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POLICY BRIEF

TRANSITIONING TO THE 2021 OPTIMAL FORMULARY FOR ANTIRETROVIRAL DRUGS FOR CHILDREN: IMPLEMENTATION CONSIDERATIONS

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1. BACKGROUND

Audience for this document

National governments, donors, programme managers, procurement entities, manufacturers, implementing partners and civil society

Objective

Ensure national programmes are well-prepared to support the national adoption, procurement, and implementation of optimal paediatric ARVs in concordance with the 2021 Optimal Formulary and Limited-Use List for Antiretroviral Drugs for Children

Antiretroviral therapy (ART) optimization is a key pillar in the AIDSFree¹ agenda to reach the goal of ensuring that 95% of all infants and children living with HIV known to have HIV have access to life-saving treatment. Despite progress in recent years to provide ART to almost 1 million infants and children living with HIV, attaining the third target of 95% viral suppression will remain an elusive goal without access to more effective treatment in age- and weight-appropriate formulations.

Since 2018, WHO guidelines have recommended dolutegravir (DTG)-based regimens as the preferred first-line regimen for infants and children for whom approved DTG dosing is available. In June 2020, paediatric DTG was approved by the United States Food and Drug Administration for infants and children at least four weeks

of age and weighing at least 3 kg. In late 2020, the United States Food and Drug Administration approved one generic version of 10 mg scored dispersible DTG tablets, further expanding the access of infants and younger children to DTG, with an additional generic version approved in March 2021. As a result, the WHO Optimal Formulary and Limited-use List for Antiretroviral Drugs for Children² has been updated to include 10 mg scored dispersible DTG tablets to support timely access to optimal formulations and to implement WHO recommendations.

This policy brief outlines key considerations to facilitate effective transitions to more clinically appropriate regimens as optimal antiretroviral (ARV) drugs become available for infants and young children at the country level.



¹ Start Free Stay Free AIDS Free [website]. Geneva: UNAIDS; 2021 (<https://free.unaids.org>, accessed 28 June 2021).

² The 2021 optimal formulary and limited-use list for antiretroviral drugs for children. Geneva: World Health Organization; 2021 (<https://www.who.int/publications/item/9789240023529>).

2. MANAGING ARV DRUG TRANSITIONS

Although general guidance on transition to newly recommended ARV drugs is available (Fig. 1), child-specific issues need to be considered at the programme level when planning for paediatric ART regimen transitions.

Fig. 1. General considerations for ARV transition planning across all populations

Clinical	Supply chain and procurement	Implementation	Monitoring and evaluation
<ul style="list-style-type: none"> • Patient eligibility <ul style="list-style-type: none"> – Populations – Line of treatment – Sequencing changes – Special populations (such as pregnant women and people with TB coinfection) – Newly diagnosed versus treatment experienced – Status of suppression of viral loads 	<ul style="list-style-type: none"> • Quantification and procurement <ul style="list-style-type: none"> – Anticipated rate of transition – Production capacity of suppliers – Lead time • Management of existing stock <ul style="list-style-type: none"> – Shelf life of existing stock – Quantities of available legacy products – Quantities of legacy products in pipeline • Availability <ul style="list-style-type: none"> – Registration – Supplier capacity • Cost 	<ul style="list-style-type: none"> • Transition approach <ul style="list-style-type: none"> – Phase-in and phase-out planning – Anticipated future transitions • Training and sensitization of health-care workers • Caregiver education on the new drugs • Demand creation among users • Guidance on making ARV drug substitutions or need for additional guidance on routine monitoring • Guidance on transitioning special cases 	<ul style="list-style-type: none"> • Need for updating data collection tools to monitor usage and prescribing trends • Post-marketing surveillance <ul style="list-style-type: none"> – Adverse event reporting – Pregnancy surveillance

Clinical considerations

Eligibility. When planning for the introduction of new ARVs, programmes should identify and clearly delineate needs within different age groups, developmental considerations (such as ability to swallow solids, including tablets) and weight-band requirements for each product.

Dosing and administration guidance. When new ARV drugs for children and dosage forms for children are introduced, health-care workers should be provided clear guidance on appropriate dosing across eligible weight bands. Dosing should be harmonized with WHO weight bands³ to simplify prescribing for health-care

workers. ARV drug formulations for children, especially those for infants and younger children, may also require practical guidance on administration techniques (such as dispersing tablets in water or breast milk) and storage conditions (such as refrigeration requirements for certain oral solutions); health-care workers should therefore be trained and supported to provide effective counselling and support to caregivers so that access to optimal formulations translates to optimal health outcomes.

