



INTRODUCTION

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1. BACKGROUND

In 2016, an estimated 2.1 million children younger than 15 years and 17.8 million women were living with HIV worldwide (1). Despite advances in antenatal HIV testing and prevention of mother-to-child transmission, about 160 000 children were newly infected with HIV in 2016, mainly in low- and middle-income countries (1).

WHO recommends that all children diagnosed with HIV start antiretroviral therapy (ART) regardless of symptoms or clinical stage (2). This drive toward universal ART coverage has meant a huge increase in the number of eligible children, but less than half of the children who are eligible start treatment (3). There are many reasons for this, including barriers to access to health care and specifically HIV services, delays in HIV diagnosis, the complexity of ART regimens for children and difficulties in administering treatment to them and lack of support for families affected by HIV.

Compounding these issues is the lack of safe, effective and well tolerated drugs in formulations adapted for children of different ages, which has remained a key barrier to implementing WHO treatment guidelines in low- and middle-income countries (4). Only about one quarter of antiretroviral (ARV) drugs approved by the United States Food and Drug Administration (FDA) or the European Medicines Agency (EMA) for adults are approved for children younger than two years (5). Expediting the availability of such formulations is essential to scaling up of HIV treatment for children, to ensure that global targets can be met and that children with HIV worldwide receive the treatment they need (5).

A general paucity of treatment options for pregnant and breastfeeding women also persists as a limiting factor in treating this population and preventing vertical transmission. Efforts to ensure pregnant women are included in studies and to rapidly generate safety data for use of new compounds are urgently needed.

1.1 Challenges in developing ARV drugs for children

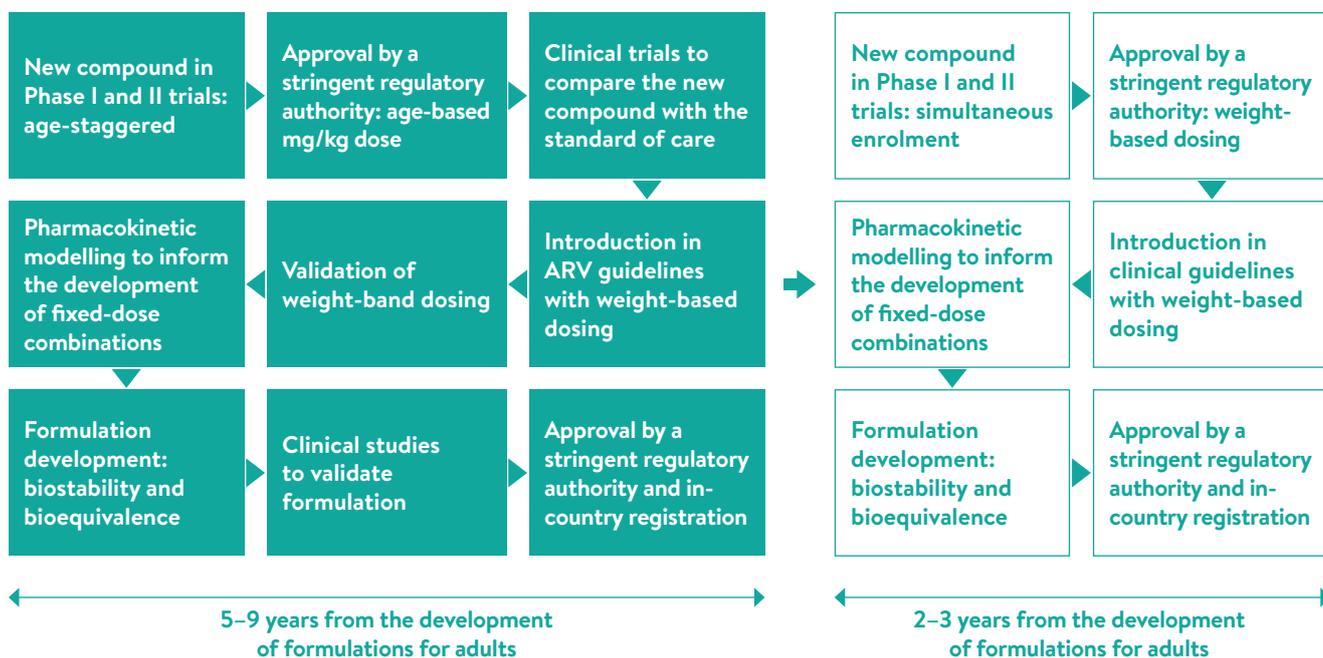
Research and development of formulations of ARV drugs for children has traditionally lagged behind those for adults, with delays of up to a decade (Fig. 1) (5). The development of drugs for children is often only considered once preclinical, Phase I and Phase II studies end, which can take many years. The development of fixed-dose combinations for children, which combine two or more drugs into a single dosage form such as a tablet, requires additional steps and results in further delays (Fig. 1).

