6 [58.5, 129.6]	4 (13%)	25 (83%)	1 (3%)
FDA Dosing ^c	52.8 [29.4, 64.8]	10 (33%)	19 (63%)	1 (3%)
SM (CYP2B6 516 TT) n = 9				
P1070 Dosing ^b	122.6 [93.2, 162.6]	0 (0%)	8 (89%)	1 (11%)
FDA Dosing ^c	245.1 [162.2, 325.1]	0 (0%)	3 (33%)	6 (67%)

^a Moore CB, et al. Abstract 903. Presented at: 20th Conference on Retroviruses and Opportunistic Infections (CROI). 2014. Boston, MA

^b Observed values

^c Predicted values

Key to Acronyms: AUC = area under the curve; CYP = cytochrome P450; EM = extensive metabolizer; FDA = Food and Drug Administration; SM = slow metabolizer

The Panel recommends that efavirenz generally not be used in children aged 3 months to <3 years. If the clinical situation demands use of efavirenz, Panel members recommend determining CYP2B6 genotype (a list of laboratories performing this testing is available at <http://www.ncbi.nlm.nih.gov/gtr/labs>). Patients should be classified as extensive CYP 2B6 516 G/G and G/T genotypes versus slow CYP 2B6 516 T/T genotype metabolizers to guide dosing as indicated by the investigational doses from IMPAAT study P1070 (see Tables 1a and 1b). Whether the doses used are investigational or FDA-approved, measuring efavirenz plasma concentrations should be considered 2 weeks post-initiation (see Role of Therapeutic Drug Monitoring). For dose adjustment, consultation with an expert is recommended. In addition, when dosing following the P1070 investigational dose recommendations, some experts would measure efavirenz concentrations at age 3 years before making the transition to the new dose.

Pharmacokinetics: Children Aged ≥ 3 Years and Adolescents

Long-term HIV RNA suppression has been associated with a mid-dosing interval concentration (C_{12}) of efavirenz of >1 mg/L in adults³⁰ although some question whether use of a single target value is valid, especially in adherent patients.³¹ Early HIV RNA suppression in children has also been seen with higher drug concentrations. Higher efavirenz troughs of 1.9 mg/L were seen in children with HIV RNA levels ≤ 400 copies/mL versus efavirenz troughs of 1.3 mg/L in children with detectable virus (>400 copies/mL).³² 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 >1.1 mg/L or AUC >51 mcg*h/mL.³³

Even with the use of FDA-approved pediatric dosing in children aged ≥ 3 years, efavirenz concentrations can be suboptimal.^{19,33-37} Therefore, some experts recommend therapeutic drug monitoring (TDM) with efavirenz and possible 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).³² A PK study in 20 children aged 10 to 16 years treated with LPV/r 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 values were lower than PK targets. The authors therefore recommended that higher doses of efavirenz might be needed when these drugs are used together.³⁸

Toxicity: Children versus Adults

The toxicity profile for efavirenz differs for adults and children. One adverse effect (AE) 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, mild to moderate in severity, and rarely requires drug discontinuation. Onset is typically during the first 2 weeks of treatment. Although severe rash and Stevens-Johnson syndrome have been reported, they are rare. In adults, CNS symptoms are commonly reported, affecting 29.6% of patients in 1 meta-analysis of randomized trials.³⁹ 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. For patients who can swallow capsules or tablets, ensuring that efavirenz is taken on an empty stomach also reduces the occurrence of neuropsychiatric AEs. The ENCORE1 study in adults demonstrated that a dose of 400 mg of efavirenz is associated with fewer AEs but non-inferior virologic response when compared with the recommended 600-mg dose of efavirenz in adults. Despite these findings, a reduction in efavirenz dose in adults is not recommended as part of initial treatment.^{40,41} An association between efavirenz and suicidal ideation, suicide, and attempted suicide (especially among those with a history of mental illness or substance abuse) was found in a retrospective analysis of four comparative trials in adults and in the START Trial, a prospective analysis of adults.^{42,43} This association, however, was not found in analyses of 2 large observational cohorts^{44,45} and no cases of suicide were reported in a systematic review of randomized trials.³⁹ In several studies, the incidence of neuropsychiatric AEs was correlated with efavirenz plasma concentrations and the symptoms occurred more frequently in patients with higher concentrations.^{30,46-49} In patients with pre-existing psychiatric conditions, efavirenz should be used cautiously. Adverse CNS AEs occurred in 14% of children receiving efavirenz in clinical studies⁵⁰ and in 30% of children with efavirenz concentrations greater than 4 mcg/mL.²⁰ CNS AEs 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.