Transitioning to optimal ARV drug regimens for children.

Given high rates of drug resistance and suboptimal suppression of viral loads with regimens based on non-nucleoside reverse-transcriptase inhibitors (NNRTIs), their use is no longer recommended now that alternatives are

³ For the most recent guidance on dosages for ARV drugs, see <https://www.who.int/tools/aids-free-toolkit/drug-optimization>.

more widely available. Although the availability of lopinavir/ritonavir (LPV/r) solid oral formulations has improved the health outcomes of infants and young children, DTG-based regimens provide a more efficacious and tolerable option that provides the opportunity to fully harmonize regimens across paediatric age groups. The dosing approach for DTG-based regimens for children is simple to implement compared with LPV/r; 10 mg scored, dispersible tablets can be used from four weeks and 3 kg, and 50 mg film-coated tablets can be used from 20 kg onwards. Children weighing more than 30 kg can be transitioned to adult DTG-based regimens, with the advantage of reduced pill burden using triple fixed-dose combinations.⁴

For first-line preferred ART, DTG should be combined with abacavir/lamivudine (ABC/3TC) as the preferred nucleoside reverse-transcriptase inhibitor (NRTI) backbone for all infants and children aged four weeks and older until they reach 30 kg, after which tenofovir disoproxil fumarate (TDF) in combination with 3TC or emtricitabine (FTC) is the recommended NRTI backbone. DTG + 3TC + TDF is available as a triple fixed-dose combination tablet and should be offered if available.

Because of the programmatic⁵ and clinical benefits of DTG-based regimens, including superior suppression of viral loads compared with standard care,⁶ WHO recommends rapid transition to DTG-based regimens for all eligible infants and children established on first- and second-line ART, regardless of their current regimen. This transition to new optimal ARV drugs may require substitution of a single drug, such as replacing nevirapine (NVP), efavirenz (EFV) or LPV/r with DTG.⁷

The timing of transition to a DTG-based regimen for infants and children should take into consideration the availability and anticipated supply of DTG 10 mg scored, dispersible tablets in country. In case of inadequate supplies to provide DTG to all children, infants and children living with HIV initiating ART and those in greatest need

of DTG should be given priority. Children with the greatest need for DTG include infants and children living with HIV receiving NNRTI-based regimens; infants and children living with HIV who need to start rifampicin-based TB treatment; and infants and children living with HIV receiving LPV/r solid formulations who continue to have challenges in administration and/or challenges in attaining optimal viral load suppression. For infants and children living with HIV receiving rifampicin-containing TB treatment, DTG dose adjustment should align with United States Food and Drug Administration approval and support the use of DTG every 12 hours across age groups and weight bands during the TB treatment period.

Importantly, viral load testing is not considered a precondition to undertaking programmatic or individual transition to DTG-based regimens (unless raltegravir-based regimens were previously used). Although routine viral load monitoring is recommended to deliver appropriate care to children living with HIV, clinicians should not delay the transition to DTG because of a lack of documented viral load.

Weight-based dosing transitions for infants and children.

Since DTG dosing recommendations vary by weight band for infants and children older than four weeks and weighing at least 3 kg, health-care workers will require guidance on how regimens should be adjusted to account for growth and maturation as children grow.

When prescribing multimonth dispensing to infants and children living with HIV eligible according to WHO guidelines, a practice that has been scaled up during the COVID-19 pandemic, it is important to inform caregivers about the benefits of multimonth dispensing and its feasibility even with a growing child, including when to return to the clinic. Because dosing will change each time a child transitions from one weight band to the next, dosing selection must be based on a recent and accurate weight measurement.

⁴ Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach – third edition, July 2021. Geneva: World Health Organization; 2021.

⁵ Programmatic benefits include cost, simplification and consolidation of demand and procurement.

⁶ See the results of the ODYSSEY trial, which has demonstrated superior viral load outcomes among children weighing 14 kg or more randomized to DTG-based first- or second-line ART versus standard care. Turkova A. Dolutegravir-based ART is superior to NNRTI/PI-based ART in children and adolescents. 28th Conference on Retroviruses and Opportunistic Infections, virtual, 3 June–3 November 2021 (<https://www.croiconference.org/abstract/dolutegravir-based-art-is-superior-to-nnrti-pi-based-art-in-children-and-adolescents>, accessed 1 June 2021).

