Paediatric Dolutegravir 10 mg Dispersible, Scored Tablets

Implementation Memo

October 2021

CLINTON HEALTH ACCESS INITIATIVE

Unitaid

Acronyms

1L	First-line
2L	Second-line
3L	Third-line
3TC	Lamivudine
4-in-1	Abacavir/lamivudine/lopinavir/ritonavir
ABC	Abacavir
APWG	ARV Procurement Working Group
ART	Antiretroviral therapy
ARV	Antiretroviral
AZT	Zidovudine
CLHIV	Children living with HIV
DRV/r	Darunavir/ritonavir
DT	Dispersible tablet
DTG	Dolutegravir
EFV	Efavirenz
FCT	Film-coated tablet
FDC	Fixed-dose combination
Global Fund	Global Fund to Fight AIDS, Tuberculosis, and Malaria
INSTI	Integrase strand transfer inhibitor
LPV/r	Lopinavir/ritonavir
NNRTI	Non-nucleoside reverse transcriptase inhibitors
NRTI	Nucleoside reverse transcriptase inhibitors
NVP	Nevirapine
pDTG	Paediatric DTG 10 mg dispersible, scored tablets
PEPFAR	President's Emergency Plan for AIDS Relief
PI	Protease inhibitor
PK	Pharmacokinetics
PPPY	Per person per year
RAL	Raltegravir
RIF	Rifampicin
SOC	Standard of care
SRA	Stringent Regulatory Authority
TB	Tuberculosis
TLD	Tenofovir/lamivudine/dolutegravir
US FDA	United States Food and Drug Administration
WHO	World Health Organization

For any questions related to paediatric DTG 10 mg dispersible, scored tablets, please reach out to Ayokunle Abogan (aabogan@clintonhealthaccess.org)

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Summary

CHAI has developed this memo to lay out information for national HIV programmes considering the introduction of paediatric dolutegravir (DTG) 10 mg dispersible, scored tablets (pDTG), a newly available generic formulation of DTG that the World Health Organization (WHO) recommends as the preferred first-line (1L) antiretroviral therapy (ART) for children living with HIV (CLHIV) who are at least 4 weeks of age and weigh at least 3 and up to 20 kg.

pDTG also provides an optimal formulation for DTG use in second-line (2L) in younger CLHIV with confirmed 1L treatment failure of a non-DTG regimen (e.g., based on lopinavir/ritonavir [LPV/r], nevirapine [NVP], or efavirenz [EFV]).

Key Messages

- WHO recommends DTG as the preferred 1L for all adults, adolescents, and children for whom there is approved dosing
- A new 10 mg dispersible, scored tablet formulation of DTG has received SRA approval, and is anticipated to be available in countries from Q2 2021
- This new formulation will enable DTG access for children who weigh at least 3 and up to 20 kg, as well as implementation of the WHO preferred 1L regimen for all CLHIV
- For children who weigh 20 kg or more, the DTG 50 mg single film-coated tablet is recommended in combination with ABC + 3TC, and for those who weigh 30 kg or more, the FDC of TLD is recommended
- Transition to DTG for children will harmonise with adult treatment, simplify sequencing and procurement plans, lower paediatric treatment costs, and make the best available treatment accessible to children in order to improve treatment experience and outcomes

Background

Antiretroviral (ARV) optimisation is critical for all countries to realise their ambitions for reaching the 2030 Fast-Track Targets of ensuring 95% of all infants and children have access to treatment capable of achieving the best outcomes. While progress has been made with almost one million CLHIV now on ART, attaining 95% viral suppression will remain an elusive goal without access to more effective treatment in age-appropriate formulations.

