Dolutegravir (DTG)

Available Formulations

Single drug formulations	
	
Dispersible tablets	Dispersible tablets (scored)
DTG 5 mg	DTG 10 mg

Formulations for adults
DTG 50 mg DTG + 3TC 50/300 mg DTG + RPV 50/25 mg DTG + ABC + 3TC 50/600/300 mg DTG + TDF + 3TC 50/300/300 mg DTG + TAF + FTC 50/25/200 mg

Formulation considerations

DTG can be taken with or without food.

DTG dispersible tablets should be ideally dispersed in water or swallowed whole. Based on limited data, crushing, chewing or mixing with other foods or liquids (breastmilk) can be considered as long as the entire recommended volume is ingested.

Dispersible tablets are not bioequivalent to film-coated tablets, and care should be taken to dose according to the formulation used. The 30-mg dispersible tablets and the 50-mg film-coated tablets provide equivalent exposure (Bollen et al.).

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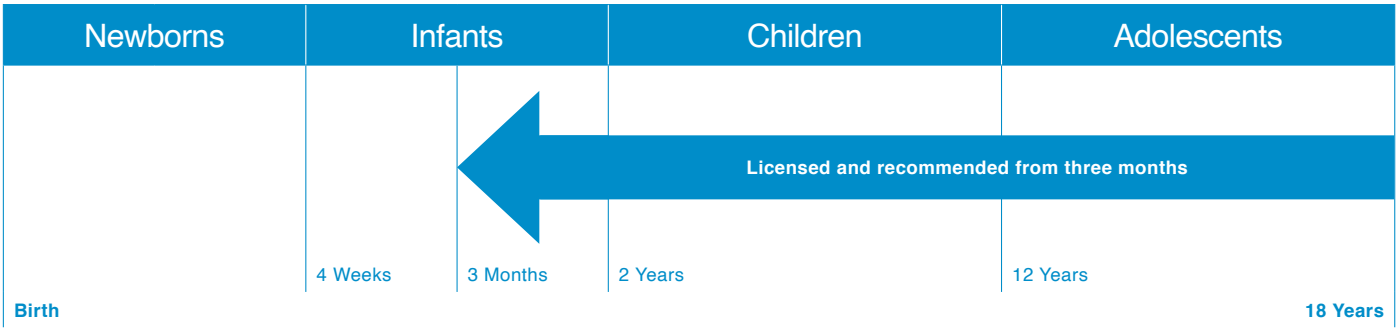
WHO dose recommendation - age



WHO recommends DTG as a first-choice regimen for all children with available dosing information. The United States Food and Drug Administration recently approved a DTG dose for children as young as four weeks weighing 3–25 kg using the DTG dispersible tablets intended for children. Until the WHO dosing recommendation is updated, WHO recommends following the doses approved by the United States Food and Drug Administration.

WHO dose recommendations – 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
DTG[a]	Film-coated tablet 50 mg	–	–	–	–	1	50 mg	1
	Dispersible tablet 5 mg	1	3	4	5	6		
	Dispersible scored tablet 10 mg	0.5	1.5	2	2.5	3		

[a]At the time of this update, the United States Food and Drug Administration approved 5-mg dispersible tablets and 10 mg scored dispersible tablets for treatment-naive or treatment-experienced INSTI-naive people at least four weeks old and weighing at least 3 kg based on data from the IMPAACT 1093 trial and ODYSSEY. The United States Food and Drug Administration and European Medicines Agency approved simplified dosing of the DTG 50-mg film-coated tablets for all children weighing at least 20 kg. DTG dispersible tablets and DTG film-coated tablets are not bioequivalent; 30-mg DTG dispersible tablets correspond to 50-mg DTG film-coated tablets. DTG 50-mg film-coated tablets are preferred for children who have reached 20 kg (unless they cannot swallow tablets). Safety monitoring remains important given the current limited experience with this dosing. 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.

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Rationale for WHO dose selection

Current dosing is based on the United States Food and Drug Administration approval of film-coated tablet and dispersible tablet formulations and the European Medicines Agency approval for the film-coated tablet formulation. In November 2020, the United States Food and Drug Administration approved the first generic DTG 10-mg scored dispersible tablet.

