



Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Efavirenz (EFV, Sustiva) (Last updated April 16, 2019; last reviewed April 16, 2019)

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

Formulations

Capsules: 50 mg, 200 mg

Tablet: 600 mg

Generic Formulations:

- 50 mg capsules
- 200 mg capsules
- 600 mg tablets

Fixed-Dose Combination Tablets:

- [Atripla *and* Generic] Efavirenz 600 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate (TDF) 300 mg
- [Symfi] Efavirenz 600 mg/lamivudine 300 mg/TDF 300 mg
- [Symfi Lo] Efavirenz 400 mg/lamivudine 300 mg/TDF 300 mg

Dosing Recommendations

Neonatal Dose:

- Efavirenz is not approved for use in neonates.

Pediatric Dose

- Efavirenz capsules can be opened and the contents used as a sprinkle preparation for infants and children who are unable to swallow capsules.

Infants and Children Aged 3 Months to <3 Years and Weighing ≥ 3.5 kg:

- The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) **does not recommend** the use of efavirenz in children aged 3 months to <3 years due to highly variable pharmacokinetics in this age group.
- **Note:** If the use of efavirenz is unavoidable due to a clinical situation, the Panel suggests using investigational doses of efavirenz in this age group (see investigational dosing [Table A](#) in the Pharmacokinetics and Dosing: Infants and Children Aged <3 Years section below). Evaluation of cytochrome P450 (CYP) 2B6 genotype is required prior to use in this age group. Therapeutic drug monitoring (TDM) should be used and efavirenz plasma concentration should be measured 2 weeks after initiation. If a child initiated efavirenz at an investigational dose while <3 years of age, some experts would also measure plasma

Selected Adverse Events

- Rash, which is generally mild and transient and appears to be more common in children than in adults
- Central nervous system (CNS) symptoms such as fatigue, poor sleeping patterns, insomnia, vivid dreams, impaired concentration, agitation, seizures, depression, suicidal ideation
- Use of efavirenz may produce false-positive results with some cannabinoid and benzodiazepine tests
- Gynecomastia
- Hepatotoxicity
- Corrected QT prolongation

Special Instructions

- Efavirenz can be swallowed as a whole capsule/tablet or administered by sprinkling the contents of an opened capsule on food as described below.
- Bedtime dosing is recommended, particularly during the first 2 to 4 weeks of therapy, to improve tolerability of CNS side effects.
- Administer efavirenz, Atripla, **Symfi**, or Symfi Lo on an empty stomach. Avoid administration with a high-fat meal, because this has the potential to increase absorption.
- When using fixed-dose combination (FDC) tablets, see other drug sections in the

concentration at age 3 years after the child transitions to the recommended dose for children aged ≥ 3 years (see the Therapeutic Drug Monitoring section in the text below). When making a dose adjustment based on efavirenz concentrations, consultation with an **expert in pediatric HIV infection** is recommended.

Children Aged ≥ 3 Years and Weighing ≥ 10 kg:

Once-Daily Doses of Efavirenz by Weight

Weight	Efavirenz Dose ^{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. Capsules may be administered by sprinkling the contents onto an age-appropriate food (see Special Instructions).

^b Some experts recommend a dose of efavirenz 367 mg/m² body surface area (maximum dose 600 mg) due to concerns about underdosing at the upper end of each weight band (see Pediatric Use in text below for details). Weight bands approximate a dose of efavirenz 367 mg/m², with a maximum dose of 600 mg.

Child and Adolescent (Weighing ≥ 40 kg) and Adult Dose:

- Efavirenz 600 mg once daily

[Atripla] Efavirenz 600 mg/Emtricitabine/TDF

Child and Adolescent (Weighing ≥ 40 kg) and Adult Dose:

- One tablet once daily
- Take on an empty stomach

[Symfi] Efavirenz 600 mg/Lamivudine/TDF

Child and Adolescent (Weighing ≥ 40 kg) and Adult Dose:

- One tablet once daily
- Take on an empty stomach

[Symfi Lo] Efavirenz 400 mg/Lamivudine/TDF

Child and Adolescent (Weighing ≥ 35 kg) and Adult Dose:

- One tablet once daily
- Take on an empty stomach

[Drug Appendix](#) for special instructions and additional information about the individual drug components.

