# **Paediatric Dolutegravir 10 mg Dispersible, Scored Tablets *Frequently Asked Questions (FAQs)***



CHAI-logo-PMS654.pdf

**Table of Contents:**

[Overview](#_Frequently_Asked_Questions)

[Advantages over LPV/r](#_Frequently_Asked_Questions_1)

[Administration](#_Frequently_Asked_Questions_2)

[Side Effects and Special Populations](#_Frequently_Asked_Questions_3)

[Transition Considerations](#_Frequently_Asked_Questions_4)

[Medication Interactions](#_Frequently_Asked_Questions_5)

[Dosing](#_Frequently_Asked_Questions_6)

# FAQs – Overview

***1. What is pDTG?***

Paediatric DTG 10 mg dispersible, scored tablets (pDTG) is a new generic formulation of DTG that is used as part of ART for CLHIV who are at least 4 weeks of age and weigh at least 3 and up to 20 kg. pDTG only has to be taken once daily and comes in a sweet, strawberry cream flavour.

***2. What are the benefits of pDTG?***

pDTG’s benefits include higher genetic barrier of resistance over NNRTIs, minimal side effects and drug interactions, simpler means of administration in comparison to LPV/r, improved adherence, and a more rapid achievement of viral load suppression.

***3. When is pDTG expected to be available?***

Two generic manufacturers, Viatris (formerly Mylan) and Macleods, have filed for regulatory approval of pDTG with the US FDA. Both Viatris and Macleods have received tentative US FDA approval. Based on this approval, procurement began and in-country delivery took place in early Q2 2021 for early adopter countries and continues to take place in Q3 2021 and beyond in all other countries that rely on Global Fund to Fight AIDS, Tuberculosis, and Malaria (Global Fund), PEPFAR, and domestic funding for ARV procurement.

# FAQs – Advantages over LPV/r

***4. How does pDTG compare to LPV/r in terms of efficacy?***

While there have been studies comparing the efficacy of DTG to LPV/r in adults, [the ODYSSEY trial](https://odysseytrial.org/2021/03/11/odyssey-trial-finds-new-drug-is-better-for-treating-children-living-with-hiv/) is the first trial to look at whether treatment combinations based on dolutegravir are effective and safe for children living with HIV (CLHIV). With [findings presented at IAS 2021](https://theprogramme.ias2021.org/PAGMaterial/PPT/3305_4870/ODYSSEY_b14kg_IAS_HIV-Pediatrics_2021_v1.0.pdf), ODYSSEY found that DTG-based regimens were superior to standard-of-care (SOC) treatment, including LPV/r-based regimens, in CLHIV who weighed between 3 and 14 kg. Children on DTG were approximately 11% less likely to experience treatment failure by 96 weeks than those on SOC regimens.

***5. How does pDTG compare to LPV/r in terms of tolerability?***

pDTG has a better side-effect profile and improved tolerability over LPV/r, which has been associated with diarrhoea, hyperlipidaemia, and decreased bone density. Side-effect data presented at IAS 2021 from [the ODYSSEY trial](https://odysseytrial.org/2021/03/11/odyssey-trial-finds-new-drug-is-better-for-treating-children-living-with-hiv/) were reassuring. In particular, excessive weight gain was not seen with pDTG (as observed in some adult trials) and blood lipid values were lower than in the control arms. There was also no statistical difference in the rate of severe adverse events between the pDTG arm and SOC arm, reaffirming that pDTG is well-tolerated.

***6. How does pDTG compare to LPV/r in terms of convenience?***

pDTG is taken once daily, whereas LPV/r is taken twice daily. The pDTG dispersible tablet eases ingestion versus the LPV/r tablet and is easier to administer than pellet and granule formulations. The pDTG dispersible tablet, with its strawberry cream flavour when dispersed in water, is also more palatable in comparison to LPV/r’s bitter taste, bolstering adherence.

***7. How does pDTG compare to LPV/r in terms of price?***

pDTG offers considerable cost savings over alternative formulations, with the new pricing agreement with Viatris and Macleods resulting in a cost of [$4.50/bottle of 90 tablets (Ex-Works).](https://clintonhealth.box.com/s/o10yxb6nzimzykwarxmplgksw4jffyct) For a child in the 10-13.9 kg weight band, the pppy cost for ABC+3TC+DTG (10 mg) is ~$117.

