Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Efavirenz (EFV, Sustiva)  
(Last updated May 22, 2018; last reviewed May 22, 2018)

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
• [Symfi Lo] Efavirenz 400 mg plus lamivudine 300 mg plus 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 tables A1 and A2 in the Pharmacokinetics and Dosing: Infants and Children Aged <3 Years section below). Evaluation of CYP2B6 genotype is required prior to use in this age group. Therapeutic drug monitoring should be used with an efavirenz plasma concentration measured 2 weeks after initiation; some experts would also measure plasma concentration at age 3 years after making the transition to the new dose (see Therapeutic Drug Monitoring in the text below). For dose adjustment based on efavirenz concentrations, consultation with an expert is recommended.

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, insomnia, 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. Clinicians should consider using an alternative to efavirenz in patients taking a drug that has a known risk of Torsades de Pointes or in patients who are at higher risk of Torsades de Pointes.

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 central nervous system side effects.
• Administer efavirenz, Atripla, 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 tablets, see other drug sections in Appendix A: Pediatric Antiretroviral Drug Information for special instructions and additional information
Children Aged ≥3 Years and Weighing ≥10 kg:

Once-Daily Doses of Efavirenz by Weight

<table>
<thead>
<tr>
<th>Weight</th>
<th>Efavirenz Dose&lt;sup&gt;a,b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 kg to &lt;15 kg</td>
<td>200 mg</td>
</tr>
<tr>
<td>15 kg to &lt;20 kg</td>
<td>250 mg</td>
</tr>
<tr>
<td>20 kg to &lt;25 kg</td>
<td>300 mg</td>
</tr>
<tr>
<td>25 kg to &lt;32.5 kg</td>
<td>350 mg</td>
</tr>
<tr>
<td>32.5 kg to &lt;40 kg</td>
<td>400 mg</td>
</tr>
<tr>
<td>≥40 kg</td>
<td>600 mg</td>
</tr>
</tbody>
</table>

<sup>a</sup> The dose in mg can be dispensed in any combination of capsule strengths. Capsules may be administered by sprinkling the contents into an age-appropriate food (see Special Instructions).

<sup>b</sup> Some experts recommend a dose of efavirenz 367 mg/m² body surface area (maximum dose 600 mg) because of concern for 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.

Adolescent (Weighing ≥40 kg) and Adult Dose:

- Efavirenz 600 mg once daily

**[Atripla]** Efavirenz plus Emtricitabine plus TDF

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

Adult Dose:

- One tablet once daily

**[Symfi Lo]** Efavirenz plus Lamivudine plus TDF: Pediatric (Weighing ≥35 kg) and Adult Dose:

- One tablet once daily

**Note:** The new fixed-dose combination (Symfi Lo), which has a lower dose of efavirenz, has not yet been discussed by the Panel. The Panel will address its use in children in a later update.

- 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](https://aidsinfo.nih.gov/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 1–2 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*.
- 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](https://aidsinfo.nih.gov/guidelines) in the text below for information about the management of mild or moderate toxicity).

Atripla and Symfi Lo Dosing in Adults with Renal Impairment:

- Because these are fixed-dose combination products and TDF and emtricitabine require dose adjustment based on renal function, Atripla and Symfi Lo should not be used in patients with creatinine clearance <50 mL/minute or in patients on dialysis.

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**Drug Interactions** (see also the Adult and Adolescent Guidelines and HIV Drug Interaction Checker)

- **Metabolism:** Co-administration of efavirenz with drugs primarily metabolized by cytochrome P (CYP) 2C9, 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 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 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 primarily been 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 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 is Food and Drug Administration (FDA)-approved for use as part of antiretroviral therapy in children aged ≥3 months and weighing ≥3.5 kg. Although the FDA has approved the use of Symfi Lo, the fixed-dose combination of efavirenz 400 mg plus lamivudine 300 mg plus tenofovir disoproxil fumarate (TDF) 300 mg, in children weighing ≥35 kg, the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) has not yet discussed pediatric use of this new formulation and the implications of using a fixed-dose combination that contains a lower dose of efavirenz in children.

**Efficacy in Clinical Trials**

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.

