PAEDIATRIC ABACAVIR/ LAMIVUDINE/ DOLUTEGRAVIR (pALD) FIXED-DOSE COMBINATION:

INTRODUCTION AND ROLLOUT PLANNING CONSIDERATIONS FOR NATIONAL PROGRAMMES

JUNE 2023

Product Acronyms

pABC/3TC	Paediatric abacavir/lamivudine 120/60 mg scored, dispersible tablet
pALD	Paediatric abacavir/lamivudine/dolutegravir 60/30/5 mg dispersible tablet
pDTG	Paediatric dolutegravir 10 mg scored, dispersible tablet

Background

Dolutegravir (DTG)-based HIV treatment regimens are recommended by the World Health Organization (WHO) for children living with HIV (CLHIV) who weigh at least 3 kg. In 2020, the United States Food and Drug Administration (US FDA) granted tentative approval of paediatric DTG 10 mg scored, dispersible tablets (pDTG) for CLHIV weighing a minimum of 3 kg and at least four weeks of age. In early 2021, national HIV programmes in low- and middle-income countries (LMICs) began to transition CLHIV from treatment regimens containing non-nucleoside reverse transcriptase inhibitor (NNRTI) and lopinavir/ritonavir to pDTG. As of the last quarter of 2022, at least 73 countries have already placed or received orders for pDTG[1] and an estimated 130,000 children have transitioned to pDTG.

pDTG currently is administered along with optimised backbone antiretrovirals (ARVs) such as abacavir/lamivudine 120/60 mg scored dispersible tablets (pABC/3TC) per the WHO's 2021 Consolidated HIV Guidelines. This brief aims to inform the transition from pDTG + pABC/3TC to the new fixed-dose combination (FDC) dispersible tablet of paediatric ABC/3TC/DTG 60/30/5 mg (pALD).

Paediatric ABC/3TC/DTG (pALD)

A new dispersible FDC of pALD will provide the regimen in one convenient tablet (see Table 1). In 2022, the US FDA approved ViiV Healthcare's FDC of pALD for CLHIV 10 kg to 24.9 kg. The generic versions are expected to have weight band dosing from 6 to 24.9 kg, following the recent, June 2023, US FDA approval of an extended indication of ViiV's product for infants aged at least 3 months and weighing at least 6 kg. US FDA tentative approval of generic pALD with an indication for use down to 6 kg is expected by the second half of 2023. Generic applications have also been sent to the WHO Prequalification Programme.

Table 1. pALD Product Profile

Tablet Strength	ABC/3TC/DTG 60/30/5 mg
Formulation	Dispersible tablets
Administration	Tablets are dispersed in water only and consumed orally once per day
Taste	Current generic products reviewed by US FDA are strawberry cream flavored
Supply	Multiple generic suppliers are expected[1], with sufficient manufacturing capacity to support the market
Price	Pricing for the generic version will be released upon US FDA tentative approval. Once further information becomes available, details will be shared on the CHAI ARV Benchmark Price Comparison list

1 Quarterly updates on regulatory filings, regulatory approvals, and supply of generic pDTG are publicly available on the MPP website's interactive Access to Medicines Tracker.

Pack size	Where possible, pack sizes that support multi-month dispensing (MMD) and other service delivery efficiencies should be prioritised

Table 2 shows the appropriate number of tablets required for each weight band. There is no requirement to split pALD tablets into two tablets, which is the case with the scored pABC/3TC and pDTG tablets.

