Tenofovir alafenamide fumarate (TAF)

Available Formulations

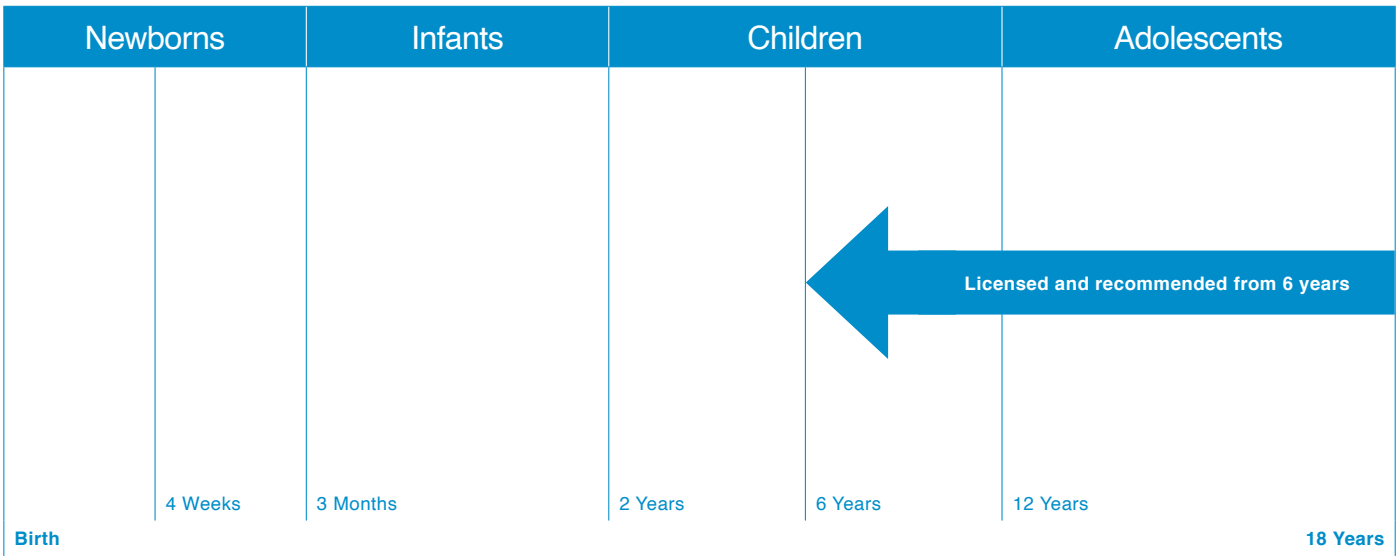
Formulations for adults
BIC + FTC + TAF 50/200/25 mg
FTC + TAF 200/25 mg
FTC + TAF 200/10 mg
EVG + COBI + FTC + TAF 150/150/200/10 mg
RPV + FTC + TAF 200/25/25 mg
DRV + COBI + FTC + TAF 800/150/200/10 mg
DTG + FTC + TAF 50/200/25 mg (United States Food and Drug Administration tentative approval)

Formulation considerations

TAF is currently only available for children in a combination tablet with other drugs. Combined with COBI as a booster drug in fixed-dose combinations, the TAF dose should be lowered from 25 mg to 10 mg due to the increase in exposure caused by the pharmacokinetic booster. If FTC + TAF is combined with a RTV-boosted regimen such as LPV/r, the United States Food and Drug Administration does not advise a dose change for TAF, whereas the European Medicines Agency does recommend lowering the TAF dose to 10 mg in combination with boosted regimens.

WHO dose recommendation - age

WHO recommends TAF as a first choice regimen for all children older than six years and weighing at least 25 kg and is available in fixed-dose combinations of TAF 25 mg without COBI in combination with FTC, FTC + BIC or FTC + RPV or FTC + DTG (D-F-TAF).



