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POLICY BRIEF

TRANSITIONING TO AN OPTIMAL PAEDIATRIC ARV FORMULARY: IMPLEMENTATION CONSIDERATIONS

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1. BACKGROUND

Audience for this document
Donors, national governments, programme managers, procurement entities and funding agencies

Objective
Ensure national programmes are well prepared to transition their paediatric ARV formularies as the Optimal Formulary and Limited-Use List for Paediatric ARVs are revised

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

Since 2013, WHO guidelines have recommended lopinavir/ritonavir (LPV/r)-based regimens for all CLHIV aged less then 3; however, the limited availability of a formulation suitable for infants and young children has remained a barrier to implementation. The 2018 WHO Antiretroviral Therapy Guidelines update now includes dolutegravir (DTG)-based regimens as the preferred first-line regimen for infants and children aged 4 weeks–10 years. The Optimal Formulary and Limited-use List for Paediatric ARVs has recently been updated to reflect the changes in the 2018 WHO HIV treatment Guidelines update. This policy brief outlines key considerations to facilitate effective transition to more clinically appropriate regimens as optimal ARV medicines and dosage forms become available.

2. MANAGING ARV TRANSITIONS

General guidance, applicable across all populations, on transition to newly recommended ARVs is available (Fig. 1), however child-specific issues need to be considered at the programme level when planning for paediatric ART regimen transitions. Examples of transition include substitution with a different ARV or replacing a specific dosage form with an improved formulation of the same ARV drug.

Clinical considerations

Patient eligibility: Unlike adult populations, paediatric ART must cover a range of age groups, developmental stages and weight bands, each potentially requiring different age-appropriate medicines and dosage forms. When planning for the introduction of new ARV products, programmes should identify and clearly delineate the age groups, developmental considerations (e.g. ability to swallow solids) and weight-band requirements for each product.

Dosing and administration guidance: When new paediatric medicines and paediatric dosage forms are introduced, healthcare workers should be provided with clear guidance on appropriate dosing across eligible weight bands. When possible, dosing should be harmonized with WHO weight bands to simplify prescribing for healthcare workers. Paediatric ARV formulations, particularly those for infants and younger children, may also require practical advice on administration techniques and/or on storage conditions; therefore, healthcare workers should be trained and supported to provide effective counselling to caregivers so that access to optimal formulations translates to optimal patient outcomes.

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

Clinical	Supply chain and procurement	Implementation	Monitoring and evaluation
■ Patient eligibility – populations – line of treatment – sequencing changes – special populations (e.g. pregnant women, TB coinfection)	■ Quantification – anticipated rate of transition ■ Management of existing stock – shelf life of existing stock – ongoing procurement of legacy products ■ Availability – registration – supplier capacity – lead time ■ Cost	■ Transition approach – phase in and phase out planning – anticipated future transitions ■ Training/sensitization of healthcare workers ■ Guidance on making drug substitution or need for additional guidance on routine monitoring	■ Need for updating data collection tools to monitor usage and perscribing trends ■ Postmarketing surveillance – AE reporting – pregnancy surveillance

Transitioning from suboptimal regimens: Though a dispersible fixed-dose combination (FDC) tablet is a convenient, simplified formulation, currently no single-tablet regimen (STR) is available to deliver preferred first-line regimens to neonates, infants or children. ABC/3TC containing NRTI-backbones are preferable for infants and children aged 4 weeks and older although AZT/3TC is still widely used. The introduction of new optimal ARVs may only require substitution of a single drug, e.g. replacing NVP or EFV with LPV/r, RAL or DTG. However, it is also be important to provide guidance on whether a change to NRTI-backbone should be made. Additionally, when planning to make a single drug substitution, it is important to provide guidance on whether viral load suppression is required prior to transition.

Age-appropriate regimen transitions: As recommendations for preferred paediatric regimens vary across different age groups and weight bands, healthcare workers will require guidance on how regimens should be adjusted in order to account for growth and maturation as paediatric patients age. For infants and children stable on their current regimen, transition to a new drug or regimen may seem unnecessary. From a programmatic standpoint however, it is important to consider the benefits of transitioning younger infants and children to age-appropriate regimens and formulations, including when they may be transitioned to adult regimens. For example, infants or younger children may be started on LPV/r oral solution or oral pellets, but transitioned to more convenient LPV/r 100 mg/25 mg tablets when they weigh 10 kg or more and can swallow tablets, and then to DTG 50 mg when they reach 25 kg[1]. If possible, harmonization between paediatric regimens and the preferred regimen for adults and adolescents is ideal (e.g. use of DTG in combination with ABC/3TC facilitates a transition to DTG in combination with TDF/3TC in adolescence).

Supply Chain and Procurement

Quantification and Procurement

The HIV-positive paediatric population is relatively small in comparison to adults, but the complexity of quantifying for different ARV products by age group and weight bands is a challenge faced by many programmes as historical rates of consumption may not accurately reflect changing policies or the evolving epidemiology of paediatric HIV infection.