Since 2013, WHO guidelines have recommended LPV/r-based regimens for all CLHIV under 3 years of age; however, the limited availability of a formulation suitable for this age bracket has remained a barrier to implementation. The 2021 WHO Antiretroviral Therapy Guidelines now recommend DTG-based regimens as the preferred 1L regimen for all children aged from 4 weeks and above.[1] Studies in adults have found DTG to achieve viral suppression at higher rates when used as 1L and as 2L in comparison to protease inhibitors (PIs). The availability of a dispersible formulation now provides younger children with access to this potent medicine in a formulation that is easy for them take. pDTG offers improved tolerability over LPV/r, has a better genetic barrier to resistance (as a distinct advantage over non-nucleoside reverse transcriptase inhibitors [NNRTIs]), and is taken once daily (whereas LPV/r and NVP are twice daily). The pDTG dispersible tablet is also more palatable with its strawberry cream flavour when dispersed in water compared to LPV/r's bitter taste, which is present to the greatest extent in the syrup and to a lesser extent in pellets and granules.

Table 1: Preferred 1L Paediatric Treatment Regimens, WHO 2021

Population	Preferred 1L Regimen	Alternative 1L
Children (≥4 weeks of age & ≥3 kg)	ABC + 3TC + DTG	ABC + 3TC + (LPV/r or RAL) TAF + (3TC or FTC) + DTG
Neonates	AZT + 3TC + RAL	AZT + 3TC + NVP

This new guidance coincided with two generic manufacturers, Viatris (formerly Mylan) and Macleods, filing for regulatory approval of pDTG with the United States Food and Drug Administration (US FDA). Viatris has since received tentative US FDA approval (19th November 2020)[2], and Macleods also received tentative US FDA approval (16th March 2021)[3]. Based on these approvals, 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. This new generic formulation unlocks DTG access to CLHIV who are at least 4 weeks of age and weigh less than 20 kg. The 2020 WHO Policy Brief included for the first time DTG dosing for children less than 20 kg (see Table 3). For children over 20 kg, abacavir + lamivudine (ABC + 3TC) is combined with the DTG 50 mg single tablet, and for those over 30 kg, the fixed-dose combination (FDC), tenofovir/3TC/DTG (TLD), is recommended.

Table 2: DTG formulations for all children from 4 weeks of age

Weight	WHO Recommended Formulation
< 20 kg	ABC/3TC (120/60 mg) dispersible dual **+ DTG 10 mg dispersible scored**
20 to 24.9 kg*	ABC/3TC (120/60 mg) dispersible dual **+ DTG 50 mg single**
25 to 29.9 kg	ABC/3TC (600/300 mg) dual + **DTG 50 mg single**
≥ 30 kg	FDC **TDF/3TC/DTG** (300/300/50 mg)

**The switch to DTG 50 mg at 20 kg should only occur if the child is able to swallow whole tablets*

[1] 2021 WHO Antiretroviral Therapy Guidelines.
[2] Viatris DTG 10 mg Dispersible, Scored Tentative US FDA Approval Letter.
[3] Macleods DTG 10 mg Dispersible, Scored Tentative US FDA Approval Letter.

Table 3: WHO recommended dosing for DTG 10 mg dispersible, scored tablet

Weight	Recommended Daily Dose	Number of Daily Tablets
3 to < 6 kg	5 mg once daily	0.5
6 to < 10 kg	15 mg once daily	1.5
10 to < 14 kg	20 mg once daily	2
14 to < 20 kg	25 mg once daily	2.5

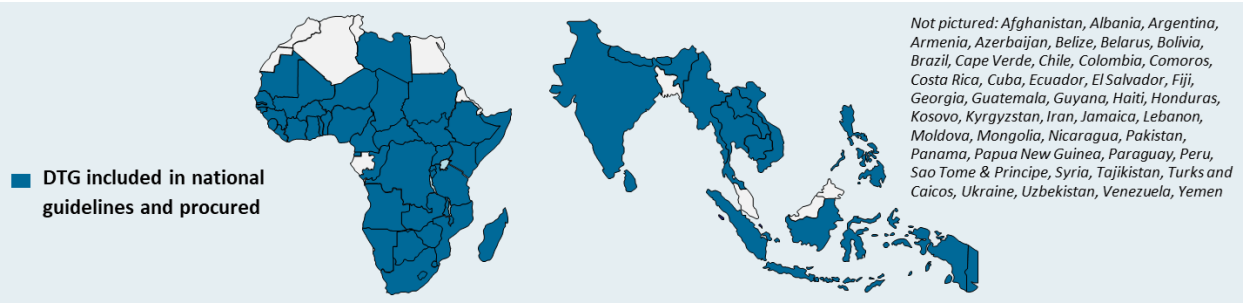
Table 4: WHO recommended dosing for ABC/3TC 120/60 dispersible, scored tablet