World Health Organization

Tenofovir alafenamide fumarate (TAF)

WHO dose recommendation – weight bands

Simplified dosing of child-friendly solid formulations for once-daily dosing for infants and children four weeks of age 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
TAF	Tablet 25/200 mg TAF + FCT	–	–	–	–	–	–	–	–	–	–	Tablet 25/200 mg TAF + FCT	1

At the time of this update, the United States Food and Drug Administration had approved TAF film-coated tablets for children older than six years in unboosted regimens such as with DTG. A fixed-dose combination containing TAF + FTC + DTG (TAF 25 mg, FTC 200 mg, DTG 50 mg fixed-dose combination) received tentative approval by the United States Food and Drug Administration and can be used once daily for children and adolescents living with HIV weighing at least 25 kg.

Rationale for WHO dosing selection

Data for TAF dosing for children older than 12 years old dosed at 25 mg once daily were formed by several studies using either boosted or unboosted regimens. These studies found that exposure with 25 mg of TAF among adolescents was similar to adults treated with the same dose. For children down to six years old, data on TAF were generated by studies with EVG + COBI + FTC + TAF 150/150/200/10 mg (Natukunda E et al. and United States Food and Drug Administration label) and BIC +FTC + TAF 50/200/25 mg (United States Food and Drug Administration label). Here the exposure of TAF was higher than for adults taking 25 mg of TAF but, with good safety and efficacy data, the United States Food and Drug Administration and European Medicines Agency still accept this dose in their respective labels, and WHO adopted it in recommendations. The United States Food and Drug Administration tentatively approved a fixed-dose combination containing TAF + FTC + DTG (25/200/50 mg) that can be used once daily for children and adolescents living with HIV weighing at least 25 kg. WHO does not recommend TAF in combination with RTV, since no data on boosting with RTV among children are currently available.

Studies supporting dosing for children

Registering TAF for children has been based on studies with adult fixed-dose combinations BIC + FTC + TAF and EVG + COBI + FTC + TAF. TAF data in these trials show safety and efficacy in children weighing down to 14 kg (Natukunda et al., Majeed et al., Gaur et al. and Cotton et al.).

In these combinations, TAF is dosed among children weighing more than 25 kg and older than six years using the adult strength tablets: FTC + TAF 200/25 mg, EVG + COBI + FTC + TAF 150/150/200/10 mg and RIL + FTC + TAF 25/200/25 mg. TAF is dosed 25 mg once daily when used in fixed-dose combinations without a COBI booster (approved by the European Medicines Agency and the United States Food and Drug Administration for children >25 kg) and 10 mg once daily when combined with COBI (approved for children weighing 25 kg or more). The United States Food and Drug Administration has also approved using FTC + TAF 200/25 mg in combination with other ARV drugs (regardless of RTV boosting) for adults and adolescents weighing more than 35 kg (United States Food and Drug Administration label).

World Health Organization

Tenofovir alafenamide fumarate (TAF)

Ongoing studies

Clinical trials at ClinicalTrials.gov

Important Information

Drug–drug interactions

TB: TAF has been studied for adults in the combination of TAF and rifampicin-based TB treatment. TAF should be doubled (standard dose administered twice daily) when combined with rifampicin. The CHAPAS4 study is currently investigating the data for this combination among children.

Toxicity

Just like TDF, TAF is a prodrug of tenofovir, but compared with TDF, TAF attains 90% lower circulating plasma concentrations of tenofovir (Ruane et al. and Podany et al.). Intracellular levels are, however, increased 2.4-fold when using TAF compared with TDF (Podany et al.). TAF is promising for use among children since, unlike TDF, TAF is not associated with side-effects related to decreasing bone mineral density and renal tube abnormalities that can be observed with TDF (Kizito et al. and Sax et al.).

Knowledge gaps

No data are available yet for TAF dosed for children weighing less than 14 kg.

Data for TAF combined with rifampicin among children are warranted before this combination can be recommended for children.