Although regulatory frameworks in both the United States and Europe have encouraged and provided incentives to programmes for developing drugs for children, the development and approval of such formulations has remained a lengthy process (5,6). Further, the shrinking market for drugs for children in high-income countries, where rates of vertical HIV transmission are now extremely low, has further reduced the incentives manufacturers have to invest in this area. Fragmentation of the market has also been an issue, resulting from the need for weight-appropriate doses and formulations (5).

1.2 Recent initiatives to accelerate the development of ARV drugs for children

In response to the need for novel approaches to accelerate and streamline the process of developing ARV drugs for children, several initiatives have been launched in recent years. The WHO-led Paediatric Antiretroviral Drug Optimization group has established a set of mid- and long-term priorities for drug development to accelerate access to optimal formulations in the context of fragmented markets for ARV

Figure 1. Stages in developing and introducing fixed-dose combinations of ARV drugs for children



Source: adapted from Penazzato et al. (5).

drugs for children (6–8). In conjunction with this, WHO treatment guidelines (2) now recommend a limited set of regimens for children and have harmonized recommendations for adults and adolescents.

WHO also recommends the use of weight bands and weight-based dosing in developing drugs (rather than age-based dosing) to simplify and facilitate the implementation of treatment guidelines. WHO weight-band dosing (9) is a simplified approach to guide age-appropriate dosing through which drugs have been successfully delivered. This approach was recently revised to incorporate allometric scaling, a method that accounts for the non-linear relationship between weight and drug clearance. The paediatric ARV drug formulary (10), developed by several international partners, provides guidance to HIV treatment programmes on product selection to deliver WHO-recommended regimens.

The Paediatric Antiretroviral Working Group provides technical guidance on weight-band dosing and pharmacokinetic and acceptability studies of ARV drugs for children (12). ARV drug manufacturers are encouraged to engage with the Paediatric Antiretroviral Working Group from an early stage when developing dosing and designing pharmacokinetic and safety studies.

Platforms have also been established to support different stages of drug development and introduction. The Paediatric HIV Treatment Initiative (11) was established to overcome intellectual property barriers that prevented individual drugs manufactured by different companies from being combined into fixed-dose combinations and to facilitate and partly support the development of key priority products.

Although these various steps have been hugely beneficial in facilitating the process of developing HIV drugs for children and bridging structural barriers, the availability of formulations for children remains inadequate. It has been

recognized that, with the development of new drugs and indeed new classes of ARV drugs, such as long-acting injectable drugs, researchers, drug manufacturers and regulators need to engage earlier in the process of developing drugs (4).

In 2016, the concept of a Global Accelerator for Paediatric Formulations (12) was developed to build on existing initiatives and accelerate

research, development, regulatory filing and introduction and uptake of key ARV drugs for children in age-appropriate formulations, with a target year of 2020. This framework aims to capitalize on existing efforts to maximize the coordination and alignment of the public and private sectors, including policy-makers, research networks, regulatory agencies, funding organizations and manufacturers.

2. OVERVIEW OF THE TOOLKIT

This section outlines the rationale, aims, objectives and intended audience of the toolkit and provides an overview of the modules.

2.1 Rationale for this toolkit

The toolkit was developed under the umbrella of the Global Accelerator for Paediatric Formulations initiative to address some of the remaining challenges in developing HIV drugs for children and to serve as a global standard for accelerating high-quality research and development in this field. It provides an opportunity to capitalize on best practices and to set standards that enable drugs and formulations to be developed and introduced more rapidly.

2.2 Aims and objectives

The aim of this toolkit is to facilitate faster, more efficient and focused development of new formulations for the effective treatment of infants, children and adolescents living with HIV by synthesizing key considerations for different stages of the drug development process.

The specific objectives of the toolkit are:

- to provide guidance to manufacturers (generic and innovator) and to researchers

engaged in developing and approving drugs and formulations;

- to establish overall standards to accelerate ARV drug investigation and approval while enabling more rapid development of formulations for children; and
- to promote alignment and coordination between key stakeholders involved in developing and approving drugs and formulations.