- The Food and Drug Administration cautions that efavirenz should not be used during the first trimester of pregnancy because of potential teratogenicity. However, after a review of updated evidence regarding teratogenicity risks, the [Perinatal Guidelines](#) do not restrict use of efavirenz in female adolescents and adults who are pregnant or may become pregnant.

Instructions for Use of Efavirenz 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 to 2 teaspoons of an age-appropriate soft food (e.g., applesauce, grape jelly, yogurt) or reconstituted infant formula at room temperature.
- Administer within 30 minutes of mixing and do not consume additional food or formula for 2 hours after administration.

Metabolism/Elimination

- **CYP2B6 is the primary enzyme for efavirenz metabolism.**
- Cytochrome P450 (CYP) 3A and CYP2B6 inducer *in vivo* and CYP2C9, 2C19, and 3A4 isozyme inhibitor *in vitro*.
- Efavirenz **is not recommended** for patients with moderate or severe hepatic impairment.
- Interpatient variability in efavirenz exposure can be explained in part by polymorphisms in CYP450, with slower metabolizers at higher risk of toxicity (see [Therapeutic Drug Monitoring](#) in the text below for information about the management of mild or moderate toxicity).

Atripla, Symfi, and Symfi Lo Dosing in Adults with Renal Impairment:

- Because these are FDC products and TDF, **lamivudine**, and emtricitabine require dose adjustments based on renal function, Atripla, **Symfi**, and Symfi Lo should not be used in patients with creatinine clearance <50 mL/min or in patients on dialysis.

Note: Symfi Lo has not been studied in children (sexual maturity rating [SMR] 1–3), and major inter-individual variability in efavirenz plasma concentrations has been found in pediatric patients in a multiethnic setting. The 400 mg dose of efavirenz may be too low in children or adolescents with SMRs 1 to 3 who weigh ≥ 40 kg. TDM is suggested by some Panel members when Symfi Lo is used in pediatric patients who weigh ≥ 40 kg.

Drug Interactions (see also the [Adult and Adolescent Antiretroviral Guidelines](#) and [HIV Drug Interaction Checker](#))

- **Metabolism:** Coadministration of efavirenz with drugs primarily metabolized by cytochrome P450 (CYP) 2C9, CYP2C19, CYP2B6, or CYP3A isozymes may result in altered plasma concentrations of the coadministered drugs. Drugs that induce CYP3A and CYP2B6 activity would be expected to increase the clearance of efavirenz, resulting in lower plasma concentrations. There is potential for multiple drug interactions with efavirenz. Importantly, dose adjustment or the addition of ritonavir may be necessary when efavirenz is used in combination with atazanavir, fosamprenavir, lopinavir/ritonavir (LPV/r), or maraviroc.
- Before efavirenz is administered, a patient's medication profile should be carefully reviewed for potential drug interactions with efavirenz.
- Corrected QT (QTc) prolongation has been observed with the use of efavirenz.^{1,2} Consider using an alternative to efavirenz in patients who are receiving a drug that has a known risk of Torsades de Pointes or in patients who are 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, and seizures have been reported, primarily 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:** See [Efavirenz](#) in the [Perinatal Guidelines](#).

Resistance

The International Antiviral Society-USA (IAS-USA) maintains a [list of updated resistance mutations](#) and the [Stanford University HIV Drug Resistance Database](#) offers a discussion of each mutation.

Pediatric Use

Approval

Efavirenz has been approved by the Food and Drug Administration (FDA) for use as part of antiretroviral (ARV) therapy in children aged ≥ 3 months and weighing ≥ 3.5 kg. The FDA has also approved the use of

Symfi Lo, the fixed-dose combination of efavirenz 400 mg/lamivudine 300 mg/tenofovir disoproxil fumarate (TDF) 300 mg, in children weighing ≥ 35 kg.

