**Introduction of Paediatric Dolutegravir (DTG) 10 mg Dispersible, Scored Tablets (pDTG) in *Country X***

Transition Plan 2021

*October 2021*

# Introduction & Background

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]](#footnote-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]](#footnote-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* |

**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 |

*[Provide a background on the pediatric landscape in country. Cover the following elements:*

* *Number of CLHIV and number of CLHIV on ART*
* *Current ART regimens (as per country guidelines)*
* *Viral suppression rates*
* *Why is there a need to switch to optimal regimens?*
* *MOH decision to switch to pDTG, eligible populations, etc.]*

# Scope and Purpose

The purpose of this document is to support the [relevant HIV/ AIDS programme in country] manager and officers, treatment centers and facilities, the Ministry of Health Pharmacy Department as well as technical assistance providers to plan and implement a transition to the new preferred pediatric regimen.

Having a transition plan in place reduces and removes certain risks. When new regimens are introduced, it is important, for example, to ensure active communication to healthcare workers (HCWs) and create a comprehensive and appropriate orientation curriculum. Similarly, forecasting and quantification, especially timing of procurement and delivery of new medicines, is important to ensure that the country is prepared to begin the transition and that there will be no shortages. National level quantification plans need to be aligned with implementation plans at the levels of treatment centers. The [insert working group name] has considered all aspects of introducing pDTG as the preferred pediatric regimen for children <20 kg and the summary of the transition plan is detailed in this document.

The scope of this document is to provide key information on all aspects associated with introduction of pDTG in country X. The major sections within this document are outlined in order below:

High-Level Introduction Plan

Technical Processes

Forecasting, Quantification, and Procurement

Training Plan

Monitoring & Evaluation

Pharmacovigilance and Drug Resistance Surveillance

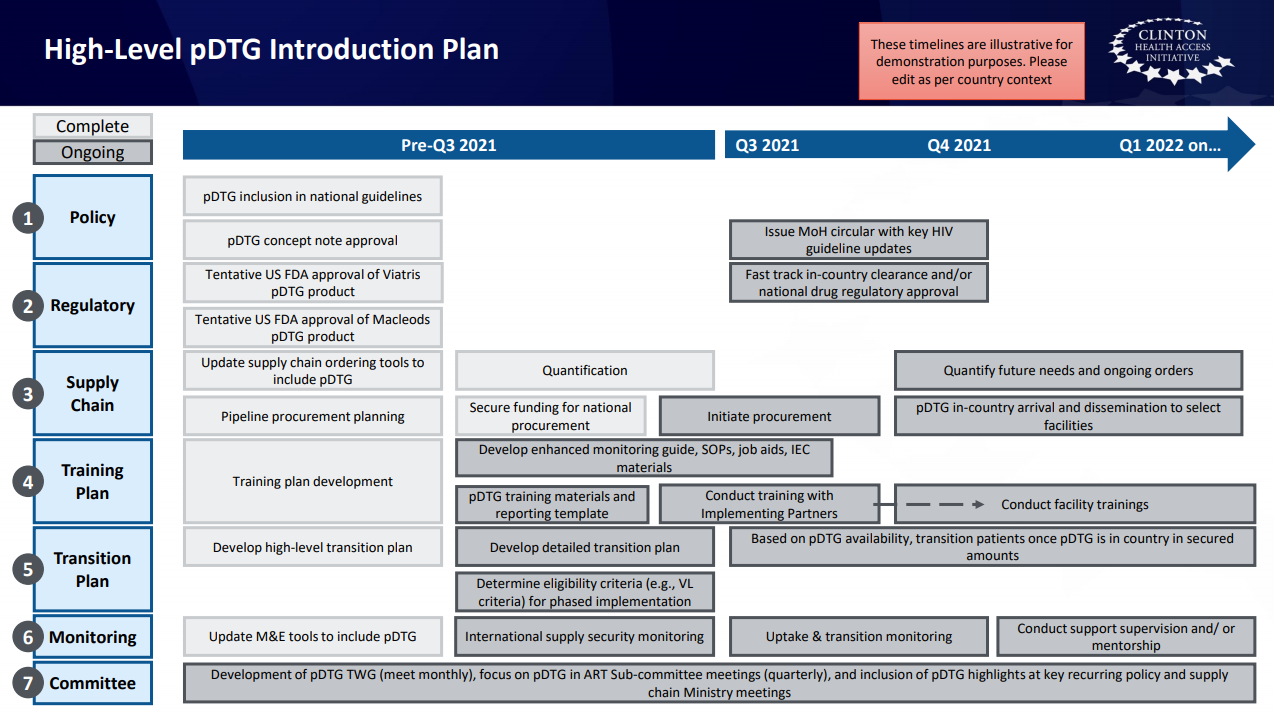
Anticipated Risks and Mitigation Strategy