- 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.\textsuperscript{11}

- 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.\textsuperscript{12-18}

- The 96-week results of the Encore1 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.\textsuperscript{19}

\textit{Pharmacokinetics: Pharmacogenomics}

Genetic polymorphisms in genes coding 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 (which has an allele frequency of 20\% in African Americans) have reduced metabolism, resulting in higher efavirenz levels in these patients than in those with the G/G or G/T genotype.\textsuperscript{20-24} 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 G/G or G/T genotype but excessive exposure in those with T/T genotype.\textsuperscript{21} Optimal dosing may require pretreatment CYP2B6 genotyping in children aged <3 years (see discussion below).\textsuperscript{20,25} Additional variant CYP2B6 alleles and variant CYP2A6 alleles have been found to influence efavirenz concentrations in adults and children.\textsuperscript{24,26-30} The \textit{CYP2B6 T983C} mutation has also been associated with reduced efavirenz clearance in African children.\textsuperscript{24}

\textit{Pharmacokinetics and Dosing: Infants and Children Aged <3 Years}

The Panel does not recommend 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.\textsuperscript{22,31} These data show age-related differences in absorption and impact of formulation on efavirenz PKs.\textsuperscript{21} 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.\textsuperscript{23} This maturation of oral clearance is postulated to result from an increase in the expression of CYP2B6 with age.\textsuperscript{23} 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 genotype.\textsuperscript{20} In children with 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.\textsuperscript{20} 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.\textsuperscript{22} IMPAACT P1070 studied children aged <3 years with HIV and HIV/tuberculosis coinfection, using efavirenz dosed by weight band based on CYP2B6 GG/GT versus T/T genotype (see Tables A1 and A2 below). 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.\textsuperscript{23} Therefore, dosing tables have been modified so that infants and young children with T/T genotype will receive a reduced dose. Additional analyses are needed to confirm that this dose is appropriate for this subset of patients. The modified doses listed in Tables A1 and A2 are under investigation.
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 also from data collected during 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 B).

The FDA-approved doses are lower than the CYP2B6 extensive metabolizer (EM) doses and higher than the CYP2B6 slow metabolizer (SM) 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 underdosing in CYP2B6 EMs. Estimates of efavirenz area under the curve (AUC) for FDA dosing using P1070 data were calculated using the following equation:

\[
P1070\text{-observed AUC} \times \left( \frac{\text{FDA dose}}{\text{P1070 CYP2B6 genotype-directed study dose}} \right)
\]

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. The P1070 dosing for children aged 3 to 36 months leads to higher levels than seen with FDA recommendations for adults receiving 600 mg daily. However, the higher doses reduced the frequency of low AUCs (<35 mcg*h/mL) with P1070 EM dosing (11% P1070 EM dosing vs. an estimated 32% with FDA dosing). The lower P1070 dose for SM genotype is predicted to reduce the frequency of high AUCs from 56% to 11% compared to the FDA genotypic agnostic dose (a dose given without consideration of genotype) in this population.

The Panel does not recommend use of efavirenz in children aged 3 months to <3 years. If the clinical situation demands use of efavirenz, the Panel recommends determining CYP2B6 genotype prior to use.

### Table A1. Protocol P1070 Dosing for Patients with CYP2B6-516-G/G and -G/T Genotypes (Extensive Metabolizers [EM])

<table>
<thead>
<tr>
<th>Weight</th>
<th>Efavirenz Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 kg to &lt;7 kg</td>
<td>300 mg</td>
</tr>
<tr>
<td>7 kg to &lt;14 kg</td>
<td>400 mg</td>
</tr>
<tr>
<td>14 kg to &lt;17 kg</td>
<td>500 mg</td>
</tr>
<tr>
<td>≥17 kg</td>
<td>600 mg</td>
</tr>
</tbody>
</table>

### Table A2. Protocol P1070 Dosing for Patients with CYP2B6-516-T/T Genotype (Slow Metabolizers [SM])

<table>
<thead>
<tr>
<th>Weight</th>
<th>Efavirenz Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 kg to &lt;7 kg</td>
<td>50 mg</td>
</tr>
<tr>
<td>7 kg to &lt;14 kg</td>
<td>100 mg</td>
</tr>
<tr>
<td>14 kg to &lt;17 kg</td>
<td>150 mg</td>
</tr>
<tr>
<td>≥17 kg</td>
<td>150 mg</td>
</tr>
</tbody>
</table>