⁷ For guidance on transitioning children who do not have suppressed viral loads on an NRTI backbone, see the 2021 WHO consolidated HIV guidelines.

Special consideration should be given to addressing dosing changes when infants and children living with HIV approach the upper limit of their current weight band. This will minimize the risk of underdosing children who are not brought to the clinic monthly.⁸ For children expected to cross into a new weight band before their next appointment, a clinical decision needs to be made about the weight band to be used to prescribe the child's ARV drugs.⁹ If returning to the facility is not feasible and the caregiver has access to an accurate scale, a weight increase and increased dosing can be discussed with the caregiver by phone or text message.

Note that only six dosing changes are anticipated over the first 10 years of life, and only two dosing changes are needed within the first two years of life. Although dosing changes require consideration, they are few and not expected to be major barriers to multimonth dispensing for eligible infants and children living with HIV.

Supply chain and procurement

Quantification and procurement

The population of children and young adolescents living with HIV (0–14 years old) is relatively small compared with adults living with HIV, but many programmes face the challenging complexity of quantifying different ARV drugs by age group and weight bands since historical rates of consumption may not accurately reflect changing policies or the evolving epidemiology of HIV infection among children.

With increasing coverage of maternal ART reducing the vertical transmission of HIV, the number of children acquiring HIV continues to decline. The global demand for ARV drug regimens for newborns and infants has therefore decreased overall. However, the introduction of HIV birth testing and improved access to HIV diagnostics for HIV-exposed infants may increase the identification of previously untested HIV-exposed infants, thus increasing the demand for regimens suitable for newborns and younger children. Similarly, the identification of previously undiagnosed older children living with HIV missed by infant

diagnosis services may increase demand for ARV drug products for children.

In addition, although many programmes define children as 0–14 years, children as young as 10 years may be transitioning to ARV drug formulations for adults, including 50 mg DTG tablets at a body weight of 20 kg. Programmes therefore need to adjust forecasting for ARV drug products for children to consider the changing rates of vertical transmission of HIV and improved diagnosis for younger infants and to define the age group and weight bands requiring specific ARV drug formulations and regimens for children.

Quantifying formulations for children accurately requires understanding the weight band distribution of the children needing the ARV drugs. However, these data are often not collected or are collected based on the child's age and not weight. Setting up monitoring systems to capture this information is an important long-term goal. In the absence of this data, technical working groups can use standard age-to-weight conversions to estimate the weight band breakdown of the relevant children.¹⁰

Although introducing 10 mg scored, dispersible DTG tablets is a priority and focus for national programmes in 2021, quantification exercises should account for all ARV drugs included in the optimal formulary to deliver optimal and alternative first-, second-, and third-line ART regimens for children, including NRTI backbone products. National quantification and supply plans should consider:

- the cost of formulations for children;
- the need to adjust formulations and doses over time because of weight changes;
- phasing out the existing stock of suboptimal products;
- the lead times between orders and delivery; and
- the switching of any orders in the pipeline of LPV/r- and NNRTI-based regimens to DTG 10 mg (if feasible).

Because of the relatively low volume but broad range of products required, it is recommended that supply planning for ARV drugs for children include:

- quarterly order cycles;
- staggered deliveries for large orders;

⁸ Reaching Impact and Epidemic Control (RISE). Technical guide for healthcare workers on pediatric multi-month dispensing (MMD). Washington (DC): United States Agency for International Development; 2021 (<https://icap.columbia.edu/wp-content/uploads/Technical-Guide-for-Healthcare-Workers-on-Pediatric-Multi-Month-Dispensing-MMD.pdf>, accessed 28 June 2021).

⁹ The child should be prescribed according to the next weight band; prescribed based on their current dose but with an intention to transition to the new dosing after a defined time frame; or have their weight evaluated and dosing adjusted before the next scheduled appointment.

¹⁰ Doherty K, Essajee S, Penazzato M, Holmes C, Resch S, Ciaranello A. Estimating age-based antiretroviral therapy costs for HIV-infected children in resource-limited settings based on World Health Organization weight-based dosing recommendations. *BMC Health Serv Res.* 2014;14:201.