2.3 Toolkit audience

This toolkit targets:

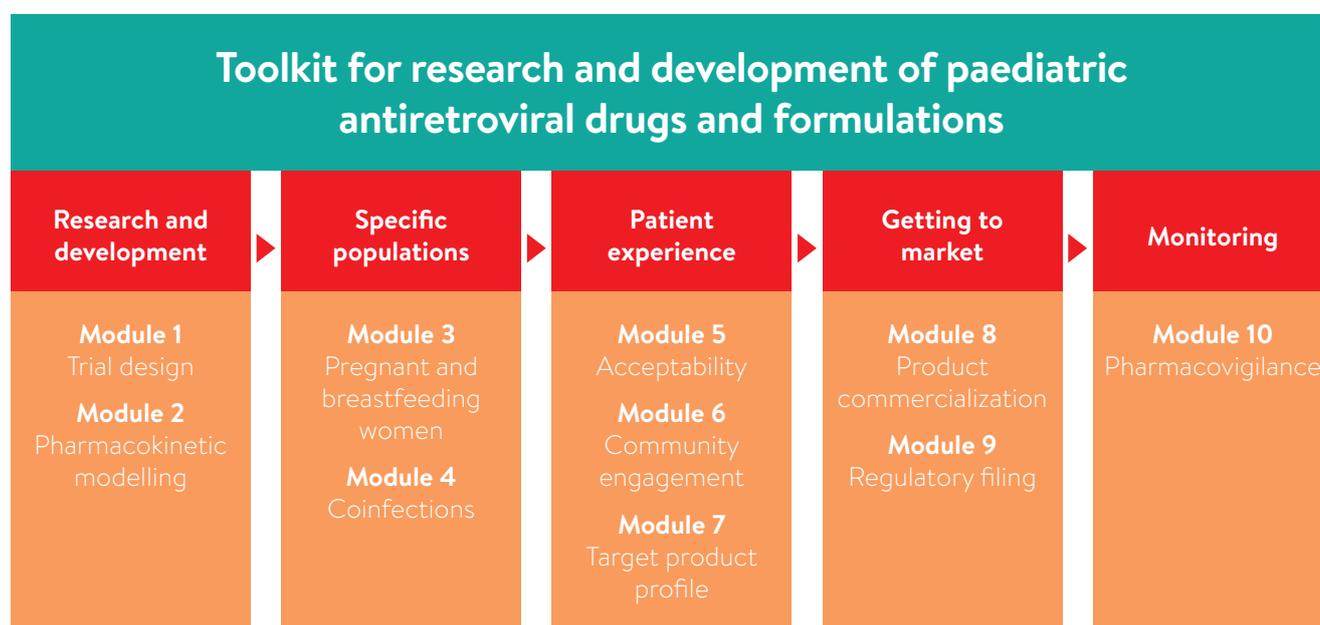
- innovator and generic drug manufacturers;
- researchers involved in research and development related to HIV drugs for children; and
- nongovernmental and other organizations with an interest in drug development.

2.4 Overview of the modules

The toolkit comprises 10 modules, each addressing a key area in the research and development of HIV drugs for children (Fig. 2).

The first two modules address the generation of data to support regulatory approval of ARV

Figure 2. Outline of the modules included in this toolkit



drugs for children, by carefully designing and implementing clinical trials and pharmacokinetic modelling studies. Traditionally, research studies among children have been delayed until sufficient adult data on pharmacokinetics, safety and efficacy have been obtained. Studies to ascertain correct dosing are then carried out sequentially, starting with older age groups.

Module 1 on trial design discusses the key barriers to including children and adolescents in clinical trials. These include ethical concerns as well as issues relating to market fragmentation and the reluctance of manufacturers to invest resources in clinical trials involving children. This module discusses the various ways of obtaining safety and efficacy data, by maximizing the use of available data, advance planning of studies involving children and using innovative trial designs to generate the required data quickly and efficiently without compromising patient safety. Recommendations include enrolling adolescents in adult clinical trials and simultaneous enrolment across different weight bands for younger children.

Module 2 on pharmacokinetic modelling addresses how to establish appropriate pharmacokinetic targets and doses for neonates and other children and describes some of the innovative methods that have been developed to answer these questions.