With TAF, safety or efficacy is not related to plasma pharmacokinetic end points among adults or children. In the studies with TAF involving children, safety and efficacy were comparable with data for adults, although plasma area under the curve was 171% relative to the area under the curve for adults for children 6–11 years old. More research into the correlation between intracellular tenofovir diphosphate, plasma TAF or plasma TFV levels and toxicity will give more insight in the safety of these formulations compared with other regimens.

Greater weight gain has been reported with TAF than with TDF among adults. The effect TAF has on children's weight and the longitudinal weight effects of TAF treatment needs to be determined.

World Health Organization

Tenofovir disoproxil fumarate (TDF)

Available Formulations

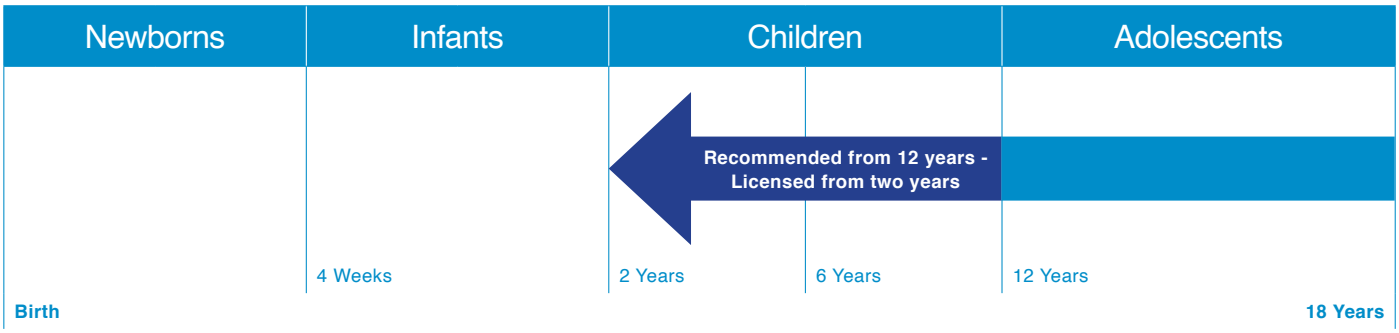
Formulations for adults
EFV + FTC + TDF 600/200/300 mg
RPV + FTC + TDF 25/200/300 mg
3TC + TDF 300/300 mg
DOR + 3TC + TDF 100/300/300 mg
EVG + COBI + 3TC + TDF 150/150/300/300 mg
EFV + 3TC + TDF 600/300/300 mg
EFV + 3TC + TDF 400/300/300 mg
DTG + 3TC + TDF 50/300/300 mg

Formulation considerations

None.

WHO dose recommendation - age

TDF is known to cause bone mineral density loss and decline in renal function parameters among adults and is also suspected of causing this effect among children. TDF is therefore not recommended for children younger than 12 years. The extent of the renal and bone toxicity has not been fully elucidated, but with adequate alternative NRTI regimens available, TDF for children 2–12 years old remains an alternative regimen.



WHO dose recommendation – weight bands

None.

World Health Organization

Tenofovir disoproxil fumarate (TDF)

Rationale for WHO dosing selection

Not applicable, not recommended. Except for adolescents living with HIV weighing more than 30 kg, a fixed-dose formulation of TDF + 3TC + DTG 300/300/50 mg (TLD) can be used and is preferred.

Ongoing Studies supporting dosing for children

Clinical trials at ClinicalTrials.gov

Important information

Toxicity

TDF is known to cause bone mineral density loss and decline in renal function parameters among adults and is also suspected of causing this effect among children. TDF is therefore not recommended for children younger than 12 years. The extent of the renal and bone toxicity has not been fully elucidated, but with adequate alternative NRTI regimens available, TDF for children 2–12 years old remains an alternative regimen.

Drug–drug interactions

None

Knowledge gaps

Dosing TDF for children with reduced renal function.

World Health Organization