- quarterly reviews of stocks in-country (at the health facility, regional warehouse and central warehouse levels) and in the procurement pipeline; and
- the potential need for buffer stocks of some products to minimize stock-outs.

Supply planning for ARV drugs for children should also support client-centred care, such as multimonth dispensing, which may require more frequent commodity review meetings at the district, regional and national levels to reconcile multimonth dispensing with the distribution of existing national stock and to inform quantification and forecasting. Many resources are available to support accurate quantification and forecasting of ARV drugs for children, including the CHAI Simple Tool for ARV Forecasting of the Clinton Health Access Initiative,¹¹ the quantification and budgeting guidance brief of the Elizabeth Glaser Pediatric AIDS Foundation¹² and the United States Agency for International Development Global Health Supply Chain Program Quantification Analytics Tool.¹³

Countries should transition children as quickly as possible to the best available product based on available stock. When new, more optimal ARV drugs for children are available in the country, rapidly transitioning to optimal products is preferable to exhausting existing stocks of a suboptimal product. It is recommended that national programmes work with funders or buyers of ARV drugs for children to decide how best to address the existing stock of legacy or suboptimal formulations that are either in the country or coming into the country as they move toward the goal of providing the best available products for infants and children living with HIV. Manufacturers should also keep global and national programmes updated with accurate timelines for stock availability for more effective planning.

Availability

Including optimal ARV drug formulations for children into national protocols is the first step in enabling access to better ART regimens; however, several factors may

affect their availability and should be considered when developing a timeline for transition. This includes in-country registration by national drug regulatory agencies through routine, expedited or waiver processes as well as intellectual property rights such as patents and existing voluntary licenses enabling generic competition.¹⁴

Regulatory approval by the United States Food and Drug Administration or receipt of WHO prequalification¹⁵ does not guarantee availability since suppliers may not invest in commercializing a product until they are assured of orders. Because of the inherently limited size of the ARV drug market for children, some new products may be vulnerable to long lead times, especially if small orders are placed.

The product life cycle of an ARV drug formulation – introduction, growth, maintenance and exit from the market – also affects supply availability. The demand for and availability of active pharmaceutical ingredients for a given formulation and other formulations that rely on the same active pharmaceutical ingredients affect supply availability, as does the volume of demand for the final formulation. Understanding the appropriate demand at each phase of a product's life cycle is important to ensure that appropriate capacity for active pharmaceutical ingredients is available to meet demand. The introduction of DTG for children, for example, benefits from the fact that the DTG + 3TC + TDF formulation market has entered the maintenance phase of its life cycle. Because of this, sufficient DTG active pharmaceutical ingredient is available to make formulations for both adults and children. Alternately, an active pharmaceutical ingredient that is used for formulations that have changed from the WHO Optimal Formulary to the Limited-Use List or that have become non-essential often have a longer lead time and might be more expensive to procure.

Another important consideration is buffer stock, which is necessary to ensure uninterrupted supply and access to ARV drugs by mitigating against the risk of stock-outs. During product transitions, a larger initial order may be required to create sufficient stock levels in accordance with national policy. An estimate of monthly consumption

¹¹ CHAI Simple Tool for ARV Forecasting. Boston: Clinton Health Access Initiative; 2021 (<https://clintonhealth.app.box.com/s/sbar7zpk4mfi76rc2hyfexcal2yu45r>, accessed 28 June 2021).

¹² Quantification and budgeting for rapid and sustainable access to new pediatric antiretroviral therapies. San Francisco: Elizabeth Glaser Pediatric AIDS Foundation; 2020 (https://www.pedaids.org/wp-content/uploads/2020/11/Pediatric-ARV-Quantification-Budgeting_EGPAF-Unitaid_Jan2021.pdf, accessed 28 June 2021).

¹³ Quantification analytics tool. Washington (DC): USAID Global Health Supply Chain Program; 2021 (<https://www.ghsupplychain.org/quantificationanalyticstool>, accessed 28 June 2021).

¹⁴ For information on the patent and licencing status of WHO-recommended ARVs in low- and middle-income countries, see MedsPal (<https://www.medsPal.org>, accessed 7 July 2021).