Table 2. Weight-based Dosing Comparisons Between Various DTG-based Regimens

Weight Band	Number of Tablets Per Day	
	pABC/3TC 120/60 mg + pDTG 10 mg	pALD: ABC/3TC/DTG 60/30/5 mg
3 to 5.9 kg	1 + 0.5	N/A – use separate products
6 to 9.9 kg	1.5 + 1.5	3
10 to 13.9 kg	2 + 2	4
14 to 19.9 kg	2.5 + 2.5	5
20 to 24.9 kg	3+ 1 DTG (50 mg) tablet	6

It is expected that separate pABC/3TC and pDTG tablets will still be used for children in the 3 to 5.9 kg weight band, at least for the time being, given that the dosing ratio of DTG and ABC/3TC is different for this lower weight band and therefore not amenable to the dose ratio of the FDC.

pALD Introduction Considerations

With regulatory approvals for generic pALD expected in the second half of 2023, country programmes should begin to plan for generic pALD introduction, ensuring that they are not overstocked with pDTG and pABC/3TC. This important step is necessary to avoid preventable wastage. National programmes should consider the following:

1. Forecasting and Quantification

- **Review current stock status and pipeline orders** for pDTG and pABC/3TC to plan for maintenance of patients between 3 to 5.9 kg and transition for patients who are at least 3 months of age and weighing a minimum of 6 kg.
- **Quantify pALD needs** based on eligibility criteria, approved weight bands (see Table 2 above), and existing stock levels of pDTG and pABC/3TC.
    - Procurement of pDTG will still be required for CLHIV in the 3 to 5.9 kg weight band, for CLHIV receiving rifampicin-based treatment for tuberculosis (TB) co-infection, and for children on second-line and third-line treatment who have not previously taken DTG.[2] Therefore, some pDTG should be retained when conducting quantification and forecasting exercises.
    - To help facilitate quantification, the USAID Global Health Supply Chain Program's Procurement and Supply Management (GHSC-PSM) contract developed an algorithm to guide the transition to pALD. GHSC-PSM has started country-specific conversations based on this algorithm.[3] The proposed algorithm can be found in **Figure 1.**
    - Guidance:
        - Convert all stocks into number of treatments for a single weight band to easily compare the stock status. GHSC-PSM uses the 10 to 13.9kg weight band for this purpose with

2 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).

3 For any transition specific questions, please reach out to your local GHSC-PSM field office or contact: pALD-TransitionTeam@ghsc-psm.org.

dosages of: pABC/3TC, 60-tab bottle (Bottle lasts for 1 month [2 tablets per day]); pDTG, 90-tab bottle (Bottle lasts for 1.5 months [2 tablets per day]).

- The excess pABC/3TC monthly treatments are estimated at over 30%, but this percentage can be changed depending on each country's context. Some countries may have a higher need for pABC/3TC after the transition to pALD since it may be needed for a large number of patients that use it with DTG 50 mg or other non-nucleoside reverse transcriptase inhibitor (NNRTI)/ protease inhibitor (PI)/ integrase strand transfer inhibitor (INSTI) products. In some countries, the majority of the patients that currently use pABC/3TC would transition to pALD and the percentage would be lower.

- To enable accurate quantification of stocks needed, paediatric HIV cohort weight band data should be collected. Recognising this may be a challenge, programmes can consider collecting weight band data from a small number of representative sites or utilising published reference data.