Toxicity: QTc prolongation

CYP2B6 genetic variants are known to slow efavirenz clearance. The CYP2B6*6 allele is associated with reduced clearance and increased efavirenz-induced CNS toxicity, hepatic injury and treatment discontinuation.^{30,46} Homozygous carriers of the CYP2B6*6 allele (CYP2B6*6/*6) may be at increased risk for efavirenz-induced rate corrected QT (QTc) prolongation. The CYP2B6*6 allele codes for the CYP2B6 516 G>T complementary DNA nucleotide change.⁵¹ The effect of efavirenz on the QTc interval was

evaluated in a study in 58 healthy adult subjects enriched for CYP2B6 polymorphisms. A positive relationship between efavirenz concentration and QTc prolongation was observed. The mean QTc prolongation and its upper bound 90% confidence interval are 8.7 ms and 11.3 ms in subjects with CYP2B6*6/*6 genotype following the administration of a 600-mg daily dose for 14 days.¹ Drugs that prolong the mean QTc interval by more than 20 ms have a substantially increased likelihood of being pro-arrhythmic. While the data on drugs that prolong the mean QTc interval by more than 5 ms but less than 20 ms are inconclusive, some of these drugs have been associated with pro-arrhythmic risk.⁵² Alternatives to efavirenz should be considered when coadministered with a drug with known risk of *Torsades de Pointes*, for example quinidine or clarithromycin, or when administered to patients at higher risk of *Torsades de Pointes*.²

Toxicity: Potential Risk of Teratogenicity

In prior Perinatal Guidelines, efavirenz use was not recommended before 8 weeks' gestational age, because of concerns regarding potential teratogenicity. Although this caution remains in the package insert, a large meta-analysis has been reassuring that risks of neural tube defects after first-trimester efavirenz exposure are not greater than those in the general population.^{2,53} As a result, the current Perinatal Guidelines do not include the restriction of use before 8 weeks' gestation, consistent with both the British HIV Association and World Health Organization guidelines for use of ARV drugs in pregnancy (which note that efavirenz can be used throughout pregnancy).^{54,55} Importantly, women who become pregnant on suppressive efavirenz-containing regimens should continue their current regimens.

For a comprehensive discussion, see [Efavirenz](#) in [Appendix B](#) of the [Perinatal Guidelines](#).⁵⁶

Therapeutic Drug Monitoring

Note: See [Role of Therapeutic Drug Monitoring](#) section.

In the setting of potential toxicity, it is reasonable for a clinician to use TDM to determine whether the toxicity is due to an efavirenz concentration in excess of the normal therapeutic range.^{57,58} Dose reduction would be considered appropriate management of drug toxicity; however, dose reduction should be used with caution. Also, TDM **should be considered** when dosing efavirenz in children aged 3 months to <3 years due **to increased clearance and** variable PK properties in this young age group. An efavirenz concentration, measured 2 weeks after initiation, and consultation with an expert, **should be considered** for dose adjustment. **In addition**, some experts would measure efavirenz concentrations at age 3 years after making the transition to the new dose if dosing was initiated at age <3 years using investigational dose recommendations. The currently accepted minimum effective concentration of efavirenz is a mid-dose concentration (C_{12}) greater than 1 mg/L in adults and concentrations >4.0 mg/L are associated with CNS side effects.³⁰ A recent study in children showed that a higher proportion of children with a C_{12} <1 mg/L had evidence of viral replication compared to those with a C_{12} >1 mg/L.⁵⁹ However, the validity of use of a single target has been called into question.³¹ In addition, a lower limit C_{12} >0.7mg/L was most predictive of virologic outcome in a study of 180 adults.⁶⁰

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