¹⁵ For additional information on the current WHO prequalification status of DTG products for children, see <https://extranet.who.int/pqweb/medicines/dossier-status>.

adjusted for any stock-outs should be used to determine the quantity and timing of initial buffer stock orders to enable the rollout of new products at the desired time. Most countries aim for six months of buffer stock, but national policies vary and may also vary by product. Reviewing stock availability and supply is especially important given the high volume of children who will be transitioning or initiating onto 10 mg scored, dispersible DTG tablets.

In the COVID-19 era, many national HIV programmes have pushed buffer stock from central medical stores to provinces and facilities. In a decentralized stock management system, having systems in place to ensure visibility of stock levels at all levels of the national HIV programme is important to ensure that national stock challenges can be assessed and mitigated rapidly. Further, given the unpredictable nature of COVID-19, national HIV programmes should continue to retain sufficient stock levels of optimal ARV drugs for children in case of any disruptions in supply and delivery.

Monitoring and evaluation

Toxicity monitoring

The accelerated introduction of new ARV drugs often occurs in the context of limited clinical experience outside trial settings. When introducing new drugs, countries should consider routine toxicity monitoring critically important, especially regarding the long-term toxicity and tolerability of new products. As national toxicity monitoring and pharmacovigilance systems are put in place or strengthened, enhanced monitoring

at sentinel sites and using observational cohort studies can provide important opportunities to identify early signals of adverse events among infants and children. These should include laboratory abnormalities as well as potential drug effects on growth and development. Since infants and children are increasingly exposed to maternal ART, enhanced monitoring should also be considered in the context of new product introduction for adults, and the safety of ARV drug exposure through breastfeeding should be ensured in the short and longer term, among both HIV-infected and HIV-uninfected infants exposed to ARV drugs during breastfeeding.

Importantly, pharmacovigilance systems can be developed or strengthened as efforts to optimize ARV drugs for children are underway; the transition to optimal formulations can happen concurrently with pharmacovigilance strengthening activities. Moreover, existing pharmacovigilance systems can be modified to include newly available and optimal ARV drugs for children rather than developing parallel systems, which can be both time and cost intensive. Lastly, updating pharmacovigilance reporting forms and systems is important to capture adverse drug reactions during DTG introduction and possible drug intolerance to DTG. WHO has developed an ART toxicity monitoring tool that provides step-by-step instructions and reporting tools for countries to implement both passive pharmacovigilance surveillance, as well as active adverse drug monitoring at selected sentinel sites, for new ARV drugs for children.¹⁶ In addition, Module 10 of the WHO Toolkit for research and development of paediatric antiretroviral drugs and formulations contains a module that specifically addresses pharmacovigilance for paediatric ARVs.¹⁷



¹⁶ WHO implementation tool for monitoring the toxicity of new antiretroviral and antiviral medicines in HIV and viral hepatitis programmes. Geneva: World Health Organization; 2018 (<https://apps.who.int/iris/handle/10665/273053>, accessed 28 June 2021).

¹⁷ Toolkit for research and development of paediatric antiretroviral drugs and formulations. Geneva: World Health Organization; 2018 (<https://apps.who.int/iris/handle/10665/273151>, accessed 28 June 2021).

Box 1 provides additional information on best practices and key enablers to support a rapid transition to optimal ARV drugs for children.

Box 1. Best practices to ensure a rapid transition to optimal ARV drugs for children

National HIV programmes should reflect on the lessons learned from TLD, DTG 50 mg and recent new introductions of ARV drug products for children to strengthen the ability to provide rapid access. Below are a set of best practices and key enablers to help to ensure seamless and rapid ARV drug transitions.

- **National governance.** Coordinate centrally with key stakeholders, including procurement agents, implementing partners and community networks to update national guidelines and essential medicines lists and develop national transition plans. Ensure buy-in and agreement from all ARV drug stakeholders and decision-makers.
- **National registration.** Ensure that products are registered (or waivers received) and that shipping and national distribution processes are aligned with national transition plans.
- **Procurement planning.** Quantify current national stock levels, verify demand and pipeline orders, develop national forecast and procurement plans and incorporate optimal ARV drugs into supply plans. Monitoring supply availability, including lead times, from manufacturers will be essential to inform supply planning.
- **Community engagement.** Engage community networks of people living with HIV across all stages of national transition to help to ensure effective and appropriate implementation of national product rollout plans.
- **Information, education and communication materials.** Develop and disseminate key messaging and job aids for clinicians, patient and caregiver groups and facility-level staff. Key resources include health-care worker training materials, stock management and reporting tools, standard operating procedures and caregiver counselling materials.
- **Uptake monitoring.** Actively monitor uptake and deploy targeted interventions to improve uptake when required. National programmes should develop a comprehensive monitoring plan, track uptake trends, monitor consumption patterns and product expiry dates and support adjustment of the supply plan accordingly.
- **Pharmacovigilance monitoring.** Ensure that robust pharmacovigilance systems are implemented to monitor outcomes. National programmes should monitor adverse drug reactions, drug resistance, toxicity and treatment failure, in accordance with WHO guidance.