With increasing coverage of maternal ART, the incidence of new paediatric infections continues to decline sharply in recent years due to a reduction in perinatal transmission. As a consequence, the global demand for neonatal and infant regimens has decreased. However, the introduction of birth testing as well as improved access to HIV diagnostics for infants may also increase identification of previously untested infants, thus increasing the need for regimens suitable for neonates and younger infants.

Additionally, though many programs define the paediatric age group as 0–15 years, children as young as 10 years may be transitioning to adult formulations, including DTG 50mg tablets at a bodyweight of 25kg[1]. It is therefore important for programmes to adjust forecasting for paediatric ARV products in order to take account of changing MTCT rates and improved diagnoses in younger infants, and to define the age group requiring specific paediatric ARV formulations and regimens. Furthermore, in order to determine quantification accurately, programmes should develop systems enabling them to collect data disaggregated by weight band.

[1] Please refer to the AIDS Free Toolkit for latest Annex on Dosages of ARV Drugs.

Availability

Inclusion of optimal paediatric ARV formulations into national protocols is the first step in enabling access to better ART regimens; however, there are factors that may impact their actual availability that should be taken into account 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.

Regulatory approval by the United States Food and Drug Administration (USFDA) or receipt of WHO prequalification (WHO PQ) does not guarantee availability, as suppliers may not invest in commercializing and/or manufacturing a product until they are assured of procurement. Due to the inherently limited size of the paediatric ARV market, some new products may be vulnerable to long lead times particularly when smaller orders are placed. For other products, supplier capacity may be constrained, particularly during early stages of commercialization when demand is uncertain or when manufacturers are unable to keep up with a sudden increase in demand. (See Case study: Supplier capacity of LPV/r oral pellets).

Paediatric HIV programs have required optimized paediatric ARV formulations for decades; new products such as ABC/3TC/EFV (ALE), ABC/3TC/LPVr (4-in-1) and DTG 10 mg scored tablets are expected to be approved in late 2019 or early 2020. Unfortunately, drug development is often unpredictable and timelines for the approval of new ARV products may shift. Although several new pipeline products are anticipated in the near future, programmes should be prepared for possible delays in the approval and availability of new paediatric ARV formulations which may have an effect on policy and internal decision-making. (See Case Study: Accelerated Introduction of Paediatric Dolutegravir Formulations).

Monitoring and Evaluation

Toxicity Monitoring/Pharmacovigilance

Accelerated introduction of new ARVs often occurs in the context of limited clinical experience outside of trial settings. When introducing new drugs countries should consider routine toxicity monitoring of critical importance, especially regarding the long term toxicity and tolerability of new products. As national toxicity monitoring and pharmacovigilance (PV) systems are put in place or strengthened, enhanced monitoring at sentinel sites and use of observational cohort studies can provide important opportunities to identify early signals of adverse events in 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 adult populations and the safety of ARV exposure through breastfeeding should be ensured in the short and longer term, in both HIV-infected and HIV-uninfected infants exposed to ARVs being breastfed.

WHO has developed an ART toxicity monitoring tool which provides step-by-step instructions and reporting tools for countries to implement both passive PV surveillance, as well as active ADR monitoring at selected sentinel sites, for new ARVs in paediatric populations[2].

[2] http://www.who.int/hiv/pub/toolkits/3-2-8_Pharmacovigilance_3Nov.pdf

3. RECOMMENDATIONS FOR COUNTRY PROGRAMMES TRANSITIONING TO THE 2018-UPDATED PAEDIATRIC ARV FORMULARY

- Review and collect information on current paediatric population on treatment with age and weight-band disaggregated data to inform transition decisions:
  - Distribution of regimens currently in use
  - Current weight band distribution
- Determine eligible patient populations considering:
  - Age and weight band
  - Current line of treatment
  - Supply availability
  - Consider appropriateness of maintaining stable patients on current regimens
- Maintain up-to-date market intelligence on available paediatric ARV formulations:
  - Current Optimal Formulary and Limited-use List for Paediatric ARVs[3]
  - Supply capacity through APWG memos[4]
- Develop demand forecast and share consolidated forecast of low demand products with APWG. To increase visibility of demand to suppliers, the APWG is sharing consolidated forecasts, particularly for low-volume products, with suppliers on a quarterly basis. This enables suppliers to prepare for adequate production prior to orders being placed.
- Evaluate risks of not transitioning if a product currently in use is being phased out, e.g. shifting to the Limited-use List as a transition product or lack of inclusion on either the Optimal Formulary or Limited-use List. This indicates that the use of a product is waning and that production may therefore significantly decrease over time.
- Consider systemizing the process of updating the national paediatric ARV formulary to simplify future transitions (e.g. IATT Formulary methodology).