Roles & Responsibilities

Select sites for pDTG introduction and scale-up

# High-Level Introduction Plan

*[Potentially create a graphic such as the one below, that summarizes the high-level introduction plan for pDTG-based regimens.]* A detailed discussion of each core area will be presented in this guide.

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# Technical Processes

## Establishing a dedicated technical working group (TWG) for national pDTG decision-making

*[Include information on the key decision-making body; content should include details of key stakeholders (MOH, CHAI, CDC, USAID, GF, other IP details, Community, etc.), frequency to meetings, etc.]*

## Updating National ART Guidelines

*[Provide status on guidelines review and revision; plans for dissemination to all stakeholders—either via new revised guidelines or a memorandum/ circular; provide screenshot of latest guidelines containing pDTG, if available]*

## Registering the product in-country

pDTG received its first tentative US FDA approval (through Viatris) in November 2020 and second approval through Macleods in March 2021. *[update with information on in-country registration status]* In-country product registration, clearance, and regulation will be continually monitored and are not expected to pose any challenges to introduction.

## Monitoring International Regulatory and Manufacturing Capacity

Given the large supply of DTG formulations for adults and the simplified product format and manufacturing process in contrast to recent new paediatric products such as LPV/r granules and pellets, pDTG is **not** anticipated to encounter supply concerns. The programme will monitor market intelligence, such as updates from the Antiretroviral Procurement Working Group ([APWG](https://www.arvprocurementworkinggroup.org/?l=en.)), for any updates on the supply and delivery of pDTG.

## Updating M&E tools

The [order form, dispensing logs; list all M&E tools that will be updated] will be updated to include the new formulation. Training plans for stock management and ordering are specified in Section 4.

Patient monitoring tools will also be updated to include pDTG-based formulations to ensure visibility into roll-out progress.

# Forecasting, Quantification, and Procurement

## Forecasting and Quantification

*[Insert summary of how the quantification was done or will be done, including all assumptions; also provide update on orders placed, expected delivery dates, and when pDTG volumes will be reviewed next]*

The chart below provides a high-level overview of the national transition plan divided by public/private and phase I/ phase II.

|  |
| --- |
| ***Table 5: National Roll-Out High-Level Summary at Facility-Level for Patients*** |
|  |

## Transition Plan

### Current Stock on Hand and Pipeline

*[summarize SOH and pipeline of legacy regimens and pDTG]*

### Transition of Existing Patients

*[specify transition strategy for existing patients—*Given the significant benefits of pDTG, the WHO recommends that all existing stable children and children failing treatment 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.   
  