Doses approved by the European Medicines Agency and the United States Food and Drug Administration by May 2021

Body weight	European Medicines Agency	United States Food and Drug Administration
3.0–5-9 kg	5-mg dispersible tablets[a]	5-mg dispersible tablets
6.0–9.9 kg; <6 months old	10-mg dispersible tablets[a]	15-mg dispersible tablets
6.0–9.9 kg; >6 months old	15-mg dispersible tablets[a]	15-mg dispersible tablets
10.0–13.9 kg	20-mg dispersible tablets[a]	20-mg dispersible tablets
14.0–19.9 kg	25-mg dispersible tablets/40-mg film-coated tablets[a]	25-mg dispersible tablets/40-mg film-coated tablets
20.0–29.9 kg	30 mg dispersible tablets/50-mg film-coated tablets[a]	30-mg dispersible tablets/50-mg film-coated tablets
30–39.9 kg	50 mg film-coated tablets	50-mg film-coated tablets
>40 kg	50 mg film-coated tablets	50-mg film-coated tablets
[a]Also licensed by the European Medicines Agency as the same daily dose given twice daily.		

There is currently a discrepancy between the United States Food and Drug Administration and European Medicines Agency in the dosing advice for children younger than six months weighing 6.0–9.9 kg. For these children, the European Medicines Agency recommends decreasing the dose to 10 mg. The WHO-recommended dosing follows the dosing recommended by the United States Food and Drug Administration because it is more practical, since all children weighing 6.0–9.9 kg will receive the same dose (United States Food and Drug Administration label and European Medicines Agency product characteristics).

For infants who received RAL-containing ART for a limited duration (such as no more than three months) and without evidence or suspicion of treatment failure, the PAWG concluded that switching to standard (once-daily) weight-appropriate DTG is reasonable while encouraging the generation of direct evidence to evaluate this approach. Of note, although DTG can be dosed twice daily for adults with suspected INSTI resistance, this approach cannot be safely extrapolated to children given differences in pharmacokinetics. Alternative regimens should be considered and, where possible, informed by appropriate HIV drug resistance testing.

Studies supporting dosing for children

The proposed dosing for children is supported by data from the IMPAACT P1093 (Wiznia et al. and Ruel et al.) and ODYSSEY trial data (Bollen et al. and Waalewijn et al.) that formed the basis of the filing by the United States Food and Drug Administration and European Medicines Agency.

Ongoing studies involving children

Clinical trials at ClinicalTrials.gov

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Important information

DTG use has been associated with excessive weight gain in some studies of adults. The effect on children needs further study.

Significant drug–drug interactions

TB treatment: for all weights and ages with approved DTG dosing, the United States Food and Drug Administration recommends administering the weight-based DTG dose twice daily if taken with rifampicin based on its customary approach of extrapolating drug–drug interaction data from adults. Direct pharmacokinetic data for children support the use of DTG twice daily for children weighing more than 25 kg (Waalewijn et al.). The DTG dose will need to remain twice daily for two weeks after the last dose of rifampicin has been given since the enzyme-inducing effect of rifampicin slowly fades away after discontinuing the drug. The PAWG highlights the need to continue to collect confirmatory evidence for lower weight bands but, as reflected in the dosing table, endorses immediate uptake of twice-daily dosing of DTG when taken with rifampicin for all children (at least four weeks and weighing at least 3 kg).

Diabetes: the total daily dose of metformin should not be higher than 1000 mg because of potential toxicity of increased metformin levels caused by DTG inhibiting OCT2 transporters.

Mineral supplement: divalent cations such as iron, magnesium or calcium interfere with the absorption of DTG. It is therefore recommended that DTG be taken two hours before or six hours after products that contain these elements, such as multivitamins.

Knowledge gaps

DTG–rifampicin interaction: pharmacokinetic and safety data for children weighing less than 25 kg.

Currently no data on DTG use is available for children younger than four weeks.

Limited data are available about dispersing DTG dispersible tablets in substances other than water.

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