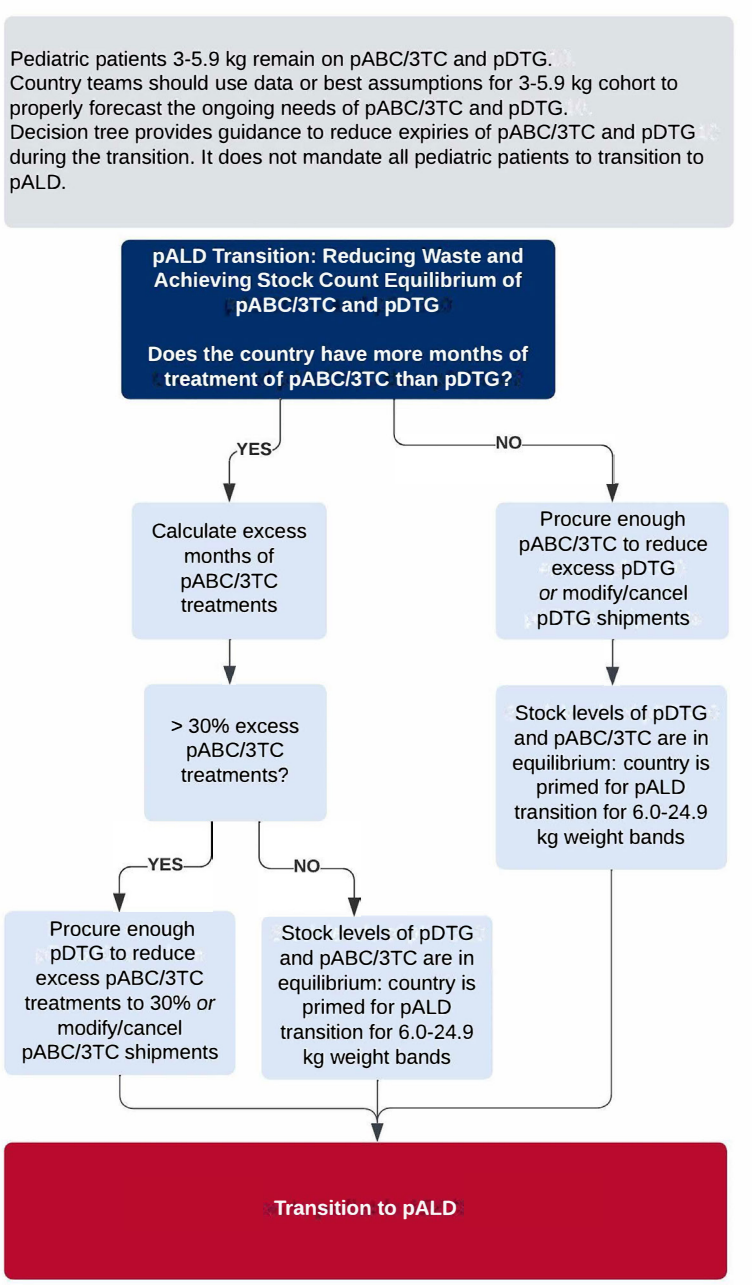

Figure 1. GHSC-PSM pALD transition algorithm[3]

2. Procurement and Introduction

- **As noted above, countries should continue to quantify for some pDTG and pABC/3TC for certain groups of CLHIV.** However, when planning orders, countries will need to account for a reduction in pDTG quantities once pALD is approved and available.
    - Plan future procurement of pDTG and pABC/3TC for children with TB co-infection, children 3 to 5.9 kg, and some children on second- and third-line treatment. Plan for procurement of pALD for children who are at least three months in age and weighing 6 to 24.9 kg.
    - Consider converting future orders of pDTG to pALD (except for quantities required for the groups specified above).
- **Develop a transition plan for pALD,** likely in a phased manner to minimise wastage of pDTG and pABC/3TC. Please note, pALD is approved for children up to 24.9 kg and its use for children between 20-24.9 kg may depend on the context and the child (including whether they can swallow pills) and therefore whether they are ready to transition to other formulations available, including DTG 50 mg + ABC/3TC.
    - Although the formulation is changing, the drugs remain the same. Programmes should minimise wastage during the transition; consequently, overstocks of either pDTG or pABC/3TC should be matched with orders of the companion formulation to ensure a complete regimen.