**Table 6**: Annual Cost of Treatment Comparison (USD, Ex-Works)\*

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Product** | **3-5.9 kg** | **6-9.9 kg** | **10-13.9 kg** | **14-19.9 kg** |
| **ABC/3TC (120/60 mg Disp/Scored) + DTG (10 mg) Disp./Scored** | $49 | $88 | $117 | $146 |
| **ABC/3TC/LPV/r (60/30/40/10 mg) '4-in-1' Granules in Capsules** | $183 | $274 | $365 | $456 |
| **ABC/3TC (120/60 mg Disp/Scored) + LPV/r (40/10 mg) Pellets** | $223 | $334 | $445 | $557 |
| **ABC/3TC (120/60 mg Disp/Scored) + LPV/r (40/10 mg) Granules** | $262 | $393 | $524 | $655 |

*\*Based on global benchmark ARV prices as of November 2020 and published WHO dosing*

# FAQs – Administration

***8. How should pDTG be administered?***

Dispersible formulations allow pDTG to be easily administered to children by dispersing the medication in a small volume of water to drink, rather than having to swallow multiple pills, pellets, or granules.. Caregivers should be guided to add the recommended dose of pDTG to 5 mL [1 teaspoon] (if using 0.5 or 1.5 tablets) or 10 mL [2 teaspoons] (if using 2 or 2.5 tablets) of clean water, stir until the tablet(s) disintegrates, and administer to the child. If the tablet(s) are not dissolving (i.e., lumping), stir the solution while slowly adding additional water until they dissolve (the tablet(s) may also be crushed and then stirred to aid in dissolution). If any medicine remains in the cup after administering the solution, caregivers should add an additional 5 mL (1 teaspoon) of water to the cup, swirl, and give it to the child. This is to ensure that the child is getting the full dose. Repeat again if any medicine still remains in the cup. The child should ideally drink all the water straight away or within a maximum of 30 minutes.

***9. Can ABC/3TC 120/60 mg dispersible tablet (or other dispersible backbones) and pDTG be dispersed and administered simultaneously in the same solution?***

Yes, pDTG can be dispersed and administered in the same solution of clean water as ABC/3TC 120/60 mg DTs. Follow weight-based dosing guidelines for both pDTG and ABC/3TC 120/60 mg to determine the correct number of pills of each medicine to give to the child. When co-administering pDTG with ABC/3TC 120/60 mg DTs, use between 10-20 mL (2-4 teaspoons). Follow the same administration steps in FAQ #8 to make sure the child receives the full dose. In all dosing scenarios, it is important to make sure all tablets are properly dissolved, while still keeping in mind that large volumes of water should be avoided as it will be difficult to ensure the entire dose is consumed and may lead to spillage.

***10. Can pDTG be dispersed and administered in liquids other than water (such as juice or breast milk) or in food (such as yoghurt or porridge)?***

Ideally, pDTG should be dispersed in clean water. However, if a child is unable to take pDTG in water, it may be reasonable to mix pDTG (and ABC/3TC) with other age-appropriate liquids such as juice or breast milk or foods such as yoghurt or porridge. If needed when disbursing in food, the pDTG (and ABC/3TC) tablet can be crushed to aid in mixing. Finally, if using other liquids or foods for administration, follow the same volume recommendations as mentioned in FAQ #8 and #9 to ensure the child takes the full dose of medicine.

***11. Over how many minutes should a caregiver be advised to have their child swallow the pDTG solution (i.e., if it cannot be swallowed all at once)?***

Caregivers should be advised that children should either drink the solution straight away or within 30 minutes.

# FAQs – Side Effects and Special Populations

***12. What are the side effects associated with pDTG?***

Clinical studies (such as IMPAACT P1093), in which no participant permanently discontinued pDTG due to adverse events, suggest DTG is well tolerated in CLHIV. Events identified were attributed to the ARVs used in combination with DTG. As with all ARVs, it is possible to have side effects when taking pDTG, but side effects with pDTG are rare. pDTG may cause insomnia, fatigue, and headache. While weight gain has been a common side effect of DTG 50 mg in adults. Findings from [the ODYSSEY trial](https://theprogramme.ias2021.org/PAGMaterial/PPT/1603_3936/ODYSSEY_Weight-gain_poster_IAS_2021_A-IAS2021-01311_final.pdf) presented at IAS 2021 found no cases of excessive weight gain in children. Though there is no current evidence to suggest a problem with weight gain in children, it still must be monitored regularly. Incidence of high blood sugar following DTG has also been reported in ART-experienced adults. Related symptoms such as polyuria and polydipsia should also be monitored routinely. It is important to report all side effects and adverse events to national pharmacovigilance units.