Weight	Number of Daily Tablets
3 to < 6 kg	1
6 to < 10 kg	1.5
10 to < 14 kg	2
14 to < 20 kg	2.5

Clinical Advantages to pDTG

ARV regimens containing NNRTIs have dominated 1L ART for adults in low- and middle-income countries. Over the past two years, many countries have adopted DTG - an integrase strand transfer inhibitor (INSTI) – in the form of a once daily FDC of TLD for adult (and adolescents where eligible) 1L treatment. This provides significant potential for programmes to improve clinical outcomes, patient quality of life and adherence, reduce migration to costlier and less tolerable 2L therapy, and accelerate national progress towards the 95-95-95 goals.

Figure 1: Global adoption and procurement of DTG[3]



Today marks a pivotal point where the same benefits and opportunities which have been afforded to adults are now available for CLHIV. Access to pDTG will allow for harmonisation with adult treatment regimens to simplify treatment guidance and reduce the risk of inappropriate dosing and stock-outs.

[3] APWG Q3 2020 Anticipated Demand Forecast (September 2020).

Multiple phase 3 trials in adults confirm that DTG is superior or non-inferior to NNRTIs, PIs, and other INSTIs across virtually every relevant metric. Expected benefits to children and programmes include:

Efficacy and Use

- Superior efficacy with better virologic response than standard of care NNRTIs and PIs (based on ODYSSEY trial in children).
- Increasing NNRTI resistance necessitates transition away from EFV- and NVP-based regimens; lack of prior individual and population exposure means virtually all patients will have DTG-susceptible virus.
- DTG's high genetic barrier to developing resistance is a significant advantage over NNRTIs. Children and adolescents who have notable adherence barriers will benefit from the extra "forgiveness" of a DTG-based regimen.
- DTG is versatile for use in second-line (2L) and third-line (3L).
- A dispersible formulation of DTG allows even young infants to have access to optimal ART without the need for a cold chain or the other inconveniences of a syrup.

Note: *Precautions must still be taken in particular circumstances where needed (e.g., in concomitant use with other medicines such as rifampicin [RIF] for tuberculosis [TB] or anticonvulsants). See FAQs section for more details.*

Tolerability

- Better side-effect profile and improved tolerability over LPV/r, which has been associated with diarrhoea, hyperlipidaemia, and decreased bone density.
- Reduced neuropsychiatric side effects compared to EFV.
- In the entirety of the IMPAACT P1093 study, not a single child discontinued DTG dispersible tablets because of intolerance or toxicity.

Improved Adherence

- DTG is taken once daily, whereas LPV/r is taken twice daily.
- DTG dispersible tablet allows easier administration versus LPV/r formulations.
- With its strawberry cream flavour when dispersed in water, DTG dispersible tablet is more palatable in comparison to LPV/r's bitter taste.
- As a dispersible tablet, DTG administration is simple after adding to a small volume of clean water.

Cost Saving

- pDTG offers considerable cost savings over alternative paediatric formulations.[4] For a child in the 10-13.9 kg weight band, the per patient per year (pppy) cost for ABC+3TC+DTG (10 mg) is ~US$117, compared to US$365 for ABC/3TC/LPV/r (4-in-1), a savings of US$248 pppy.

Table 5: 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*

[4] Unitaid-CHAI pDTG Pricing Agreement Announcement (November 2020)

Alternatives

In 2021, the FDC of ABC+3TC+LPV/r (4-in-1) in a granular form may also receive global stringent regulatory authority (SRA) approval. While not offering all the benefits of DTG highlighted above, this is an improved option of the current LPV/r granule and pellet formulations that are available for CLHIV <20 kg. The 4-in-1 will be first made by Cipla and is currently being reviewed by the US FDA.

