Efavirenz (EFV)

Available Formulations

Single drug formulations

Tablet (scored)
EFV 200 mg

Formulations for adults
EFV 600 mg EFV + FTC + TDF 600/200/300 mg EFV + 3TC + TDF 400/300/300 mg EFV + 3TC + TDF 600/300/300 mg

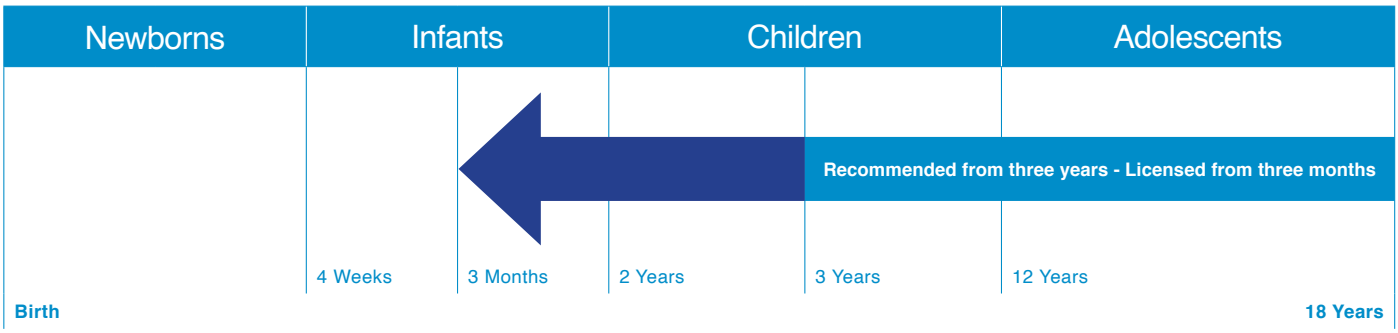
Formulation considerations

Bedtime dosing of EFV-containing regimens is recommended, especially during the first 2–4 weeks of therapy, to improve the tolerability of central nervous system side-effects.

Administer EFV on an empty stomach. Avoid administration with a high-fat meal because this increases absorption and result in high drug levels with potential side-effects.

The oral liquid is not recommended because of high variability and the difference in bioavailability from tablet formulations.

WHO dose recommendation - age



World Health Organization

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WHO dose recommendation – weight bands

Simplified dosing of child-friendly solid formulations for once-daily dosing for infants and children four weeks and older

Drug	Strength of paediatric tablet	Number of tablets or capsules by weight band once daily					Strength of adult tablet	Number of tablets by weight band once daily
		3 – <6 kg	6 – <10 kg	10 – <14 kg	14 – <20 kg	20 – <25 kg		25 – <35 kg
EFV[a]	Tablet (scored) 200 mg	–	–	1	1.5	1.5	200mg	2

[a]EFV is not recommended for children younger than three years and weighing less than 10 kg.

Rationale WHO dose selection

Although the United States Food and Drug Administration has approved EFV for children from three months weighing more than 3.5 kg, WHO does not recommend EFV for children yunger than three years because of highly variable pharmacokinetics in this age group. EFV for children younger than three years is only recommended if CYP2B6 genotyping is available to determine the appropriate dose; however, genotyping is expensive and, most importantly, not accessible to many clinics, in particular in low- and middle-income countries, and it is rarely used in clinical practice.

The WHO dose selection was based on the use and availability of 200-mg scored tablets. Because weight-band dosing recommendation on the United States Food and Drug Administration label resulted in a potential risk of underdosing of EFV for children (Cressey et al., Fillekes et al.), a higher EFV dose was selected to avoid underdosing, especially among CYP2B6 extensive metabolizers.

Important information

CYP2B6 genotype

EFV is primarily metabolized by ***CYP2B6*** and its pharmacokinetics is affected by polymorphisms in the ***CYP2B6*** gene. The ***CYP2B6-516-T/T*** genotype results in reduced metabolism of EFV and occurs frequently in all populations; a study of adults in the United States and Italy found a frequency of 24% among White study participants, 31% among Black study participants and 35% among Hispanic study participants (Haas et al.). Determining CYP2B6 genotype before starting EFV is recommended but is not available in low- and middle-income countries.

Infants and children younger than three years

WHO does **not recommend** using EFV for children between three months and three years old. Data from the IMPAACT 1070 study have shown that achieving target trough concentrations among children younger than three years or weighing less than 13 kg is difficult (Bolton Moore et al.). Apart from ***CYP2B6*** genotype, age-related differences, EFV formulation and variability in ***CYP2B6*** maturation all affect EFV pharmacokinetics among these young children (Hamed Salem et al.). The IMPAACT 1070 study has suggested EFV doses based on both weight bands and ***CYP2B6*** genotype. See the United States Food and Drug Administration guideline for the suggested doses for the younger children. Note that these doses are investigational and require extensive therapeutic drug monitoring.

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Toxicity

The observed adverse reactions for children are similar to those for adults, except for rash. Rash occurred more frequently among children (32–46% for all children included in clinical trials) and was often more severe than among adults (European Medicines Agency and United States Food and Drug Administration labels). Close monitoring of this adverse reaction is recommended.

Current ongoing trials involving children

Clinical trials on ClinicalTrials.gov

Knowledge gaps

None

Research priorities according to PADO4

None

Drug–drug interactions

No dose adjustments are needed for EFV during rifampicin-based TB treatment (more information: www.hiv-druginteractions.org).

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