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*.*

[*categorically mention if there is a separate strategy for stable patients vs those failing treatment*]

Starting *[insert relevant month and year here]*, eligible existing CLHIV on non-optimal regimens *[insert relevant patient category here]* will begin a phased substitution onto a pDTG-based regimen. A summary of the proposed regimen substitution is summarized in Table 6 below.

|  |  |  |
| --- | --- | --- |
| ***Table 6: Proposed Optimal Regimen Substitution for CLHIV (4 weeks of age and weighing <20 kg)*** | | |
| ***Current Regimen*** | ***Confirmed Viral Suppression\**** | ***Confirmed Treatment Failure\*\**** |
| ***Recommended Regimen*** | ***Recommended Regimen*** |
| ***ABC****/3TC/****LPV/r*** | ***ABC****/3TC/****DTG*** | ***AZT****/3TC/****DTG*** |
| ***ABC****/3TC/****EFV*** |
| ***ABC****/3TC/****NVP*** |
| ***AZT****/3TC/****LPV/r*** | ***AZT****/3TC/****DTG*** | ***ABC****/3TC/****DTG*** |
| ***AZT****/3TC/****EFV*** |
| ***AZT****/3TC/****NVP*** |
| *Other* | *Seek expert opinion* | |
| *\** *Viral suppression is defined as HIV-1 RNA <1,000 copies/ml from a test completed within the past 12 months. However, viral load testing should not be a barrier to pDTG access.*  *\*\* Following national HIV treatment failure guidelines.*  ***Note:*** *Absence of viral load testing should not be a barrier to pDTG access.* | | |

### Initiation of New Patients

All newly initiating children living with HIV on ART over 4 weeks of age and weighing between 3-20kg should initiate on pDTG with ABC/3TC (120/60mg) dispersible scored tablets. Dosing for both products should be determined based on the child’s weight. *[specify strategy for new patients]*

### Multi-month dispensing strategy

*[include country’s guidance on MMD for CLHIV, eligibility, etc.]*

### Funding/ Funding Gap

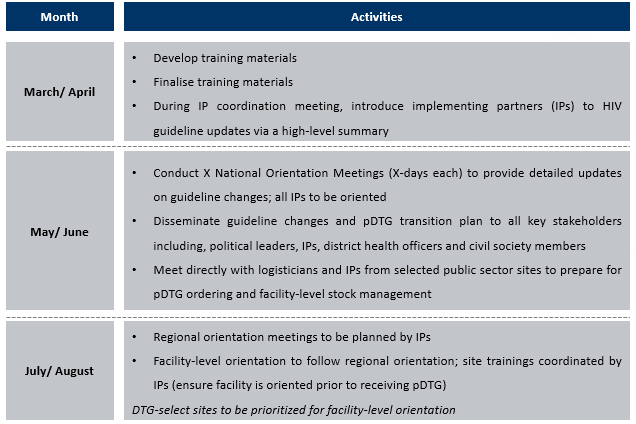
*[summarize the funding strategy and any potential funding gap for pDTG]*

# Training Plan

## Training Cascade

Healthcare worker (HCW) training should be implemented as part of a transition to a new product, even if the training is minimal. This reduces confusion and potential unintended misuse of the product.

In this case, a training summary with timeline is show below*.* This timeline will be followed in terms of materials development, dissemination, and training nationally. IPs will be expected to ensure that their facilities receive the appropriate pDTG orientation prior to XX 2021 to ensure a smooth roll-out.



*[potentially list the sites that will be prioritized for training according to the transition plan]*

## Mode of Training

*[edit the below, as per context; should include format of trainings (Central-level training followed by facility-level, etc.), attendees, trainer details, COVID-19 considerations]*

The initial orientation will be done at a Central Training for IPs which will involve X-Y personnel *[insert those responsible for delivering the training and the intended attendees]* from each IP depending on the size of the IP and number of facilities supported. The central level orientations will be conducted by Ministry of Health personnel with support from CHAI. Each IP will then be responsible for orientating their respective sites and ensuring proper mentorship to support the *Guidelines Circular* that will be issued. The facility-based orientations will be conducted by the trained IP personnel and Ministry of Health Resource persons.

While the intention is to conduct in-person trainings, the format of training might change in light of Covid-19 restrictions in the country.

Orientation materials will include a power point presentation, flip chart, and desktop job aid.