* Investigational doses are based on IMPAACT study P1070. Evaluation of CYP2B6 genotype is required. Therapeutic drug level monitoring is recommended with a trough measured 2 weeks after initiation of efavirenz and at age 3 years for possible dose adjustment.
Patients should be classified as extensive CYP2B6-516-G/G and -G/T genotype metabolizers (EMs) or slow CYP2B6-516-T/T genotype metabolizers (SMs) to guide dosing as indicated by the investigational doses from IMPAACT study P1070 (see Tables A1 and A2). Whether the doses used are investigational or FDA-approved, measuring efavirenz plasma concentrations should be considered 2 weeks after initiation (see Therapeutic Drug Monitoring 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.\(^{32}\) Consultation with an expert 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 making the transition to the new dose.

**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.\(^{20,33-37}\) 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 dose was efavirenz 13 mg/kg (367 mg/m\(^2\)) and the range was from 3 to 23 mg/kg (69–559 mg/m\(^2\)).\(^{38}\) A PK study in 20 children aged 10 to 16 years treated with LPV/r 300 mg/m\(^2\) twice daily plus efavirenz 350 mg/m\(^2\) 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.\(^{39}\)

**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.\(^{40}\) 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.\(^{41}\) 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 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.\(^{19,42}\)

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.\(^{43,44}\) This association, however, was not found in analyses of two large observational cohorts\(^ {45,46}\) and no cases of suicide were reported in a systematic review of randomized trials.\(^ {41}\) 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.\(^ {47-51}\) In patients with pre-existing psychiatric conditions, efavirenz should be used cautiously. Adverse CNS events occurred in 14% of children receiving efavirenz in clinical studies\(^ {52}\) and in 30% of children with efavirenz concentrations >4 mcg/mL.\(^ {21}\) 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.\textsuperscript{47,48} Homozygous carriers of the CYP2B6*6 allele (CYP2B6*6/*6) may be at increased risk for efavirenz-induced rate QTc prolongation. The CYP2B6*6 allele codes for the CYP2B6-516-G>T complementary DNA nucleotide change; 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 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 efavirenz 600 mg daily for 14 days.\textsuperscript{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.\textsuperscript{54} Consider using an alternative to efavirenz in patients 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.\textsuperscript{2}

\textbf{Toxicity: Potential Risk of Teratogenicity}

In prior versions of the Perinatal Guidelines, efavirenz use was not recommended before 8 weeks’ gestational age because of concerns regarding potential teratogenicity. Although this caution is still included in the package insert, and efavirenz use has been associated with significant teratogenic effects in nonhuman primates, results of a large meta-analysis have been reassuring that risks of neural tube defects after first-trimester efavirenz exposure are not greater than those seen in the general population.\textsuperscript{2,55} 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 antiretroviral drugs during pregnancy (both of which note that efavirenz can be used throughout pregnancy).\textsuperscript{56,57} Importantly, women who become pregnant on suppressive efavirenz-containing regimens should continue their current regimens.

For a comprehensive discussion, see \textit{Efavirenz} in Appendix B of the \textit{Perinatal Guidelines}.\textsuperscript{58}

\textbf{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.\textsuperscript{59,60} 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. An efavirenz concentration, measured 2 weeks after initiation, and consultation with an expert should be considered to inform 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 ($C_{12}$) >1 mg/L in adults, and concentrations >4.0 mg/L are associated with CNS side effects.\textsuperscript{48} A recent study in children showed that a higher proportion of children with a $C_{12}$ <1 mg/L showed evidence of viral replication than those with a $C_{12}$ >1 mg/L.\textsuperscript{61} However, the validity using a single target has been called into question.\textsuperscript{62} In addition, a lower limit $C_{12}$ >0.7 mg/L was most predictive of virologic outcome in a study of 180 adults.\textsuperscript{63} 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.\textsuperscript{62}

\textbf{References}