Efficacy in Clinical Trials

Efavirenz-based regimens have proven virologically superior or noninferior 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 the virologic response of dolutegravir plus abacavir/lamivudine to the virologic response of efavirenz/TDF/emtricitabine at Weeks 48 and 144. The differences were most likely due to more drug discontinuations in the efavirenz group.¹¹

In clinical trials in adults and children with HIV, efavirenz used in combination with two nucleoside reverse transcriptase inhibitors (NRTIs) has been associated with excellent virologic response. **FDA approval of Symfi (efavirenz 600 mg/lamivudine/TDF) was based on the results from a clinical trial that compared the use of TDF to the use of stavudine when each drug was administered with lamivudine and efavirenz.**¹² **This trial showed that these regimens were similarly effective.** The 96-week results of the Encore I trial, a randomized trial in adults, showed that efavirenz 400 mg used in combination with TDF and emtricitabine was noninferior to efavirenz 600 mg used in combination with TDF and emtricitabine.¹³ Efavirenz used in combination with two NRTIs or with an NRTI and a protease inhibitor has been studied in children and has shown virologic potency and safety that is comparable to what has been seen in adults.¹⁴⁻²⁰

FDA approval of Symfi Lo (efavirenz 400 mg/lamivudine 300 mg/TDF 300 mg) was based on a comparison between efavirenz 400 mg and efavirenz 600 mg, both taken with emtricitabine 200 mg plus TDF 300 mg in 630 ARV-naïve adult participants with a mean age of 36 years (range 18–69 years). Sixty-eight percent of participants were male, 37% were of African heritage, 33% were of Asian ethnicity, 17% were Hispanic, and 13% were Caucasian. This study showed similar rates of viral load suppression and toxicities among participants in each group.¹³ **Since efavirenz clearance is related to age and to CYP2B6 polymorphisms, and since allele frequency varies by ethnicity, some members of the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) recommend caution when using the lower-dose efavirenz formulation in pediatric patients weighing ≥ 40 kg and suggest the use of therapeutic drug monitoring (TDM) in these patients.**

Pharmacokinetics: Pharmacogenomics

Genetic polymorphisms in the genes that code for enzymes involved in the metabolism of efavirenz may alter enzyme activity, which causes a high degree of interpatient variability in drug exposure. CYP2B6 is the primary enzyme for efavirenz metabolism, and pediatric patients with the CYP2B6-516-T/T genotype have reduced metabolism, resulting in higher efavirenz levels in these patients than in those with the G/G or G/T genotypes.²¹⁻²⁵ **The CYP2B6-516-T/T allele frequency varies by ethnicity. In a study of adults from the United States and Italy, this allele had a frequency of 24.4% among white study participants, a frequency of 31.3% among black study participants, and a frequency of 34.9% among Hispanic study participants.**²⁶ **A retrospective study confirmed the inter-individual variability of efavirenz plasma concentration among pediatric patients in a multi-ethnic, high-income setting, and the differences could be explained in large part by polymorphisms in drug metabolizing genes as well as by age at treatment initiation and time from treatment initiation.**²⁷ IMPAACT P1070 has shown that aggressive dosing with approximately 40 mg/kg of efavirenz using opened capsules resulted in therapeutic efavirenz concentrations in 58% of children aged < 3 years with the G/G or G/T genotypes, but excessive exposure occurred in those with the T/T genotype.²⁸ Optimal dosing may require pretreatment CYP2B6 genotyping in children aged < 3 years (see discussion below).^{25,28} Additional variant CYP2B6 alleles and variant CYP2A6 alleles have been found to influence efavirenz concentrations in adults and children.^{25,29-33} The CYP2B6 T983C mutation has also been associated with reduced efavirenz clearance in African children.²⁵

Pharmacokinetics and Dosing: Infants and Children Aged <3 Years

The Panel **does not recommend** the use of efavirenz 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.^{23,34} These data show age-related differences in absorption and impact of formulation on efavirenz PKs.²⁴ Also, 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.²⁴ This maturation of oral clearance is postulated to result from an increase in the expression of CYP2B6 with age.²⁴ The CYP2B6-516-G/G genotype is associated with the greatest expression of hepatic CYP2B6 when compared with the CYP2B6-516-G/T or -T/T genotypes.²¹ In children with the CYP2B6-516-G/G genotype, the oral clearance rate of efavirenz has been shown to be higher in children aged <5 years than in older children.²¹ Efficacy data for opened capsules with contents used as a sprinkle preparation suggest acceptable palatability and bioavailability for infants and children aged <3 years; however, the difficulty associated with sprinkling the contents of opened capsules contributes to the variability of PK measures in this age group.