## Key Communication Documents

*[list all the documents that the MOH intends to disseminate, examples below]*

The Ministry will disseminate the following materials:

Updated HIV Guidelines and Circular à reprint and dissemination of the updated HIV Guidelines which includes a section highlighting all key changes allowing facilities to plan (of which the orientations will focus)

VL Testing Guidance Circular à provide detailed guidance on VL for substitution of existing patients onto pDTG-based regimens

Stock Management and Ordering Circular à guidance for public sector facilities on how to appropriately order and manage existing stock to limit wastage and ensure no expiries

High-level communication from the Ministry regarding HIV Guideline updates to patients and civil society

pDTG Healthcare Worker (HCW) Training Curriculum à for HCW to refer to the national guidance on pDTG and how to prescribe it

pDTG Job Aid for HCWs à serve as a tool for facility use by HCWs who have been trained on pDTG and serve as an on-hand reference for key clinical guidance and recommendations

## Community Engagement

In order to ensure a strong understanding of the product, Country X will plan to work closely with communities. Through active engagement at the global and national level, the Community Advisory Board (CAB) will lead the development of treatment literacy materials for communities.

Country X’s engagement with the community is summarized in Table 7 below:



# Monitoring & Evaluation

Careful monitoring of the stock on hand and consumption rates is important before and during transition as the scale-up of orientation could alter consumption rates in country. Product uptake will be monitored using the *XYZ* on a bi-monthly basis. Availability of stock at the warehouses will be monitored using the *Central Level stock status reports* and any interventions to increase/ decrease central supply depending on the product uptake will be brainstormed at the monthly Commodity Security Group meetings. Availability of stock at the facilities will be monitored on a bi-monthly basis using *XYZ* data. Stock re-distribution to avert stock outs or wastage will be recommended using this data. Monitoring is particularly important given the high volume of patients that will be transferring or initiating onto pDTG.

Phase I facilities will be prioritized for all orientation, mentorship, and monitoring activities to ensure a smooth product introduction.

*A summary of all product monitoring activities for the duration of the DTG Transition is below:*

|  |  |
| --- | --- |
| ***Monitoring Area*** | ***Monitoring Tools*** |
| ***International Supply Chain*** | *International manufacturing capacity and supply of pDTG will be monitored to ensure available volumes of stock via in-country access to* [*ARV Procurement Working Group*](https://www.arvprocurementworkinggroup.org/?l=en.) *(APWG) information; CHAI and USAID serve on this committee and will inform the country of key developments* |
| ***Rapid Consumption Monitoring*** | *The CHAI* [*Rapid Consumption Monitoring Tool*](https://clintonhealth.app.box.com/s/dfr43vh9s6z85h7tacgwir28i98dvpus) *can be used to monitor uptake on a monthly basis in the early stages of rollout, to compare the actual consumption of pDTG at the facility level against forecasted uptake trends in the hopes of identifying any potential issues of under consumption or overconsumption* |
| ***Domestic Stock-On-Hand and Patient Consumption*** | *Warehouse Issues Data*  *Central Level Online Stock Status Dashboard*  *ARV Stock Status* |
| ***Facility Orientation Monitoring*** | *IPs will provide necessary updates in order to monitor orientation coverage by district and facility* |
| ***Facility-Level Mentorship*** | *Mentorship will occur monthly for the first six months and thereafter quarterly following pDTG national introduction at facilities to ensure efficient uptake. Facilities that are identified as struggling will be provided with additional support and an intervention strategy* |
| ***Pharmacovigilance and Drug Resistance Surveillance*** | *Monitoring details are in the following section* |
| ***Total DTG Transition Review*** | *A total review of the pDTG roll-out process will occur 9-13 months following national pDTG introduction to capture key learnings in order to improve new product introductions in the future* |

# Pharmacovigilance and Drug Resistance Surveillance

## Pharmacovigilance (PV)

As with all ARVs, it is possible to have side effects when taking pDTG. However, in clinical studies, no participants permanently discontinued DTG due to adverse events from pDTG. Possible side effects include insomnia, fatigue, and headache. These side effects tend to be most common on first taking pDTG and tend to improve with time (approximately 1-2 months).