3. RECOMMENDATIONS FOR COUNTRY PROGRAMMES TRANSITIONING TO THE 2021 OPTIMAL FORMULARY AND LIMITED-USE LIST FOR ANTIRETROVIRAL DRUGS FOR CHILDREN

- Review and collect information on the current population of children receiving treatment with data disaggregated by age and weight band to inform transition decisions:
 - distribution of regimens currently in use;
 - current weight-band distribution;
 - months of stock on hand of current regimens;
 - months of stock of orders in the pipeline (of current regimens); and
 - the shelf life of existing ARV drugs in the country.
- Determine the eligible populations of children, considering:
 - age and weight band;
 - current regimen (such as NNRTI-based regimens);
 - supply availability; and
 - initiation of rifampicin-based TB treatment.
- Maintain up-to-date market intelligence on available ARV drug formulations for children:
 - the current Optimal Formulary and Limited-use List for Antiretroviral Drugs for Children;¹⁸ and
 - supply capacity through ARV Procurement Working Group newsletters and website.¹⁹
- Develop demand forecast and share a consolidated forecast of low-demand products with the ARV Procurement Working Group.²⁰ To increase the visibility of demand to suppliers, the ARV Procurement Working Group is sharing consolidated forecasts with suppliers every quarter, especially for low-volume products and products in transition. This enables suppliers to prepare for adequate production before orders are placed.
- Evaluate the risks of not transitioning if a product currently in use is being phased out: for example, the product recently shifted to the Limited-use List or is no longer included on either the Optimal Formulary or Limited-use List. This indicates that the use of a product is decreasing, and production may significantly decrease over time.
- Consider systematizing the process of updating the national ARV drug formulary for children to simplify future transitions (such as by using the Optimal Formulary method).
- Stagger new orders for ARV drug formulations for children. It is recommended that country programmes plan for 12 months of demand with quarterly deliveries.
- Avoid stockpiling optimal formulations beyond six months of stock, since the timelines for rollout may be delayed for unforeseen reasons, resulting in wastage and perhaps shortages for other programmes.

¹⁸ The Optimal Formulary and Limited-use List for Antiretroviral Drugs for Children was updated in 2021 to support the transition and implementation of preferred and alternative ART regimens recommended for infants and children in the WHO guidelines across all lines of treatment.

¹⁹ ARV Procurement Working Group [website]. ARV Procurement Working Group; 2021 (<https://www.arvprocurementworkinggroup.org/arv-procurement-working-group-documents>, accessed 28 June 2021).

²⁰ To share forecasts for low-demand products with the ARV Procurement Working Group, contact it through its website: <https://arvprocurementworkinggroup.org/home>.

4. RESOURCES FOR COUNTRY PROGRAMMES TO SUPPORT THE TRANSITION TO NEW ARV DRUGS FOR CHILDREN IN 2021

The 2021 Optimal Formulary and Limited-use List for Antiretroviral Drugs for Children

The Optimal Formulary and Limited-use List for Antiretroviral Drugs for Children has been updated to support the transition to optimal WHO-recommended regimens for children, given the rapidly evolving treatment landscape and the risks inherent in the uncertain timelines for developing drugs for children. Publication of the Optimal Formulary and Limited-use List provides guidance to country programmes, procurement entities and funding agencies on the minimum set of ARV drug dosage forms for children needed to deliver WHO-recommended ARV drug regimens to newborns, infants and children across all lines of treatment. (<https://www.who.int/publications/item/9789240023529>, accessed 28 June 2021)

Further resources

CHAI Simple Tool for ARV Forecasting. Boston: Clinton Health Access Initiative; 2021 (<https://clintonhealth.app.box.com/s/sbar7zpk4mfi76rxc2hyfexcal2yu45r>, accessed 28 June 2021).