IMPAACT P1070 studied children aged <3 years with HIV and HIV/tuberculosis coinfection, using doses of efavirenz that were determined by weight band based on CYP2B6-516-G/G and -G/T **genotypes (children with G/G and G/T genotypes were considered extensive metabolizers [EMs]; children with T/T genotypes were considered slow metabolizers [SMs].** See Table A below). When doses were used without regard to genotype, a dose of approximately 40 mg/kg per day 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 participants with T/T genotypes. This dose is higher than the FDA-approved dose of efavirenz.²⁸ Therefore, **doses were** modified so that infants and young children with the T/T genotype received a reduced dose. The doses listed **for P1070** in Table A are **investigational**.

Investigational Dosing for Children Aged 3 Months to <3 Years By CYP2B6 Genotype

Table A. Comparison of Efavirenz Doses Used in P1070 and the FDA-Recommended Doses

Weight	Protocol P1070 Dosing for Patients with CYP2B6-516-G/G and -G/T Genotypes (Extensive Metabolizers) ^a	Protocol P1070 Dosing for Patients with CYP2B6-516-T/T Genotype (Slow Metabolizers) ^a	FDA-Approved Dosing for Children Aged 3 Months to <3 Years (Without Regard to CYP2B6 Genotype)
5 kg to <7 kg	300 mg	50 mg	150 mg
7 kg to 7.5 kg	400 mg	100 mg	150 mg
7.5 kg to <10 kg	400 mg	100 mg	200 mg
10 kg to <14 kg	400 mg	100 mg	200 mg
14 kg to <15 kg	500 mg	150 mg	200 mg
15 kg to ≤17 kg	500 mg	150 mg	250 mg

^a Investigational doses are based on IMPAACT study P1070.²⁸ Evaluation of CYP2B6 genotype is required. Therapeutic drug level monitoring is recommended, with a trough measured 2 weeks after initiation of efavirenz and again at age 3 years for a possible dose adjustment.

The FDA-approved doses of efavirenz for use in infants and children aged 3 months to <3 years were derived from a population PK model that was based on data from older subjects in PACTG 1021 and PACTG 382, and also from data collected during AI266-922, a study that assessed the PKs, safety, and efficacy of capsule sprinkles in children aged 3 months to 6 years (see Table A).

The FDA-approved doses are lower than the CYP2B6 EM doses and higher than the CYP2B6 SM doses **from the P1070 study**. There is concern that FDA-approved doses may result in frequent underdosing in CYP2B6 EMs. PK modeling, based on P1070 PK data, was used to generate estimates of the percentage of participants who were likely to reach therapeutic efavirenz target concentrations on FDA-indicated dosages,

according to the participants' genotypes.²⁸ The frequency of area under the curve (AUC) in the target range of 35 to 180 mcg·h/mL and C_{24h} in the target range of 1 mg/L to 4 mg/L, a systemic exposure similar to that shown to be safe and effective in older children and adults, was calculated.²⁸ The P1070 genotype-based dosing resulted in approximately 80% of EM participants and 90% of SM participants achieving the targeted AUC, whereas the FDA-approved dosing would result in an estimated 63% of EM participants and 44% of SM participants achieving the target AUC. In addition, using FDA-approved dosing would result in an estimated one-third of EM children with subtherapeutic efavirenz exposures and more than half of SM children with AUCs above the target range.

The Panel **does not recommend** use of efavirenz in children aged 3 months to <3 years. If the clinical situation demands the use of efavirenz, the Panel recommends determining CYP2B6 genotype prior to use (see a [list of laboratories that perform this test](#)). Patients should be classified as extensive CYP2B6-516-G/G and -G/T genotype metabolizers or slow CYP2B6-516-T/T genotype metabolizers to guide dosing as indicated by the investigational doses from IMPAACT study P1070 (see Table A). Whether the doses used are investigational or approved by the FDA, measuring efavirenz plasma concentrations should be considered 2 weeks after initiation (see the Therapeutic Drug Monitoring section below). The mid-dose efavirenz plasma concentration target of 1.0 to 4.0 mg/L derived from adult clinical monitoring data is typically also applied to trough concentrations. A study of 128 African children (aged 1.7–13.5 years) suggests that the C_{24h} threshold for increased risk of unsuppressed viral load is C_{24h} 0.65 mg/L.³⁵ Consultation with an expert **in pediatric HIV infection** is recommended before adjusting dose. In addition, when following the P1070 investigational dose recommendations, some experts would measure efavirenz concentrations at age 3 years before transitioning the child to the recommended dose for children aged ≥3 years.