***13. How should pDTG be used in CLHIV with TB?***

DTG interacts with the TB medicine RIF such that DTG levels in the blood are reduced. Children receiving TB treatment with RIF should have their daily standard dose of pDTG doubled for the duration of TB treatment (i.e., they should be given their daily standard dose of pDTG twice a day – one dose in the morning and one dose in the evening). This has been evaluated in the ongoing ODYSSEY trial with the 50 mg film tablet formulation and demonstrated to be safe in CLHIV more than 6 years of age and over 20 kg. The treatment of CLHIV less than 6 years of age on RIF should reflect a country’s national guidance. Further, caregivers should follow local guidelines on when to switch back to standard once daily doses after a child completes TB therapy.

# FAQs – Transition Considerations

***14. Should children who are stable on other regimens be transitioned to pDTG? Should children who are unstable on other regimens be transitioned to DTG?***

Given the significant benefits of pDTG highlighted in this document, the WHO recommends that all existing virally suppressed children over 4 weeks of age and who weigh 3 to <20 kg be transitioned to pDTG. While some children may be stable on their current regimen, pDTG’s substantial clinical and administrative benefits over other existing regimens mandates stable children be transitioned to pDTG (in the absence of any known contraindications).  
  
Similarly, children over 4 weeks of age and who weigh 3 to <20 kg who are unstable on their current regimen should be transitioned to pDTG. pDTG is recommended as part of second-line and third-line regimens and thus children with elevated viral loads can be safely transitioned to pDTG. As noted in FAQ #15 below, adherence counselling and assessment of resistance to partner drugs in patients’ current regimen should be conducted to maximize their chance of success on their new regimen.

***15. Is a viral load test required before switching a patient to pDTG?***

Routine viral load monitoring is encouraged as a good practice in the care of patients on ART in accordance with WHO recommendations. However, viral load testing should not be a requirement for transitioning to any optimal regimen. All children over 4 weeks and who weigh 3 to <20 kg should be transitioned to pDTG irrespective of viral load status. This includes stable patients and those currently failing their first- or second-line regimens. A viral load test should not be a barrier to pDTG access.   
  
As pDTG is recommended as part of second-line and third-line regimens, children with elevated viral loads can be safely transitioned to pDTG. However, a child failing their current regimen would nevertheless benefit from counselling to identify and limit any adherence barriers to maximize their chance of success on their new pDTG-based regimen. In addition, for children with detected viral failure, an assessment of resistance to partner drugs in their current regimen is also warranted to inform future treatment decisions.

# FAQs – Medication Interactions

***16. What are the interactions between DTG and commonly prescribed medications?***

Drugs that are metabolic inducers may decrease the plasma concentrations of DTG. This includes some anticonvulsants such as phenytoin or phenobarbital. Co-administration with these anticonvulsants is not recommended with DTG. Consult expert opinion or consider substituting DTG with EFV as an alternative. RIF lowers DTG levels and co-administration is not recommended at standard doses. Clinical studies support twice-daily dosing DTG for children treated for TB with RIF-containing regimens. Iron, aluminium, magnesium, and calcium-containing medicines bind with and reduce absorption of DTG. If co-administered, DTG should be taken with food to enhance DTG absorption or taken at alternate times (6 hours apart).

# FAQs – Dosing

***17. How does dosing differ between DTG dispersible and film-coated tablets?***

Dispersible tablets have greater bioavailability than film-coated tablets (FCTs). For example, DTG dose exposure of 50 mg FCT is approximately equal to 30 mg of dispersible tablet (i.e., 3 x 10 mg DTs). In the event that there is a need to transition between the two formulations, ensure appropriate DTG dosing, especially in older children. The originator (ViiV) 10 mg FCT and the 10 mg dispersible tablet are **NOT** interchangeable.

***18. How was the dosing of pDTG determined?***

Drug absorption and metabolism in children is affected by many factors, notably their growth and maturation as reflected by weight, body surface area, and age. Accurate determination of the safe and effective dosing of a drug for any individual depends on an understanding of the drug’s pharmacokinetics (PK) (what the body does to the drug), through PK studies. These are usually conducted in adults first, and then studies in children aim to find the right dose in children of different ages and weights to achieve the same levels as in adults. Two randomised, multi-country PK studies were conducted in children (ODYSSEY & IMPAACT P1093) and have provided the necessary safety data and dosing of pDTG in children.

***19. Why does pDTG dosing jump from 0.5 to 1.5 between the 3 to <6 kg and 6 to <10 kg weight bands?***

Drug metabolism in young children varies significantly as they age. The PK studies of pDTG in children showed considerable variability in drug levels for children in the 6 months – 2 years of age and 2 – 6 years of age groups, with some children having levels that were lower than the target levels determined in adult studies. For this reason, a higher dose in those age groups was studied and found to reliably achieve the target drug levels for all children studied. Those ages roughly correspond to the weight bands of 6 to <10 kg, 10 to <14 kg, and 14 to <20 kg.