Module 3 addresses issues relating to pregnant and breastfeeding women, another population poorly represented in drug development studies. This module recognizes the close interaction between maternal and infant health and the importance of expanding access to treatment for pregnant and breastfeeding women for preventing vertical transmission and treating the mother. Including pregnant women in clinical trials and pharmacokinetic studies is encouraged. It is also recommended that protocols allow women becoming pregnant during a trial involving non-pregnant adults to stay on the investigational drug (or, if they stop the investigational drug, to remain in the study), with appropriate follow-up to monitor pregnancy and infant outcomes. A more inclusive approach to involving pregnant women in

clinical trials will also enable and facilitate research on pharmacokinetics among neonates.

Module 4 on coinfections discusses challenges relating to treating people living with HIV who are coinfecting with hepatitis B or C viruses or tuberculosis (TB), an issue of particular importance in low- and middle-income countries, where most children living with HIV reside. To accelerate access to appropriate drugs, adolescents coinfecting with TB or hepatitis B or C should also be eligible for enrolling in trials for adults, and consideration should be given to including coinfecting children in trials for children. The potential for drug–drug interactions should be considered early in ARV drug development, so that timely and effective solutions can be found. This process can be facilitated by more effective communication between clinicians, researchers and drug manufacturers.

Module 5 on acceptability recognizes the need for better understanding of how the acceptability of formulations for children should be defined, assessed and reported. Treating children poses specific challenges around the acceptability of

formulations, which can affect adherence and in turn resistance, which can compromise efficacy. Current regulations require drug companies to consider the specific needs of children, including the appropriateness of a formulation. Studies of acceptability should be carried out early enough to enable a formulation to be modified if required. This module emphasizes the need for standardized protocols for evaluating all components of acceptability in the target age groups and for using standardized metrics. It advocates for systematically including acceptability studies in all research protocols involving children and stringent reporting of study findings. Good communication should be established across stakeholder groups, including formulation scientists, clinicians, research teams, social scientists and regulators, and children and their caregivers should be involved from an early stage.

Module 6 on community engagement describes the importance of involving the paediatric community throughout the process of drug development. The paediatric community involves not only children and adolescents living with HIV but also their parents and caregivers.



Recommendations for facilitating community engagement in HIV drug development include working with community advisory boards and establishing community engagement plans, which describe strategies and mechanisms to help researchers collaborate with the relevant community. Engaging community members early in the research process is also advocated for, as is using appropriate language in all communications.

Module 7 explains the role of target product profiles in establishing the desired attributes of products before they become available. The purpose of target product profiles is to guide industry in developing products that meet the needs of the target users, by outlining the critical attributes of a product needed to ensure that it is fit for purpose. This module discusses considerations for designing target product profiles that will facilitate the development of optimal formulations.

Module 8 on product commercialization addresses factors related to commercializing and launching a pharmaceutical product. Once a drug or formulation becomes available, carefully planning its introduction to the market is important, so that production can match demand. This can be achieved by coordinating procurement and the strategic management of demand and is facilitated by rationalizing paediatric formularies.

Module 9 on regulatory filing describes key regulatory considerations for expediting submissions for regulatory approval for drugs for children. Recommendations are made for simpler paediatric study plans and paediatric investigation plans; simultaneous product development for adults and adolescents; and a concurrent rather than sequential approach to enrolling children in clinical trials across weight bands. Using standardized weight bands for dosing in trials involving children is recommended to facilitate implementation once a drug has been approved.

Module 10 on pharmacovigilance addresses key issues around safety and post-marketing surveillance and monitoring to better understand the risks and safety profile of ARV drugs for children in low- and middle-income countries. WHO recommends a combination of standardized toxicity monitoring, integrated within national health systems, and active surveillance for adverse drug reactions. Better pharmacovigilance systems are needed in many low- and middle-income countries, including improving data management systems to collate data from multiple sources, training health-care workers and using existing data sets better.

In summary, the need for early and continual collaboration between the paediatric research community, innovator and generic pharmaceutical companies, regulatory authorities and policy-makers is a recurring theme throughout this toolkit. Good communication and alignment of stakeholders throughout the process of drug development can ultimately ensure that the development of optimized ARV formulations for children can be accelerated and that appropriate treatment options are made available to children living with HIV throughout the world.

2.5 Next steps

This toolkit is intended as a resource for those involved in developing HIV drugs for children. It will be reviewed periodically and updated when major revisions are required.

Although the focus of this toolkit is HIV among children, many of the principles outlined here are relevant to other disease areas. The toolkit will therefore be disseminated beyond the HIV field with the goal of stimulating acceleration for optimal products for children in other disease areas.

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