Accelerating access to optimal child-friendly antiretroviral formulations for children living with HIV: lessons learned from eight sub-Saharan African countries. San Francisco; Elizabeth Glaser Pediatric AIDS Foundation; 2020 (<https://www.pedaids.org/resource/accelerating-access-to-optimal-child-friendly-antiretroviral-formulations-for-children-living-with-hiv>, accessed 28 June 2021).

Toolkit for research and development of paediatric antiretroviral drugs and formulations. Geneva: World Health Organization; 2018 (<https://apps.who.int/iris/handle/10665/273151>, accessed 28 June 2021).

WHO implementation tool for monitoring the toxicity of new antiretroviral and antiviral medicines in HIV and viral hepatitis programmes. Geneva: World Health Organization; 2018 (<https://apps.who.int/iris/handle/10665/273053>, accessed 28 June 2021).

Surveillance of antiretroviral toxicity: global HIV, hepatitis and STIs programme: what's new in person-centred HIV patient and antiretroviral drug toxicity monitoring: technical brief. Geneva: World Health Organization; 2020 (<https://apps.who.int/iris/handle/10665/333000>, accessed 28 June 2021).

MedsPal. The medicines patents and licences database. Geneva: Medicines Patent Pool; 2021 (<https://www.medspal.org>, accessed 7 July 2021).

Access to medicines tracker. Geneva: Medicines Patent Pool; 2021 (<https://medicinespatentpool.org/progress-achievements/access-to-medicines-tracker#Interactive-Map/>, accessed 7 July 2021).

Online learning [website]. Online learning courses in pharmacovigilance. Uppsala: Uppsala Monitoring Centre; 2021 (<https://www.who-umc.org/education-training/online-learning>, accessed 28 June 2021).

ARV Procurement Working Group procurement consortium

The ARV Procurement Working Group facilitates country access to optimal and limited-use ARV drug products with low or fragmented demand by promoting quarterly order placement cycles either directly through its procurement consortium members or indirectly for other procurement channels by aligning order timelines.

(<https://www.arvprocurementworkinggroup.org>)

Members

- Clinton Health Access Initiative
- Ethiopia Pharmaceuticals Supply Agency
- Global Fund to Fight AIDS, Tuberculosis and Malaria
- Global Health Supply Chain – Procurement and Supply Management Program
- i+solutions
- Kenya Medical Supply Authority
- Pan American Health Organization
- South Africa National Department of Health
- United States President’s Emergency Plan for AIDS Relief (PEPFAR) through the Office of the United States Global AIDS Coordinator, the United States Agency for International Development and the United States Centers for Disease Control and Prevention
- United Nations Children’s Fund
- United Nations Development Programme
- Unitaid

Observing members

- African Community Advisory Board
- Drugs for Neglected Diseases initiative
- Elizabeth Glaser Pediatric AIDS Foundation
- Enfants et VIH en Afrique
- ICAP at Columbia University
- International AIDS Society
- Médecins Sans Frontières
- Medicines Patent Pool
- Organisation of Eastern Caribbean States
- WHO

Country case studies

Case studies from Uganda and Haiti (below) highlight lessons learned and country experiences to support ART optimization and the introduction of optimal DTG formulations for children.

Case study: Lessons learned from optimizing ART for children in Uganda

In Uganda, an estimated 100 000 children younger than 15 years are living with HIV. Although ART coverage has improved over the past five years, only 65% of children living with HIV were receiving ART in 2019 versus 85% of adults. One explanation for the persistent treatment gap among children in Uganda is the complexity of treatment regimens, especially for young children. As a result, children have consistently lower rates of viral suppression than adults.

As of June 2018, 52% of infants and children living with HIV in Uganda were still receiving suboptimal NNRTI-based treatment regimens instead of the WHO-recommended first-line regimens of LPV/r- or DTG-based regimens. To address this challenge, Uganda's Ministry of Health initiated efforts to optimize ART for children to expand the use of simplified and effective ART regimens. The initiative included transitioning children and adolescents weighing 20 kg or more to 50 mg DTG tablets for first-, second- and third-line ART.

