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 AIDSFree[1] 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 Children[2] 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/i/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

- Patient eligibility
  - 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

Supply chain and procurement

- Quantification and procurement
  - Anticipated rate of transition
  - Production capacity of suppliers
  - Lead time
- Management of existing stock
  - Shelf life of existing stock
  - Quantities of available legacy products
  - Quantities of legacy products in pipeline
- Availability
  - Registration
  - Supplier capacity
- Cost

Implementation

- Transition approach
  - 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

Monitoring and evaluation

- Need for updating data collection tools to monitor usage and prescribing trends
- Post-marketing surveillance
  - 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 bands[3] 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 programmatic[5] 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 Foundation[12] 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 prequalification[15] 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/sbar7zpk4mfi76rxc2hyfexcal2yu45r, 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 pharmocovigilance 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.