Pharmacokinetics: Children Aged ≥3 Years and Adolescents

Even with the use of FDA-approved pediatric dosing in children aged ≥3 years, efavirenz concentrations can be suboptimal.^{21,36-40} Therefore, some experts recommend 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 dose was efavirenz 13 mg/kg (367 mg/m²) and the range was from 3 mg/kg to 23 mg/kg (69 mg/m²–559 mg/m²).⁴¹ A PK study in 20 children aged 10 to 16 years who were treated with LPV/r 300 mg/m² and 75 mg/m² twice daily plus efavirenz 350 mg/m² once daily showed that lopinavir trough values were adequate but suggested that the efavirenz trough values were lower than PK targets. The authors therefore concluded that higher doses of efavirenz might be needed when these drugs are used together.⁴²

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 and 27% of adults.⁴³ 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 one meta-analysis of randomized trials.⁴⁴ These symptoms usually occur early in treatment and rarely require drug discontinuation, but they can sometimes 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 efavirenz 400 mg is associated with fewer AEs and a noninferior virologic response when compared with the recommended 600-mg dose of efavirenz in adults.^{13,45}

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.^{46,47} This association, however, was not found in analyses of two large observational cohorts,^{48,49} and no cases of suicide were

reported in a systematic review of randomized trials.⁴⁴ 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.⁵⁰⁻⁵⁴ In patients with pre-existing psychiatric conditions, efavirenz should be used cautiously. Adverse CNS events occurred in 14% of children who received efavirenz in clinical studies⁵⁵ and in 30% of children with efavirenz concentrations >4 mg/L.²² CNS AEs may be harder to detect in children because it is difficult to assess 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.^{50,51} Homozygous carriers of the CYP2B6*6 allele (CYP2B6*6/*6) may be at increased risk for efavirenz-induced QTc prolongation. The CYP2B6*6 allele codes for the CYP2B6-516-G>T complementary DNA nucleotide change;⁵⁶ therefore, CYP2B6*6/*6 carriers can be categorized as SMs. The effect of efavirenz on the QTc interval was evaluated in a study of 58 healthy adult subjects that collectively represented a variety of 58 healthy adult subjects, with a mix of CYP2B6 polymorphisms represented within the group. 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 efavirenz 600 mg daily 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.⁵⁷ Consider using an alternative to efavirenz in patients who are receiving a drug that has a known risk of Torsades de Pointes (e.g., quinidine, clarithromycin) or in patients who are at higher risk of Torsades de Pointes.²

Therapeutic Drug Monitoring

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.^{58,59} 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 oral clearance and variable PK properties in this young age group. **TDM should also be considered when using a lower dose of efavirenz, such as the dose found in Symfi Lo, in children weighing ≥40 kg. Two weeks after the initiation of efavirenz in patients aged <3 years, clinicians should measure the plasma concentration of efavirenz. In cases where a dose adjustment may be necessary, clinicians should consult an expert in pediatric HIV infection prior to adjusting dosage. If a child initiated efavirenz at an investigational dose while <3 years of age, some experts would also measure plasma concentration at age 3 years after the child transitions to the recommended dose for children aged ≥3 years.**

The currently accepted minimum effective concentration of efavirenz is a mid-dose concentration (C_{12h}) >1 mg/L in adults, and concentrations of >4.0 mg/L are associated with CNS side effects.⁵¹ A recent study in children showed that a higher proportion of children with a C_{12h} <1 mg/L showed evidence of viral replication than those with a C_{12h} >1 mg/L.⁶⁰ However, the validity using a single target has been called into question.⁶¹ In addition, a lower limit of C_{12h} > 0.7mg/L was most predictive of virologic outcome in a study of 180 adults.⁶² Findings from a study of 128 African children (aged 1.7–13.5 years) suggest that the C_{24h} threshold for increased risk of unsuppressed viral load is C_{24h} 0.65 mg/L.³⁵

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