Weight gain has been a common side effect of DTG 50 mg in adults. The ODYSSEY trial found no incidences of excessive weight gain in children, and though there is no current evidence to suggest a problem with weight gain in children, it must be monitored regularly.

Incidence of high blood sugar following DTG has also been reported in ART experienced adults. Related symptoms such as polyuria, polydipsia should also be monitored routinely.

All side effects and adverse events must be reported to *[insert relevant unit/ site information and populate with country’s PV approach and protocols; include following elements:*

*Who should HCW report to in case of any adverse drug reactions? How? (are there forms, websites, etc.?)*

*What is the timeline for reporting these AEs? (example from Uganda: Serious reactions should be reported within 24 – 48 hours and all other reactions should be reported as soon as possible but not later than 15 days)]*

## Drug Resistance Surveillance

*[mention the bodies within the country that will be monitoring drug resistance, if relevant]*

# Anticipated Risks and Mitigation Strategy

*[See below examples of risk types/ categories; please add/ edit as relevant]*

|  |  |  |
| --- | --- | --- |
| ***Risks and Mitigation Strategy*** | | |
| ***No.*** | ***Risk*** | ***Mitigation Strategy*** |
| ***Supply Chain Risks*** | | |
| ***1*** | ***Funding for ARVs*** *(if inadequate)* |  |
| ***2*** | ***National supply and distribution challenges*** |  |
| ***3*** | ***International manufacturing capacity*** |  |
| ***5*** | ***Slow uptake of DTG based regimens*** |  |
| ***6*** | ***Regulatory challenges*** |  |
| ***7*** | ***High stock levels of legacy formulations*** |  |
| ***Communication Risks*** | | |
| ***8*** | ***Resistance to regimen change by patients*** |  |
| ***9*** | ***Resistance to change of prescription patterns by prescribers*** |  |
| ***Facility-Level Risks*** | | |
| ***10*** | ***HCW constraints*** |  |
| ***11*** | ***Occurrence of previously unidentified side effects*** |  |
| ***COVID-19 Risks*** | | |
| ***12*** | ***Travel restrictions*** |  |
| ***13*** | ***Restrictions on in-person meetings*** |  |

# Roles & Responsibilities

|  |  |
| --- | --- |
| **STAKEHOLDERS** | **KEY RESPONSIBILITIES** |
| **National** | * National HIV Programme:   + Coordination, mentoring/ coaching, collaboration, monitoring and evaluation, and support supervision   + Budgeting and planning * Warehouses: Procurement and distribution of commodities * Supply Chain unit: Forecasting, quantification and procurement of commodities |
| **District** | * Reporting with support from the district biostatistician * Provide oversight and support to health facilities to implement transition to pDTG * Support supervision and mentorship to health facilities to support implementation |
| **Implementing Partners** | * Jointly work with district teams and mentors to train and mentor health workers on pDTG * Support reporting, data use and performance reviews at the health facility level through the district |
| **Health Facility** | * Transition eligible children living with HIV to pDTG * Routinely collect patient data and ensure accurate and complete documentation in the registers * Quantification and ordering supplies * Client and caregiver education |
| **Civil Society** | * Develop treatment literacy materials, provide adherence support, and generate demand |

# Select Sites for pDTG introduction and scale-up

*[Provide detailed list/ screenshots of all facilities where pDTG will be introduced]*

1. [2021 WHO Antiretroviral Therapy Guidelines](https://apps.who.int/iris/rest/bitstreams/1357089/retrieve). [↑](#footnote-ref-1)
2. [Viatris DTG 10 mg Dispersible, Scored Tentative US FDA Approval Letter](https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2020/214521Orig1s000TAltr.pdf).

   3 [Macleods DTG 10 mg Dispersible, Scored Tentative US FDA Approval Letter.](https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2021/214566Orig1s000TA_ltr.pdf) [↑](#footnote-ref-2)