Table 3. Supply Planning: One-Year supply for One Child Living with HIV weighing 10-13.9 kg

<table>
<tr><th colspan="2">pABC/3TC 120/60 mg + pDTG 10 mg</th><th colspan="2">pALD: ABC/3TC/DTG 60/30/5 mg</th></tr>
<tr><th>Product</th><th># of Bottles/Year</th><th>Product</th><th># of Bottles/Year</th></tr>
<tr><td>DTG 10 mg (90-tab bottle)</td><td>8 bottles</td><td rowspan="5">pALD 180-tab bottle

OR

90-tab bottle</td><td rowspan="5">8 bottles

OR

16 bottles</td></tr>
<tr><td>ABC/3TC 120/60 mg (30-tab bottle)</td><td>24 bottles</td></tr>
<tr><td colspan="2">OR</td></tr>
<tr><td>DTG 10 mg (90-tab bottle)</td><td>8 bottles</td></tr>
<tr><td>ABC/3TC 120/60 mg (60-tab bottle)</td><td>12 bottles</td></tr>
</table>

3. Training and Capacity Building

- **Modify materials in the paediatric HIV training package** to include content on pALD.
    - pALD and pDTG administration will be nearly identical and simplified, given that pALD tablets do not need to be broken in half (see Table 2). Training needs are expected to be minimal.
    - Update national- and facility-level product ordering, prescription and stock monitoring tools so that these tools include the ability to order, prescribe, and monitor the consumption of pALD.
- **Conduct national-level refresher trainings** on paediatric antiretroviral therapy (ART) administration and supply management, including new content on pALD.

- **Engage communities of people living with HIV (including caregivers of CLHIV)** to support demand generation and caregiver literacy.

4. Monitoring

- **Review and adapt monitoring and evaluation (M&E) systems** and regimen coding to ensure that the uptake monitoring of DTG-based products is simplified, functional, and accounts for different regimens and formulations.
- **Review pDTG and pABC/3TC phase-out and pALD uptake** on an ongoing basis and course-correct as needed.

As additional tools and resources are developed to support national pALD decision-making and introduction, they will be published on the HIV New Product Introduction Toolkit at www.newhivdrugs.org. This information will also be shared on the AIDS Free Toolkit and WHO Paediatric ARV Dosing Dashboard.

ABOUT THE PDTG TASK TEAM OF GAP-F'S PRODUCT ACCESS AND TREATMENT DELIVERY (PATD) WORKING GROUP

The pDTG Task Team is a GAP-f forum for coordination among partners involved in the introduction of paediatric DTG-based regimens. The pDTG Task Team is a platform to share what partners are already doing, identify where work can be complementary, and most importantly, identify the gaps that need to be addressed and where GAP-f and partners could help ensure that paediatric DTG-based regimens can be scaled-up as quickly as possible. Organizations participating in the pDTG Task Team include: Clinton Health Access Initiative (CHAI); Drugs for Neglected Diseases initiative (DNDi); Elizabeth Glaser Pediatric AIDS Foundation (EGPAF); Global Fund to Fight AIDS, Tuberculosis and Malaria; International AIDS Society (IAS); International Center for AIDS Care and Treatment Programs (ICAP); Médecins Sans Frontières (MSF); Medicines Patent Pool (MPP); Pan American Health Organization (PAHO); Paediatric-Adolescent Treatment Africa (PATA); Therapeutics Research, Education, and AIDS Training in Asia (TREAT Asia); UNAIDS; UNICEF; PEPFAR implementing agencies US Agency for International Development (USAID), US Centers for Disease Control and Prevention (US CDC) and US Department of State; and World Health Organization (WHO).

ABOUT THE GLOBAL ACCELERATOR FOR PAEDIATRIC FORMULATIONS (GAP-F)

GAP-f is a WHO Network hosted within the Research for Health Department in the Science Division at WHO and was created to respond to the paediatric treatment gap. Following the resolution at the 69th World Health Assembly on promoting innovation and access to quality, safe, efficacious, and affordable medicines for children, GAP-f was conceived to build on and formalize the model developed within the HIV community to provide a sustainable mechanism that ensures that safer, more effective, and more durable paediatric formulations are developed and made available to children against an accelerated timeline. More information is available at https://www.who.int/initiatives/gap-f.

Signatory: This brief was developed by the GAP-f pDTG Task Team

Website: https://www.who.int/initiatives/gap-f | **Email:** gap-f@who.int