Given the potential close market entry of these paediatric products, countries should consider introduction implications outlined below, with the primary focus being expediting access to DTG. Per the WHO's recommendation to provide DTG-based ART as the preferred 1L regimen, the LPV/r 4-in-1, alongside the current LPV/r pellet and granules formulations, should be an alternative option for infants and younger children who cannot tolerate DTG.

Transition Considerations

Implementing the new WHO recommendations will continue to require careful consideration of existing regimens and the timelines associated with introducing and scaling up new formulations.

To achieve rapid adoption and uptake of pDTG and a smooth transition from less optimal paediatric regimens, decision-makers should develop a strategy and implementation plan that may include the following actions:

Determine timelines for transition to pDTG. Programmes should determine an introduction strategy, which should prioritise WHO-preferred regimens and proactively switch patients on inferior regimens, such as those containing NVP or LPV/r to DTG-based ART. Programmes should consider what the policy, guidelines, supply chain, and budgetary implications and requirements are for the transition. Tools to assist with planning and implementation of pDTG are available on CHAI's HIV New Product Introduction Toolkit. Programmes should aim to transition all patients on legacy regimens to pDTG. This approach provides a simple protocol, avoids complex criteria and checklists, and potentially avoids viral load and other requirements that will fragment and delay the transition process. It enables the programme to share uniform, consistent, and clear messaging and guidance on DTG administration and side effects to patients and care givers.

Determine current stock in the country and orders in the pipeline. When planning the timing of new product introduction, countries that have existing stocks of LPV/r pellets or granules should consider utilising these stocks to enable transition to new formulations with minimal wastage. When new, more optimal ARVs such as pDTG are available in the country, rapidly transitioning to optimal products may be preferable to exhausting existing stocks of an inferior product. For example, with regards to NVP-based regimens, large buyers such as PEFPAR indicated stocks can be allowed to expire in the interest of providing the highest quality treatment to children. CHAI has a number transition tools on the New Product Introduction Toolkit, such as the CHAI Simple Tool,

to help programmes plan and to evaluate phase-in strategies for the multiple new paediatric regimens.

Monitor supply availability from manufacturers. National programmes should monitor market intelligence, such as updates from the Antiretroviral Procurement Working Group (APWG), for any capacity constraints related to new and existing products. Given the large supply of DTG in 1L for adults and the simplified product format in contrast to recent new paediatric products, pDTG is not anticipated to encounter supply concerns. Supply planning should also account for lead times on orders to minimise the risk of stock-outs. Up-to-date information from the APWG and contact details can be found here.

Develop forecasts and procurement plans. These quantifications should consider the phase-out of existing stock of alternative products and may include switching pipeline orders of LPV/r and NNRTI-based regimens to pDTG. Programmes should work closely with procurement agencies in country to ensure alignment between procurement and implementation plans. All country programmes are encouraged to share their forecasts for paediatric formulations with the APWG to support coordination and ensure that manufacturers are prepared to meet demand.

Develop and disseminate key messaging and job aides for clinicians, patient and caregiver groups, and facility-level staff. Smooth transition to pDTG requires programmes to plan and develop tools ahead of time to assist with treatment optimisation. Key resources may include product memos, which describe the product's key features and use, job aides, such as wall chart algorithms to decide if a patient is eligible for the transition, and trainings to ensure effective uptake of the new product. It is also critical that pDTG is fully integrated into existing systems for ordering and reporting, and patient information systems. CHAI and partners are developing a host of tools for pDTG introduction, and these are available on CHAI's HIV New Product Introduction Toolkit here.

Actively monitor uptake and deploy targeted uptake interventions where required. National programmes should develop a comprehensive monitoring plan, track uptake trends, monitor consumption patterns, and support adjustment of supply plan accordingly.

Ensure a robust pharmacovigilance system can monitor patient outcomes. National systems should monitor adverse drug reactions, drug resistance, toxicities, and treatment failure, in line with WHO guidance.

pDTG Frequently Asked Questions

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.

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 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, 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 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). 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
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**Based on global benchmark ARV prices as of November 2020 and published WHO dosing*

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 tablets 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.

12. *What side effects are associated with DTG use?*

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 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.

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

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).

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 table (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.