Although the data are still being analysed, including data on suppression of viral loads, the initial results are very promising. The transition of children and adolescents to more optimal regimens across all age bands (< 3 years; 3–9 years; 10–14 years; and 15–19 years) greatly improved from 34% in June 2019 to 97% in March 2021. Many lessons learned from Uganda's experience can inform efforts to optimize ART for children in other countries.

First, developing tools and establishing clear mechanisms to identify and monitor children eligible for optimization are important. In Uganda, the review of client charts, an ART optimization checklist and an action-oriented line listing tool were critical for identifying children eligible for optimization. Moreover, using optimization for children stickers placed in the children's charts made it easy for any health-care worker to identify eligible children for optimization. Second, continuous quality improvement (CQI) activities are important tools that can be leveraged to support ART optimization. Prioritizing CQI to improve viral load suppression among children, for example, led to activities targeting the transition to optimal regimens. In addition, active stock monitoring and management are critical and help to identify signs of stock-outs or inadequate stock early, facilitating links with national or joint medical stores for stock replenishment or redistribution. Lastly, using data from relevant sources for monitoring and decision-making is essential for guiding the ART optimization process. Uganda developed indicators for ART optimization for children that were incorporated into a PEPFAR surge dashboard, and weekly meetings were convened to monitor and address any challenges that emerged.

As data continue to be analysed, additional findings from Uganda's efforts to optimize ART for children will be shared in a forthcoming publication.

Case study: Introducing DTG formulations for children in Haiti

Haiti accelerated the introduction and scale up of pediatric DTG due to a growing evidence of clinical and programmatic benefits of DTG for children down to 4 weeks of age and 3 kg. Haiti accomplished this through coordination and collaboration between a multitude of stakeholders and partners. Haiti's national HIV program is directly coordinated by the national AIDS program (PNLS), and service delivery is provided at the Ministry of Health's public and private health facilities. Clinical implementing partners are funded by the United States Government through PEPFAR and the Global Fund.

Haiti has begun actively transitioning children living with HIV to an optimized regimen for HIV treatment, consisting of paediatric formulations of dolutegravir, as 5 mg and 10 mg dispersible tablets (pDTG). Collaboration between the Ministry of Health, United States Government, the Global Fund, and civil society, through joint quantification, coordinated procurements, regular meetings of the national pediatric HIV technical working group (pediatric TWG) and transparent and complete data sharing led to the successful transition of children who were found to be failing their non-DTG-based regimen and those newly initiating antiretroviral therapy (ART). The Haiti team is now in the process of transitioning children living with HIV who are virally suppressed to a pDTG-based regimen.

The United States Government, through PEPFAR, and the Global Fund provide support for commodity procurement and distribution to health facilities with a funding split of 60% PEPFAR, and 40% Global Fund. Frequent communication between donors and in-country stakeholders enables coordinated monitoring and reporting of paediatric case finding and treatment metrics, which inform paediatric commodity forecasting processes. In addition, a robust reporting system, with biometric coding for HIV patients, enables the Haiti team to maintain a database with key patient demographics, such as patient ART regimen, weight, viral load, and utilisation of multimonth dispensing, with monthly updates. This system enabled the Haiti team to quantify the appropriate amount of pDTG 5 mg, and subsequently pDTG 10 mg, that was required for the country to meet the needs of children living with HIV.

Through existing protocols and systems in place, the United States Government, through PEPFAR, supported Haiti's pediatric ARV optimization efforts with an initial investment for an order of DTG 5 mg, which arrived February 2021 and was immediately distributed to 104 health facilities. Prior to the arrival of DTG 5 mg, the clinical personnel proactively updated the pediatric standard treatment guidelines and communicated the change to clinicians and supply chain professionals. The pediatric TWG, utilized the robust patient data to develop supply plans, anticipate product demands and provide an initial allocation by facility. Preparations for the arrival of pDTG began approximately six months prior to DTG 5 mg arrival in country and included colleagues from the United States Government, who coordinated directly with ViiV, PNLS and other stakeholders. Furthermore, experiences and lessons learned from the introduction of DTG 5 mg led to the rapid introduction of DTG 10 mg, which is a more cost-effective pediatric DTG formulation.

Thus, collaboration coupled with availability of detailed patient data contributed to the seamless introduction of pDTG. The Haiti team plans to share results on the impact of pDTG on children living with HIV achieving the second and third 95s at upcoming clinical scientific meetings.



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